HIV-associated cognitive disorders in children and adolescents: methodological investigations and validating a quick screening tool.

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BSc (Biological Human Life Sciences), BSc.Hons (Psychology), MSocSci (Psychology)

Thesis presented for the Degree of

DOCTOR OF PHILOSOPHY IN NEUROSCIENCE (PSYCHIATRY)

in the Department of Psychiatry and Mental Health,

Faculty of Health Sciences,

UNIVERSITY OF CAPE TOWN

June 2019

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ACKNOWLEDGEMENTS

Proverbs 27:17

As iron sharpens iron,

so one person sharpens another.

This PhD is not the work of one person alone; I consider it is a collective effort by many, each making their own unique contributions to my pursuit of knowledge. I am deeply appreciative of every effort, no matter how small.

Without financial assistance I would not have been able to complete this PhD;
To the National Research Foundation DAAD In-Country Scholarship (2014), who provided me with financial assistance at the early stages of my studies.
And to the South African Medical Research Council's National Health Scholars Programme (the brain child of Professor Bongani Mayosi), who provided me with financial assistance to complete my studies (2015-2018). I am honoured to have been part of Prof Mayosi's dream to advance 100 PhD's in health sciences within 10 years. Hamba kahle, Prof Mayosi.

Professor Jaqueline Hoare, for her mentorship and support, as well as expertise in child and adolescent psychiatry. I am deeply appreciative of all the time you spent working with me on this thesis – thank you.

Professor Dan Stein, for his mentorship and expertise in neuroscience and psychiatry. A special thank for also providing me with funding at the very start of this journey.

Professor Kevin Thomas, who has taught me most of what I know about conducting research, for his mentorship and encouragement, as well as expertise in neuropsychology and statistical analysis.

Professor Heather Zar, for having me as a student on her CTAAC project and expertise in child and adolescent health.

Professor Landon Myer, for his expertise and guidance in child and adolescent health and statistical consultation.

Professor Ned Sacktor, for his expertise in screening for HIV-associated neurocognitive disorders and giving us permission to validate his tool for use in children and adolescents.

Professor Caroline Kuo, for teaching and guiding me through the process of systematic search and review, and continual encouragement.

Dr Jonathan Ipser, for assistance in conducting meta-analysis and for teaching me the basics of neuroscience research in my early days at UCT.

Tembela Molwana, Yvonne Sani, Mluleki Matiwane and Charity Oduro for their hard work done assisting with data collection and capturing.

Dr Sana Mahtab and Dr Nana Akua Asafu-Agyei, for their assistance with recruitment and participant contact maintenance.

The Health Sciences Library at the University of Cape Town, for assistance with sourcing full text articles and initial guidance on systematic searches. To Adri Winckler and her team at UCT Health Sciences postgrad office, for always being friendly and always encouraging me and my fellow PhD students each year as we register, yet again.

Colleagues who offered words of support and encouragement along the way: Dr JP Fouche, Dr Hetta Gouse, Dr Sarah Heany, Ms Kaylee Van Whye, Dr Leigh Schrieff-Elson, Dr Nastassja Koen, Prof Kirsty Donald, Prof Marian Jacobs, Dr Adele Marais, Dr Lisa Frigati, Sandra Swart, Kim Hendricks.

Colleagues who are more than just co-workers, they have become my dearest of friends and have been a constant source of love and support throughout this journey; Ms Taryn Amos and/or Williams (insert wink emoji), Ms Bulelwa Mtukushe (Gogo) and Dr. Mariam Karjiker (Didi).

Friends and family; Jehaan and Hashiem Edwards, Luanne Mc Anda, Lucinda Heunis, Romy and Robin Van Leeve, Michelle Adams, Autricia Cupido, Jonathan Crawford, Nadia Strauss, Joy Solomon, Dr. Zaraina Solomons-Essop, Shabieha Kamrodien, Robyn Lynch, Emmerentia Fester, Terry Rossouw, Emlyn Phillips, Basil & Hester Van Merch, Frank & Charlotte Phillips for your encouragement.

My parents; Kevin & Shirley Mc Anda, for your faith in me and instilling in me good work ethic.

The parents/caregivers and adolescents who participated in this study. Without the selfless contribution of your time for me to “pick your brains” this work would not exist. Enkosi.

To my soul sister, Candice Dietrich; for being that iron in my life. #Iron.

To my husband, Marlon Phillips; for believing in me, for loving me on my worst days, for pushing me and for the free IT support.

To my daughter, Michaela Phillips; though you be but little, you are such an inspiration to me. Mummy is finally done with her “peach D”.

Final thanks go to God, who strengthens me.

DECLARATIONS

I, Nicole Justine Phillips, do hereby declare that this thesis is based on four journal manuscripts: three of which have been published (chapters 3-4 & 6), and one under review at an international journal (chapter 5). These manuscripts have been formatted uniformly for the purposes of this thesis, with regards to referencing style and use of terms. The content of each manuscript remains unchanged from that which has been either published or submitted for publication, but the introduction, conclusion and minor additions where necessary in each has been edited in such a way as to underscore the coherence of the entire thesis, i.e. how each chapter links to the next and the others and to provide clarification regarding the work as a whole. The manuscripts included are listed below, with a description of my contribution to each. My project was nested within a larger study, the Cape Town Adolescent Antiretroviral Cohort (CTAAC). Empirical data analyses for this thesis emanated from the CTAAC neuro sub-study. My role on the CTAAC neuro sub-study project was that of project manager. Dr Leigh Schrieff-Elson and Prof Kevin Thomas trained me to administer the neuropsychological tests, how to score, interpret and quality control check all assessments. I assisted with neuropsychological testing and completion of psychosocial questionnaires where there were no language barriers between myself and the research participants. I oversaw all data collection, entry and analysis emanating from the CTAAC neuro sub-study baseline.

Chapter 3.

HIV-Associated Cognitive Impairment in Perinatally Infected Children: A Meta-analysis. Phillips, N., Amos, T., Kuo, C., Hoare, J., Ipser, J., Thomas, K. G., & Stein, D. J. (2016). *Pediatrics, 138*(5), e20160893.

In this systematic review and meta-analysis, I developed the search terms and strategy with input from my supervisors and Prof Caroline Kuo, and then conducted the database and journal searches myself. Myself and Ms Taryn Amos reviewed all papers for potential inclusion and established our level of agreement. We extracted data into spreadsheets independently and then compared our level of agreement on the data extraction. Dr Kuo checked data entry. Dr Jonathan Ipser gave consultation for the meta-analysis. Prof Dan Stein and Prof Kevin Thomas reviewed the manuscript critically for important intellectual content. Prof Jackie Hoare assisted with interpretation of the data analysis and reviewed the manuscript critically for important intellectual content. I then analysed and summarised all the data myself, and wrote the full first draft of the manuscript. My co-authors all reviewed the draft prior to submission to the journal. I managed all reviews from co-authors and journal reviewers myself.

Chapter 4.

HIV-associated cognitive disorders in perinatally infected children and adolescents: a novel composite cognitive domains score. Phillips, N. J., Hoare, J., Stein, D. J., Myer, L., Zar, H. J., & Thomas, K. G. (2018). *AIDS care*, 1-9.

This manuscript was the first based on the empirical data obtained from the CTAAC neuro sub-study research project. I checked and cleaned the data prior to analysis. I conducted all

descriptive and inferential statistical analyses myself. My statistical analyses were checked by Prof Kevin Thomas, who also reviewed the manuscript critically for important intellectual content. Prof Dan Stein, Prof Landon Myer and Prof Heather Zar reviewed the manuscript critically for important intellectual content. Prof Jackie Hoare, PI of the CTAAC neuro sub-study, helped with interpretation of the results and reviewed the manuscript critically for important intellectual content. I drafted the manuscript myself and all co-authors read and reviewed the manuscript prior to submission to the journal. I managed all reviews from co-authors and journal reviewers myself.

Chapter 5.

Youth perinatal HIV-associated neurocognitive disorders: association with functional impairment. Phillips, N. J., Thomas, K. G. F., Mtukushe, B., Myer, L., Zar, H. J., Stein, D. J. & Hoare, J. (2018). Under review at *JAIDS*. Submitted to journal on 14 June 2019.

This manuscript followed chapter 4, as described above and was also based on empirical data collected on the CTAAC neuro sub-study. I checked and cleaned the data prior to analysis. Ms Bulelwa Mtukushe assisted me with hand scoring and interpretation of the Vinelands Adaptive Behavior Scales, which was analysed as part of this paper. I conducted all descriptive and inferential statistical analyses myself. My statistical analyses were checked by Prof Kevin Thomas, who also reviewed the manuscript critically for important intellectual content. Prof Dan Stein, Prof Landon Myer and Prof Heather Zar reviewed the manuscript critically for important intellectual content. Prof Jackie Hoare, PI of the CTAAC neuro sub-study, helped with interpretation of the results and reviewed the manuscript critically for important intellectual content. I drafted the manuscript myself and all co-authors read and

reviewed the manuscript prior to submission to the journal. I managed all reviews from co-authors and journal reviewers myself.

Chapter 6.

Screening for HIV-Associated Neurocognitive Disorders in Perinatally Infected Adolescents: y-IHDS Validation. Phillips, N. J., Thomas, K. G. F., Myer, L., Sacktor, N., Zar, H. J., Stein, D. J. & Hoare, J. (2018). *AIDS*, 33(5): 815-824.

This manuscript followed chapter 5, as described above and was also based on empirical data collected on the CTAAC neuro sub-study. I checked and cleaned the data prior to analysis. I applied the youth HIV-associated neurocognitive disorders classification criteria to each individual participant's neuropsychological data to create a profile for each. This was done by using the cognitive domains established in chapter 4 and functional assessments done in chapter 5. I conducted all descriptive and inferential statistical analyses myself. My statistical analyses were checked by Prof Kevin Thomas, who also reviewed the manuscript critically for important intellectual content. Prof Dan Stein, Prof Landon Myer and Prof Heather Zar reviewed the manuscript critically for important intellectual content. Prof Jackie Hoare, PI of the CTAAC neuro sub-study, helped with interpretation of the data analysis and reviewed the manuscript critically for important intellectual content. I drafted the manuscript myself and all co-authors read and reviewed the manuscript prior to submission to the journal. I managed all reviews from co-authors and journal reviewers myself.

I confirm that no part of this thesis has been submitted in the past, or is being, or is to be submitted for a degree in this or any other university. I hereby grant the University of Cape Town free license to reproduce this thesis in whole or part for the purposes of research or teaching.

This thesis is presented for examination in fulfilment of the requirements for the degree of Doctor of Philosophy in Neuroscience, Psychiatry.

Signed,

Signed by candidate

Nicole Justine Phillips June 2019

ABSTRACT

Title: HIV-associated cognitive disorders in children and adolescents: methodological investigations and validating a quick screening tool.

Background

Perinatal HIV-infection is associated with both cognitive and functional impairment. Accurate measurement and screening for these conditions is key in ensuring that these vulnerable children and adolescent receive the care they need.

Objectives

I sought to carry out the following: 1) to undertake a systematic review to determine the cognitive effects of living with HIV in children and adolescents, 2) to determine a statistically sound method for assessing cognitive impairment, 3) to determine the association between cognitive impairment and measures of functional impairment and the relative risk of having functional impairment in the presence of cognitive impairment and 4) to validate a quick screening tool to screen for HIV-associated neurocognitive disorders in children and adolescents living with HIV.

Methods

This study was nested within a larger longitudinal study, titled, the Cape Town Adolescent Antiretroviral Cohort (CTAAC). This study is a quantitative cross-sectional study. Each aim led to a study using appropriate methodology. For aim 1; electronic systematic searches were conducted to find relevant literature, which were then assessed by two independent reviewers, data were extracted and then meta-analysed. For aims 2-4; data were collected from research participants enrolled into the CTAAC study. Data scoring, capturing and inferential statistics were conducted in SPSS 25.

Results

With regards to aim 1, I found that there are both consistencies and inconsistencies in the literature regarding which cognitive domains are most affected by HIV. Findings from the meta-analysis showed that the cognitive domains of executive function, processing speed and working memory are the most affected. With regards to aim 2, I demonstrated statically, that composite cognitive domain scores (as opposed to global scores), were more accurate in detecting HIV-related cognitive differences in adolescents. With regards to aim 3; I found that the functional impairment was strongly and significantly associated with degree of cognitive impairment and that adolescents had an increased risk of having functional impairment if they had cognitive impairment. With regards to aim 4; I demonstrated the statistical validity of the youth International HIV Dementia Scale (y-IHDS) to screen for HIV-associated neurocognitive disorders in children and adolescents. The y-IHDS displayed high sensitivity, as well as high positive and negative predictive values for screening for all forms of cognitive impairment.

Conclusion

Assessment of cognitive and functional impairment in HIV-infected children and adolescents requires special considerations. Methods need to be child/adolescent and time sensitive, and should be contextually appropriate. The methodological approaches and screening tool validated here are a start in addressing these kinds of issues both locally and globally. Neurocognitive disorders are common and can cause clinically significant functional impairment, they are however underrecognized in busy clinical settings. The screening adapted and validated here is an easy to use, quick tool which should be rolled out as part of routine care for all children and adolescents attending antiretroviral (ARV) clinics.

CHAPTER 1: INTRODUCTION

Perinatal Human Immunodeficiency Virus continues to be of major concern in resource-poor countries, most notably in sub-Saharan Africa. 19% of the global number of people living with HIV reside in South Africa, making it the country with the greatest burden of the disease (UNAIDS, 2016). An estimated 9600 - 22 000 children were newly infected with HIV via perinatal transmission in South Africa (UNAIDS, 2016).

There is little consensus on where HIV establishes a reservoir in the body. Some experts agree that these may be in the CD4 T-cells and other postulate that it may be in the brain (M. J. Churchill, Deeks, Margolis, Siliciano, & Swanstrom, 2016). While HIV latent reservoirs may be established in the brain, the mechanism by which they cause CNS and cognitive damage and its role in the persistence of the HIV infection is still unclear (Fois & Brew, 2015). HIV reservoirs in the brain may cause tissue damage which then causes neurocognitive degeneration and dysfunction in perinatal acquired HIV (M. Churchill & Nath, 2013; M. J. Churchill et al., 2016). There are a range of other factors which may also cause cognitive impairment such as early diagnosis of an AIDS defining illness (Smith et al., 2006), CNS infections and environmental issues (for example; ARVs during pregnancy, access to ARVs and social factors) (Brown, Lourie, Psychiatry, & Disciplines, 2000). Pinpointing and exact cause of HIV-associated cognitive impairment in children and adolescents is complex and multifaceted.

Children can present with central nervous system (CNS) problems more frequently than adults with CNS disease, due to the infection being present during key neurodevelopmental periods (Tardieu et al., 2000). HIV-infection in the brain can have consequences for cognitive functioning. The effects of HIV on the CNS and cognitive functioning ranges from pervasive to being very subtle, with encephalopathy being at the

very severe end of the spectrum (Donald, Hoare, Eley, & Wilmshurst, 2014). In a review by Laughton and colleagues (Laughton, Cornell, Boivin, & Van Rie, 2013b) looking at neurodevelopment in perinatally HIV-infected children, they found that with regards to general cognition children living with HIV performed more poorly than HIV-uninfected controls. Another important finding from the Laughton et al. (2013) review, is that HIV-infected children diagnosed with an AIDS-defining illness performed significantly worse than HIV-infected children who did not have an AIDS-defining illness.

Compared to typically-developing peers who are not infected with HIV, HIV-infected children and adolescents are at high risk for experiencing numerous threats to psychosocial development (Smith et al., 2006) and consequent behavioural and emotional dysfunction. Apart from cognitive functioning, another equally important aspect of development reviewed by Laughton et al. (2013) is that of adaptive functioning. While cognitive functioning gives an indication of how well a child is able to perform mentally, it may not accurately depict how well a child is able to function in real life situations (Laughton et al., 2013). For example, children may be able to function adequately at home or in social situations even though they perform poorly on cognitive measures.

Wachsler-Felder and Golden (2001), in a review of the literature to that point, reported that HIV has been consistently shown to have behavioural, cognitive, emotional, developmental, and educational effects on the child infected with this disease (Jana L Wachsler-Felder & Charles J Golden, 2002). What is unknown and largely understudied in child and adolescent samples, is the range and severity of HIV-associated cognitive impairments in children and adolescents. Various studies have been done on the behavioural and emotional difficulties of HIV-infected children and adolescents, but very few focused specifically on everyday functioning.

Prevalence of HIV-associated cognitive impairment

The topic of HIV-related cognitive disorders in children infected with HIV is an understudied area. The great paucity of literature focusing on HIV-related neurocognitive impairment, and lack of clinical consensus in children is concerning given the high prevalence rates of HIV-infected children in sub-Saharan Africa, and globally. A number of studies have investigated neuropsychological impairment in HIV-infected children (S. E. Cohen et al., 1991; Jeremy et al., 2005; Le Doaré, Bland, & Newell, 2012; Lindsey, Malee, Brouwers, & Hughes, 2007). However, none of these studies directly address the issue of a possible spectrum of HIV-related neurocognitive disorders in children and how to screen for them.

Defining the spectrum of HIV-associated neurocognitive disorders in children

HIV-associated neurocognitive disorders (HAND) in the adult HIV literature encompasses the following three categories: (1) HIV-associated asymptomatic neurocognitive impairment (ANI), (2) HIV-1 associated mild neurocognitive disorder (MND), and (3) HIV-1 associated dementia (HAD) (Antinori et al., 2007), and applies to HIV-infected adults only.

A handful of studies have examined neurological complications, development (Lindsey et al., 2007), cognitive impairment (Bagenda et al., 2006) and HIV encephalopathy (HIVE) (Lobato, Caldwell, Ng, Oxtoby, & Consortium, 1995) in children and adolscents. HIVE would be considered the neurocognitive disorder on the severe end of the spectrum. For many years the majority of literature in the pre-Antiretroviral Therapy (ART) era focused on HIVE, as this condition was highly prevalent in perinatal transmission, where treatment was often not available. The importance of understanding a spectrum of neurocognitive disorders (NCD) from mild to major has developed recently as many perinatally infected

children have survived into adolescence. The prevalence of HIVE has declined in the ART era, however adolescents living with HIV are more likely to have scholastic failure, suggesting the possibility of milder NCD in these youths (Sohn & Hazra, 2013). Using the 'traditional' definition for HAND for paediatrics is not ideal for many reasons: (1) the HIV infection manifest differently in children than in adults (for example; adults may experience a decline in already attained cognition while children may struggle to achieve age-appropriate cognitive milestones), (2) paediatric developmental milestones are not taken into account, and (3) measuring or quantifying the level of global functioning is different in children (school, home, social, etc.) compared to adults (work, home life, social activities, etc.).

Developing a clear definition of paediatric "HAND", or neurocognitive disorders, is key in being able to characterize, diagnose, and ultimately treat it.

The first published work (to my knowledge) which investigated and described a spectrum of HIV-associated neurocognitive disorders in children and adolescents is that by Hoare and colleagues (Hoare et al., 2016a). This is also the first published work to establish criteria by which diagnoses of HIV-associated neurocognitive disorders can be made in children and adolescents. These criteria are based on the Frascati criteria but have been adapted for children and adolescents. The criteria draw on the child/adolescent's cognitive performance and functional ability, with the taxonomy structured as follows: major neurocognitive disorder = performance of >2SD below the mean in two separate cognitive domains, plus the presence of functional impairment; minor neurocognitive disorder = performance of >1SD below the mean in two separate cognitive domains, with or without functional impairment; and no neurocognitive disorder = no cognitive impairment.

The above criteria was developed on a mixed cohort which included ART naïve participants, slow-progressors (Hoare, Fouche, Spottiswoode, Donald, Philipps, Bezuidenhout, Mulligan, Webster, Oduro, & Schrieff, 2012) and HIVE participants, with a

very wide age range. This work needs to be further expanded and implemented on a sample which is more representative of the Western Cape population of HIV-infected children and adolescents; i.e.: larger sample, well-matched controls, narrower age range and with all participants stable on ARVs. More specifically, a spectrum of HIV-associated neurocognitive disorders in children and adolescents needs to be well-defined and distinguished from other learning and neurodevelopmental disorders. A detailed description of the assessment of these disorders is also necessary.

Assessing cognitive impairment

Accurate assessment of HIV-associated cognitive impairment in perinatally infected children and adolescents is challenging because cognitive impairments present differently in children and adolescents compared to adults (Tardieu et al., 2000). There is no globally accepted method for assessing cognitive impairment. Some researchers assess individual neuropsychological tests, others, global scores which encompass a variety of tests, and others make use of composite domain scores. The statistical method by which these various scores are derived differ significantly between the different researchers.

Assessing functional impairment

Assessing children and adolescent's adaptive and everyday functioning is important because cognitive ability alone may not give an accurate or comprehensive picture of the child's overall functioning. Understanding the association between functioning and cognitive impairment is important in terms of knowing which aspects of development present the most challenges for individual children. No studies investigating the association between functioning and HIV-associated cognitive impairment have been conducted in children and/or adolescents in low-resourced regions. An ideal assessment of functional impairment would

involve detailed observation of the individual in their social, familial, and academic environments (Antinori et al., 2007). Such assessment alongside and already lengthy neuropsychological test battery would place enormous pressure on healthcare systems, particularly in low-resource settings. Thus, the most time- and cost-efficient ways to measure functional impairment involve administration of standardized questionnaires that gather information from patients themselves and/or from their close relatives. When assessing functioning by means of standardized questionnaires, special considerations should be made with regards to the psychometric properties the scales display in low- and middle-income settings.

Screening for neurocognitive disorders

A cognitive screening tool should ideally, not be longer than a few minutes and should not require specialized training and equipment. Screening for milder forms of cognitive impairment is important to prevent progression to more severe forms (T. Barber et al., 2014).

Administration of a full neuropsychological test battery can take up to 6 hours to complete. Formal neuropsychological testing can only be conducted by an experienced and qualified neuropsychologist or clinical psychologist. In a low-resourced country, like South Africa, this is not feasible at community clinics for many reasons; (1) lack of dedicated space, (2) lack of experienced and qualified neuropsychologists, (3) lack of medical funds to pay for these kinds of detailed clinical assessments, (4) lack of funding to purchase neuropsychological test equipment, and (5) limited time constraints due to the large numbers of patients to be seen at the clinics. A quick screening tool would be best suited for use in community-based clinics.

The International HIV Dementia Scale (IHDS) has been well studied and validated in numerous adult populations (Joska et al., 2011; Lawler et al., 2010; Sacktor et al., 2005; Wojna et al., 2007). The IHDS is an internationally well-known tool used to accurately screen HIV-infected adults for the risk of HIV-associated cognitive impairment. The IHDS is considered to be a quick and valid screening tool for the use of screening for possible HIV-dementia in adults. All previous research into the validation of the IHDS has been conducted in adult populations. The validity, relevant cut-off scores, and appropriateness of use, has not yet been determined for HIV-infected youth. This particular tool, or any other quick screen, has not yet been adapted and/or validated to screen for cognitive impairment in HIV-infected children.

Short- and long-term consequences of cognitive and functional impairment

Cognitive and functional impairment persists in the era of ARVs, which means that children and adolescents may struggle to perform at school and achieve their expected milestones. For example; HIV-infected adolescents may not be able to thrive in a mainstream school curriculum.

ARVs increases the life-expectancy of HIV-infected adolescents to be able to reach adulthood. As adults they would be expected to become self-sufficient, which means securing employment and managing their own chronic medical illness. However, given that they are at high risk for both cognitive and functional impairment, self-sufficiency may be difficult to achieve. Due to cognitive impairment some may not be able to complete their high school qualifications in order to enter the job market. And those who are able to achieve their high school qualifications may not be able to attain work which requires a high level of mental or even physical competency.

Given the short- and long-term consequences of cognitive and functional impairment, it is important that we are able to accurately and efficiently screen for these deficits in HIV-infected adolescents.

Rationale for the current study

At present there are no youth HIV-associated cognitive disorder screening tools, which have been tested and validated specifically for the use in children and adolescents. As outlined in the introduction, children who have acquired the virus via perinatal transmission are at risk for neurocognitive impairments. Each child's biological system reacts differently to the virus, resulting in a wide spectrum of cognitive impairments. These differences may be due to genetic variation and the way in which HIV is replicated in the hosts' system (Violari et al., 2019). A recent study found that HIV-infection in adolescents accelerate epigenetic aging, and is associated with poorer cognitive outcomes (Horvath et al., 2018). Significant assault to a developing brain has consequences for adult life. The current ARV treatment guidelines provide blanket coverage of all children living with HIV, thus all children are eligible to receive ARV treatment regardless of their immunological status or age. This blanket coverage was not available for South Africa's current generation of adolescents during their early developmental years and resulted in later initiation of ART for many children. Having a robust screening tool will help to identify children with potential neurocognitive disorders and help optimize treatment for those that are most vulnerable. Validating and adapting an already existing and well-known screening tool to screen for the possible presence of these varying degrees of cognitive deficits is crucial for implementing appropriate and successful interventions for these children.

The IHDS is used in adult HIV clinical settings. Adapting and validating the IHDS for use in children and adolescents is appropriate because it assess short-term memory,

processing speed and motor co-ordination, which have been identified as potentially impaired in HIV-infected children and adolescents. However, the IHDS is not without limitations, even when administered in adult populations, but of particular note here is that sensitivity and specificity may be improved by the addition of screening questions which may suggest cognitive impairment (T. Barber et al., 2014). To this end, we asked the children and adolescents if they had ever repeated a grade at school, with responses coded as either yes or no. Repeating a grade at school has been shown to be an indicator of functional impairment in the school domain (Brittain et al., 2018) and is also associated with cognitive impairment more generally (Hoare, Fouche, Spottiswoode, Donald, Philipps, Bezuidenhout, Mulligan, Webster, Oduro, & Schrieff, 2012). We refer to this modified version of the y-IHDS (i.e., a version that features increased practice opportunity on the verbal memory and motor tasks, and that includes the repeated-grades question) as the youth-IHDS (y-IHDS).

Specific Aims and Hypotheses

My study was nested within a larger research project which examined the long-term effects and outcomes of ARV treatment in HIV-infected children and adolescents. My study had four major aims:

Aim 1: To conduct a systematic review and meta-analysis to determine cognitive impairments associated with perinatal child and adolescent HIV-infection. Furthermore, I aimed to describe the degree of cognitive impairment, and the specific cognitive domains affected.

Aim 2: To investigate and test a child and adolescent-sensitive method for examining domain-specific patterns of HIV-associated cognitive impairment, by statistically creating composite cognitive domain scores. I also aimed to compare the use of these composite

domain scores to a global cognitive score, which is commonly used in HIV neuropsychological literature.

Aim 3: To investigate the association between functioning and cognitive impairment, and to determine the relative risk of having functional impairment in the presence of HIV-associated cognitive impairment in a sample of perinatally HIV-infected children and adolescents.

Aim 4: To statistically determine the sensitivity and specificity of the y-IHDS in screening for cognitive impairment, and to propose appropriate cut-off scores to screen for risk of cognitive impairment in HIV-infected children and adolescents.

Given those aims, I will test the following specific hypotheses:

Hypothesis 1: A limited number of studies specifically investigating cognitive impairment in HIV-infected children would be found. I expected to find enough data from published literature to be able to perform a meta-analysis. I also expected the domain of general intellectual functionating to be most affected by HIV, based on a quick background literature search.

Hypothesis 2: I expected to find that composite cognitive domain scores were more accurate in depicting cognitive impairment compared to the more widely used global cognitive score.

Hypothesis 3: Measures of functional impairment will be strongly and significantly associated with cognitive impairment, and that participants classified as having cognitive impairment will have an increased risk of having functional impairment as well.

Hypothesis 4: The y-IHDS will have a good sensitivity and specificity and will be valid for use in children and adolescents. The cut-off scores will be lower than those

developed for adults to account for the fact that children have not yet reached neuropsychological or cognitive maturity.

CHAPTER 2: OVERALL DESCRIPTION OF THE PROJECT AND METHODOLOGY

Research Design and Setting

My project was nested with a larger project, the Cape Town Adolescent Antiretroviral Cohort (CTAAC) neuro sub-study. The CTAAC study aims to measure the long-term benefits and/or consequences of ARV treatment in HIV-infected adolescents. CTAAC measures development in various bodily systems namely; endocrine, cardiac, live, kidney, ophthalmology, audiology, and brain. HIV-infected participants were recruited from various HIV-clinics in and around the Cape Town area. Controls were recruited from community centers. Participants enrolled into the CTAAC study were seen at The Research Centre for Adolescent and Child Health (REACH), located at the Red Cross War Memorial Children's Hospital, Cape Town. The CTAAC study enrolled 500 participants and a subset on these were referred for the sub-study, which forms the basis of the current thesis.

This study followed a quasi-experimental, quantitative design. I compared two similar groups of children, who were otherwise not randomly selected, but who only differed with regards to their HIV status. In other words, I directly compared HIV-infected (ARV treated) children and adolescents to HIV-uninfected (controls) children in order to achieve my aims.

Participants

The CTAAC project represents a sample which is representative of the Western Cape HIV-infected child and adolescent population. These participants are representative in that their demographic matches the demographic of the population most burdened with HIV in the Western Cape, and this is how the inclusion criteria were formulated. Participants were not excluded or selected on disease severity or any other disease factors. For the larger CTAAC

study, participants were screened via self-report questionnaires and verification checks were done on their hospital records. A total sample of two hundred and forty-nine (249) children and adolescents between the ages of 9 and 12 years old from the Cape Town area were recruited via community clinics into the smaller neuro sub-study. As previously mentioned, participants were recruited as part of the larger study. They completed a full medical history screening, laboratory blood tests and demographic assessments as part of their routine medical examination at the center/clinic which they are attending. The recruiters of the larger study matched participants (HIV-infected and controls) based on age, ethnicity, gender, and socioeconomic background as far as possible, prior to enrolment.

Of the total sample, 44 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.

The sample size was statistically calculated by means of a power analysis by statisticians of the larger study, within which this study was nested. Having equal sample sizes would have been preferred. However, in the chapters which follow I made sure to use statistically robust methods to account for the unequal sample sizes.

Table 1 presents a summary of the inclusion criteria applied to both the patient and the control samples.

Table 1

Study Inclusion Criteria

Variable	HIV-infected patients	HIV-uninfected controls
Diagnosis	Known HIV-infected; vertically transmitted	Confirmed HIV-uninfected status
Treatment history	ARV-treated	N/A
Age	9 - 12 years	9 - 12 years
Developmental status	No known history of disorder	No known history of disorder
Functional status	Asymptomatic or impaired	Typically developing
Neurological history	No known other conditions	No known previous conditions
Psychiatric history	No known history of disorder	No known history of disorder

Measures

All adolescents enrolled for the neuro sub-study completed a full neuropsychological test battery. Their parents completed psychological measures related to their health as parents as well as measures related to their child's behaviour.

The neuropsychological test battery was comprised by a team of neuropsychologist and neuropsychiatrists who were the principal investigators of the neuro sub-study. The battery measure 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 test battery was administered by trained research assistants who were fluent in isiXhosa, the predominant language of the participants, and was scored and interpreted by myself. Analysis in chapter 4 - 6 are based on data derived from this battery.

Research procedure

The larger research program, which in which this project is nested, aimed to investigate the long-term effects and outcomes of ARV treatment in HIV-infected youth in Cape Town. Researchers representing the larger study recruited and telephonically contacted the parent/caregiver of each potential child/adolescent participant to schedule medical examinations at the centers mentioned above. As part of the procedures of the larger studies each participant's HIV status was confirmed by means of a HIV rapid screening test. All of the medical procedures were conducted at the Research Center for Child and Adolescent Health (REACH) at Red Cross War Memorial Children's Hospital. Information regarding the child's name and contact details were then forwarded to me in order for our study team to contact them to participate in the CTAAC neuro-substudy.

Parents of potential participants were contacted to inform them of the protocol for the current study and that their child was eligible for voluntary participation. Once children/adolescents were identified as potential participants and expressed interest in participating, individual and private sessions were arranged with them and their parents to explain the full scope of this study. At that stage, the parents could choose to further participate in this study or withdraw without prejudice. In this way we hoped to eliminate the stigma that may be attached to participating in an HIV-related research study.

Parents gave full consent for their child's participation in this study. Children signed an assent form to give their own permission to participate in this study.

The current study consisted 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 described in the papers which follow. After the completion of the neuropsychological tests, a behavioural interview was

conducted during which the child was asked questions about their life experiences. While the child completed the neuropsychological test battery, their parent/caregiver was assisted by another research team member to complete the Child Behavior Checklist (CBCL) and the Vinelands Adaptive Behavior scale – 2nd edition (VABS2).

Once they completed their participation, parents/caregivers could formally request a written report detailing their child's performance on the neuropsychological measures and the behavioural questionnaires. Parents/caregivers were also given the option to have this report conveyed over the telephone. The feedback report may also be sent to the child's school or clinic doctor, but only at the request of their parent/caregiver.

A qualified and trained team of research assistants, who is fluent in both English and isiXhosa, were appointed to administer the neuropsychological tests battery to the children and adolescents. This team also assisted parents with the completion of the parent-rated measures for this study. Each participant was tested in his or her preferred language, which was established on the day of testing by asking the child directly.

Ethical Considerations

The larger studies within which this project is nested have been ethically approved by the Human Research Ethics Committee of the UCT's Faculty of Health Sciences (HREC REF: 051/2013). I obtained ethical approval for this PhD project subsequent to the commencement of the larger study with HREC REF 823/2014. All demographic information, test scores, and any other data collected are kept strictly confidential. As much detail as is appropriate was explained to the minor participants. Adult participants were required to give their full consent before their participation in this study. Parents/caregivers gave consent for themselves and for their children. Children signed assent forms for voluntary participantion.

Consent forms were provided in English and isiXhosa. All participants were consented in their home language. All participants were tested in their language of preference.

To ensure that the controls are indeed HIV-uninfected, the parents of each of these children gave to consent to voluntary HIV testing and counseling at the Red Cross War Memorial Children's Hospital's HIV clinic. HIV testing, along with pre- and post-test counseling, is provided at this facility. Every effort was made to ensure the integrity and confidentiality of the children/adolescents and their parents. HIV-testing was ethically approved as part of the larger study's protocol.

Parents/caregivers were informed that they could formally request a written summary of results from all questionnaires completed during their participation and a report of their child's performance on the neuropsychological test measures. The summary contains general interpretative statements about what scores on each measure mean. This information could also be discussed telephonically, upon the parent/caregiver's request. Where needed, parents and/or their children were referred for further psychological help or counseling at an appropriate institution/s.

Risks and Benefits of Participation

There were no foreseeable psychological or physical risks involved in participation prior to commencing with the study. However, we acknowledged that because we were dealing with a very sensitive topic, some participants may experience social or emotional fear. Social and emotional fear may include experiences of worry about social situations and interactions with people, fear of discrimination and rejection, and anxiousness about negativity they may experience through social situations. We planned to approach these situations with empathy and understanding, should the need arise. Specifically, throughout administration of the study protocols we gave verbal encouragement and reassurance to each

of the participants (minors and adults). We managed to limit any discomfort minors and their parents experienced while completing the study protocols, and after completion of the data collection there are no serious adverse events to report on.

By participating in this research, participants helped contribute to a greater understanding of how children and their parents are affected by HIV. Participants were provided with a R200-00 travel reimbursement and a warm lunch at their study visit. The children and adolescents received a certificate of completion once they completed the neuropsychological test battery and a special treat. There were no other direct benefits to participating in this study.

Outline of the thesis

The thesis is based on four journal manuscripts: two of which have been published, and two under review in international journals at the time of submitting this thesis. These manuscripts are what comprise this thesis. The publications collectively cover the full breadth of my PhD topic; each publication addresses one aim of the thesis. Each publication captures all the material related to the aim it answers, including relevant literature reviewed, methodology pertaining to that aim, data analyzed and reported, and the overall discussion of the findings. Organizing the material of the thesis in this way facilitates my task of integrating the findings in the final chapter that synthesizes the results and discusses the implications thereof. The inclusion of these publications, together with an introduction chapter and a summary and concluding chapter, forms a coherent body of research work, which addresses in full the scope of my PhD research protocol. The coherence of this thesis revolves around two main points. Firstly, the thesis involves a single project. Each chapter describes an analysis conducted on the same cohort of patients enrolled into this study. Secondly, there is a distinct unifying theme to this thesis, namely, the description of assessment of cognitive and

functional impairment and screening for neurocognitive disorders in a cohort of perinatally HIV-infected children and adolescents.

Chapter 3 addresses aim 1 of the thesis and provides a comprehensive background and literature review relevant to the topic and is presented in the format of a journal article. The purpose of this systematic review and meta-analysis is to summarise what is already known in the field of cognitive impairment in perinatal HIV-infected children and adolescents.

Chapter 4 addresses aim 2 of the thesis and is presented as a journal article. We 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-uninfected control group.

Chapter 5 addresses aim 3 of the project and is presented as a manuscript currently under review at a peer reviewed journal. We sought to determine which functional assessment measures are closely linked to cognitive impairment in the context of perinatally HIV-infected South African children and adolescents.

Chapter 6 addresses aim 4 of the thesis and is presented as a manuscript currently under review at a peer reviewed journal. We investigated the performance of the International HIV Dementia Scale (IHDS) as a screening tool for HIV-associated neurocognitive disorders in perinatally HIV-infected children and adolescents. To our knowledge, this is the first attempt at validation of the instrument for use in this cohort.

The concluding chapter, 7, provides a summary narrative of the thesis that synthesizes the findings from all chapters to answer the aims and comment on the hypotheses of the thesis. Conclusions of the thesis as a whole are drawn, the implications of the research for the field of child and adolescent NeuroAids in general are discussed and priorities for future research are identified.

CHAPTER 3: HIV-ASSOCIATED COGNITIVE IMPAIRMENT IN PERINATALLY INFECTED CHILDREN: A META-ANALYSIS.

Phillips, N., Amos, T., Kuo, C., Hoare, J., Ipser, J., Thomas, K. G., & Stein, D. J. (2016). *Pediatrics*, 138(5), e20160893.

Abstract

Context: Research shows, conclusively, that perinatal HIV-infection has negative effects on cognitive functioning of children and adolescents. However, the extent of these cognitive impairments is unknown. Current literature does not document specific cognitive domains most affected in HIV-infected children and adolescents.

Objective: To systematically review and meta-analyse the degree of cognitive impairment, and the specific cognitive domains affected, in children and adolescents with perinatally acquired HIV-infection.

Data Sources: We systematically searched 5 electronic bibliographic databases namely: PubMed, PsychINFO, Academic Search Premier, Scopus, and WorldCat, using a search protocol specifically designed for this study.

Study Selection: Studies were selected on the basis of set a priori eligibility criteria. Titles, abstracts and full texts were assessed by two independent reviewers

Data Extraction: Data from included studies were extracted into Microsoft Excel by two independent reviewers.

Results: 22 studies were identified for inclusion in the systematic review and of this 6 studies were included in the meta-analysis. Results from the meta-analysis indicated that working memory and executive function were the domains most affected by the HI-virus.

Limitations: Only 27% of the included studies were suitable to enter into the meta-analysis. There was significant geographic bias in published studies, with only 32% (7/22) of included studies from sub-Saharan Africa.

Conclusions: The evidence supports an association between HIV-infection in children and adolescents, and cognitive impairment in the domains of executive function and processing speed, with effect size estimates also providing some support for deficits in visual memory and visual spatial ability.

In this chapter, which addresses aim 1 of the thesis, I sought to determine if there was consensus in the literature regarding which cognitive domains are most affected by perinatal HIV infection.

Perinatally acquired HIV-infection has negative effects on cognitive functioning of children and adolescents living with the virus (J. L. Wachsler-Felder & C. J. Golden, 2002). However, the exact degree (i.e.: which domains are more impaired than others, or how many cognitive domains are impaired and how many are not) of these cognitive impairments is not fully established. While it is relatively commonly reported that global cognition (with HIV-associated encephalopathy being the most severe manifestation) is affected (A. Van Rie, Harrington, Dow, & Robertson, 2007), there is no consensus in the current literature as to which specific cognitive domains are most commonly affected in HIV-infected children and adolescents. The individual domain-specific consequences (i.e.: impairment within one or more cognitive domains) of HIV on children and adolescents are likely to be more severe among perinatally infected as compared to those behaviourally infected.

"It is well established that macrophages and microglial cells are a critical reservoir of HIV in the brain" (M. Churchill & Nath, 2013) but its' role in HIV neurocognitive disorders is not yet fully established. The effects of HIV on cognitive functioning ranges from pervasive to being very subtle, with encephalopathy at the severe end of the spectrum (Donald et al., 2014; Smith et al., 2012). Regarding brain structure, investigations of the effects of HIV on the brain using neuroimaging and have discovered that HIV-infected adolescents have significant damage to neuronal microstructure (Blokhuis, Kootstra, Caan, & Pajkrt, 2016; Hoare, Fouche, Spottiswoode, Donald, Philipps, Bezuidenhout, Mulligan, Webster, Oduro, Schrieff, et al., 2012; J. Hoare et al., 2015). The more recent of these types of investigations found that brain volume for both grey and white matter was lower and that white matter hyperintensities were higher in perinatally HIV-infected children (Sophie Cohen

et al., 2016). Another recent study showed that neuronal damage was associated with altered neurometabolite levels (Van Dalen et al., 2016). These studies (Blokhuis et al., 2016; Sophie Cohen et al., 2016; Hoare, Fouche, Spottiswoode, Donald, Philipps, Bezuidenhout, Mulligan, Webster, Oduro, Schrieff, et al., 2012; J. Hoare et al., 2015; Van Dalen et al., 2016) demonstrate that compromised brain integrity is associated with impaired global cognitive functioning in perinatally HIV-infected children and adolescents. These studies provide evidence of CNS compromise in perinatally HIV-infected children and adolescents and that this has consequences for the child's cognitive abilities.

Perinatally infected children may present more frequently than adults with CNS disease (Tardieu et al., 2000) due to the vulnerability of the developing brain. The deleterious effects of the virus on the brain may be more severe in children as HIV related brain degeneration is occurring during a period of rapid brain growth and development.

A recent qualitative review (Laughton, Cornell, Boivin, & Van Rie, 2013a) of neurodevelopment in perinatally HIV-infected children found that HIV-infected children performed poorly on tests measuring performance within the following specific cognitive domains: executive functioning (most notably with regards to processing speed, working memory, planning/reasoning and attention), visual-spatial ability and visual memory, and planning/reasoning. Although it is important to have descriptive and qualitative accounts of any public health problem, in this field there is a lack of quantitative reviews.

Our limited understanding of the domain-specific cognitive impairments associated with perinatal HIV in children and adolescents is a significant barrier to treatment. To date, no systematic review has been published to assess the state of science on cognitive impairment among perinatally HIV-infected children and adolescents. Furthermore no aggregated quantitative evidence has been published on the cognitive domains that are most

affected by perinatal HIV infection. This systematic review and meta-analysis aims to address these gaps in this clinically relevant area.

METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The PICOS method (Huang, Lin, & Demner-Fushman, 2006) was used to develop the research questions, which are: "What is the extent of cognitive impairment in perinatally HIV-infected children and adolescents compared to HIV-negative controls?" and " Which cognitive domains are the most commonly affected?"

Eligibility. Titles, abstracts and full texts were assessed for inclusion by two independent reviewers (NP and TA). The following a priori eligibility criteria were applied: the study sample was composed of 1) perinatally/vertically infected children and adolescents between the ages of 6-18 years, 2) the study reported continuous data for cognitive outcomes measured by means of a standardized neuropsychological test measure/s, 3) it included a healthy control group of HIV-uninfected individuals, and 4) it was published in the English language. Review articles and case study reports were excluded. No other explicit exclusion criteria were applied. The decision to only include data for HIV-unexposed and uninfected controls is based on emerging literature that reports subtle deficits in overall cognition, motor coordination and language in this cohort (Kerr et al., 2014; Annelies Van Rie, Mupuala, & Dow, 2008).

Search Strategy. We conducted a systematic search using a search protocol specifically designed for this study (Supplement 1) in 5 electronic databases: PubMed, PsychINFO, Academic Search Premier, Scopus, and WorldCat (which includes published and unpublished grey literature). The initial screening process involved two independent

reviewers (NP and TA) who assessed the titles and abstracts yielded from the systematic search and classified studies as either "include" or "exclude" based on the eligibility criteria as set out above. Full text articles were sought for the "included" studies and for those whose abstract did not provide enough information to appropriately assess whether they met criteria for inclusion in this review. Finally, the full text articles were assessed once again by two reviewers (NP and TA) to make a final decision regarding inclusion in the review according to the eligibility. Disagreements between the two reviewers regarding the inclusion or exclusion of particular studies were settled by consultation with a third reviewer (DS).

The initial systematic search produced 1177 studies (945 database studies + 232 grey literature studies). After the removal of duplicates, 1022 studies were assessed for possible inclusion. Of the 1022 studies, after screening of the titles and full text, 891 and 109 respectively were excluded. A further 101 studies were excluded because they did not meet the eligibility criteria. Thus, 22 studies were included in the final review. See Figure 1.

Data Extraction. Data from the included studies were extracted by two independent reviewers (NP and TA) into Microsoft Excel. We extracted descriptive (e.g. country, sample demographics, measures used, etc.) and continuous outcomes data (i.e., means and standard deviations for neuropsychological tests measures) for each of the included studies.

For studies that reported only means and confidence intervals, we calculated standard deviations using the formula: *=((SQRT(N))*((upper limit – lower limit)/3.92))*. For studies that reported data for more than one patient and/or control groups (e.g.: HIV-infected treated and HIV-infected HAART naïve) we calculated the weighted means and standard deviations using the following formulae: *=SUMPRODUCT(range means, range N)/SUM(range N)* and *=SQRT(SUMPRODUCT(range standard deviation, range N)/(SUM(range N)-1)),*

respectively, to create two sets of data (i.e., HIV-infected and HIV-uninfected controls) for pair-wise meta-analysis.

Meta-Analysis. Data were analysed using RevMan 5.3 software(Higgins & Green, 2015). The main comparison for the meta-analysis was cognitive performance in HIV-infected individuals versus HIV-uninfected Control subjects who were not exposed in-utero to the virus. Separate analyses were conducted for each of the cognitive domains of interest. A random effects model was used to determine the effect of the HIV-virus on domain specific cognitive performance. Effect Size Estimates (ESE) of 0.2 were considered small, 0.4 to 0.6 moderate, and 0.8 large (Higgins & Green, 2015). Heterogeneity was assessed by means of the I^2 statistic, with higher percentage scores representing a greater proportion of variability across the ESEs that cannot be accounted for by chance alone (Deeks et al., 2003). In comparisons where studies used the same tests, the mean difference was used to calculate the effect size, but for studies using different tests, the standard mean difference was used. Random effects were used for all comparisons since there was heterogeneity between all included studies.

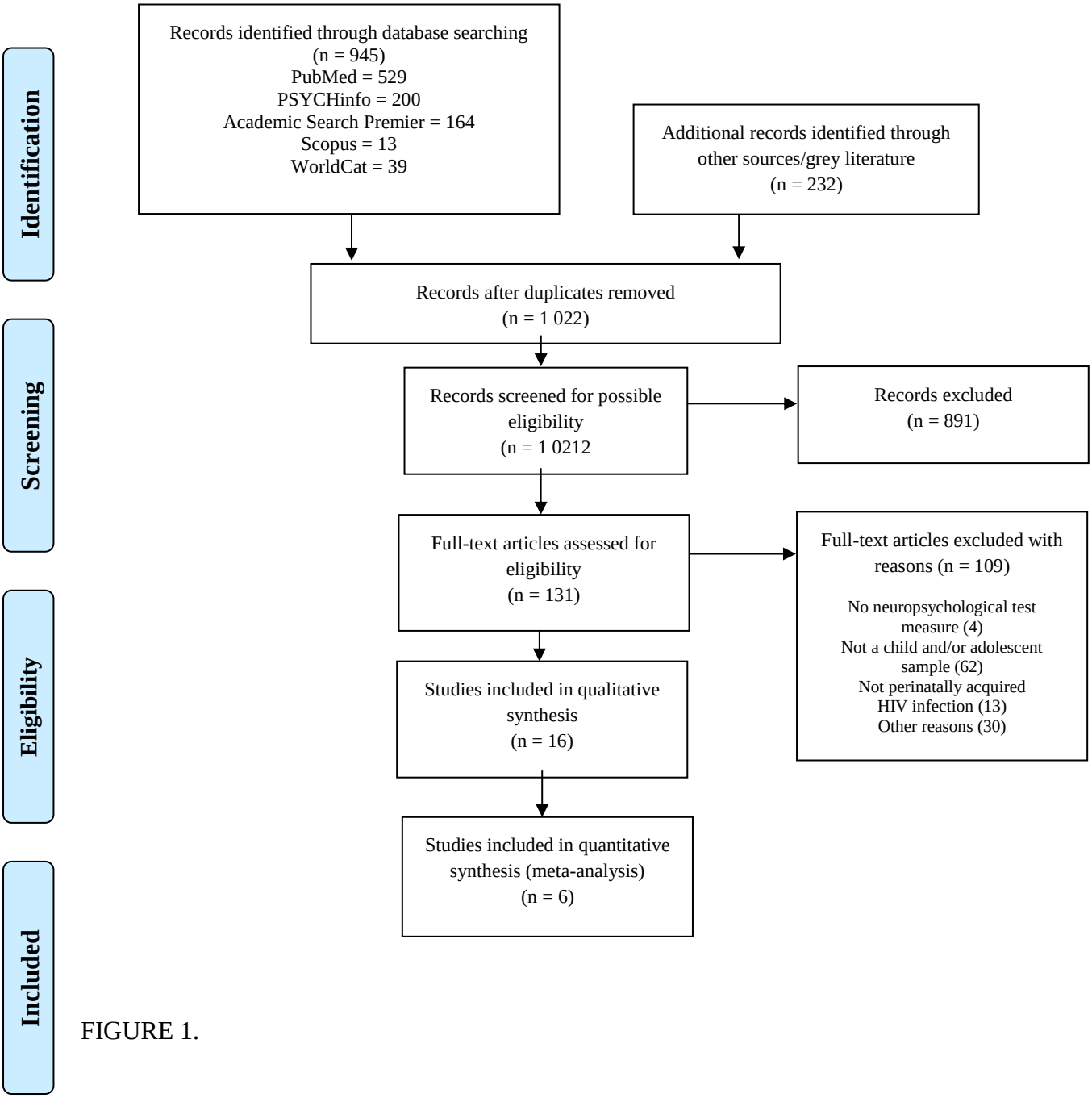

FIGURE 1.

PRISMA diagram detailing the identification of eligible studies.

Quality assessment. The Downs and Black checklist (Downs & Black, 1998) was used to assess the methodological quality of the included studies. This 27-item checklist assess the quality of randomized controlled trial (RCT) and non-RCT type studies on the following subscales: 1) reporting, 2) external validity, 3) bias, 4) confounding, and 5) power. The Downs and Black checklist has been identified as one of the two most useful tools to assess quality for non-RCT type studies (Deeks et al., 2003). Since this checklist was designed for use for both RCT and non-RCT type studies, only a subset of 16 items were applicable to the observational studies included in this review.

Assessing the methodological quality of studies is important for identifying the strengths and weaknesses of a particular study. Though the Downs and Black checklist has been identified as one of the two most useful tools to assess quality for non-RCT type studies (Deeks et al., 2003), it is important to acknowledge the fact that any quality assessment also reflects the standard of reporting of a particular study. With this in mind, the quality assessments of the studies were not included in the inferential analyses, but rather was used to evaluate the methodological rigor of studies included in this review and to provide commentary and interpretation of the generalizability of the findings. See Appendix A for the findings of the quality assessment.

RESULTS

Description of search results. The search strategy yielded a total of 1022 records (after duplicates were removed) from both database and grey literature sources. After screening for eligibility 22 studies were included. Only 6 of the included studies included data for a HIV-uninfected control group who were not prenatally exposed to the virus and only these studies were then entered into the meta-analysis. The characteristics of the final 22 included studies are presented in Table 1.

Table 1: *Characteristics of included studies.*

Study ID	Study design	Country	Domains assessed	nHIV+	tHIV+	eHIV+	eHIV-	uHIV-	HIV-infected (N)	Controls (N)	Total (N)
Angelini 2000(Angelini et al., 2000)	NR	Italy	GIQ, visual spatial ability, visuomotor coordination	1	1	1	0	0	62	0	62
Boivin 2012 a(Boivin, Busman, et al., 2010)	NR	Uganda	Learning, psychomotor speed, working memory, attention	1	1	0	0	0	28	0	60
Boivin 2010 b(Boivin, Ruel, et al., 2010)	NR	Uganda	Memory, visual spatial processing, immediate and delayed memory, executive function	1	0	0	0	0	102	0	102
*Cohen 2015(S. Cohen et al., 2015)	Cross-sectional	Netherlands	GIQ (VIQ + PIQ), processing speed, attention, working memory, executive function	1	1	1	0	1	35	37	72
Franklin 2005(Franklin et al., 2005)	Longitudinal	NR	GIQ	0	1	0	0	0	39	0	39
Fundaro 1998(Fundaro et al., 1998)	NR	Italy	Memory, visual spatial ability, language, learning, spatial organization	0	1	0	1	0	8	8	16
Hoare 2015(J. Hoare et al., 2015)	Cross-sectional	South Africa	Information processing speed, attention, working memory, visual attention, executive function	0	1	0	0	0	50	0	50
*Hoare 2012(Hoare, Fouche, Spottiswoode, Donald, Philipps, Bezuidenhout, Mulligan, Webster, Oduro, Schrieff, et al., 2012)	Cross-sectional	South Africa	GIQ, motor coordination, information processing speed, attention, working memory, visual spatial ability, visual memory, executive function	1	0	0	0	1	12	12	24
*Kandawasvika 2015(Kandawasvika et al., 2015)	Cross-sectional	Zimbabwe	GIQ, information processing, numeracy, memory, motor ability	1	1	0	1	1	32	274	306
*Keller 2004(Keller et al., 2004)	NR	USA	Visual spatial ability, visual memory, language, learning, motor coordination	1	1	1	0	0	20	13	33
Koekkoek 2008(Koekkoek, de Sonneville, Wolfs,	NR	Netherlands	GIQ, working memory, attention, information processing, executive function, visual spatial perception	1	1	0	0	1	22	0	22

Study ID	Study design	Country	Domains assessed	nHIV+	tHIV+	eHIV+	eHIV-	uHIV-	HIV-infected (N)	Controls (N)	Total (N)
Licht, & Geelen, 2008)											
Llorente 2014(Llorente et al., 2014)	Longitudinal	USA	Executive function, attention, working memory, visual spatial ability	0	1	1	1	0	76	85	161
Llorente 2004(Llorente, Turcich, & Lawrence, 2004)	NR	USA	Language, information processing speed	0	1	0	0	0	22	0	22
Martin 2006(Martin et al., 2006)	Cross-sectional	USA	GIQ (VIQ + PIQ)	0	1	0	0	0	41	0	41
Nichols 2016(Nichols et al., 2016)	Cross-sectional	USA	Visual and verbal Memory and learning	0	1	1	1	0	173	85	258
Nozyce 2006(Nozyce et al., 2006)	RCT	USA	GIQ (VIQ + PIQ)	0	1	0	0	0	274	0	274
Puthanakit 2013(Puthanakit et al., 2013)	RCT	Thailand	GIQ, memory, motor coordination	1	1	0	1	1	284	319	603
*Ravindrin 2014(Ravindran, Rani, & Priya, 2014)	NR	India	Attention, language, visual memory, verbal learning, verbal memory, visual perceptual/spatial ability, visuomotor function, fine motor skills, executive function	0	1	0	0	1	20	20	40
Rice 2012(M. L. Rice et al., 2012)	Prospective cohort	USA	Language	0	1	0	1	1	284	153	437
*Ruel 2012(Ruel et al., 2012)	NR	Uganda	Attention, GIQ, motor proficiency	1	0	0	0	1	161	106	267
Smith 2012(Smith et al., 2012)	NR	USA	GIQ, verbal comprehension, perceptual reasoning, working memory, processing speed	0	1	1	1	0	358	200	558
Walker 2013(S. Y. Walker, Pierre, Christie, & Chang, 2013)	Case-control	Jamaica	GIQ, memory, attention, fine motor coordination	1	1	1	0	0	287	0	287

NOTE: * = Denotes the studies included in the meta-analysis. NR = Not Reported, RCT = Randomized Controlled Trial, GIQ = General Intelligence Quotient/functioning, nHIV+ = HAART naïve HIV-infected, tHIV+ = HAART treated HIV-infected, eHIV+ = Encephalopathy HIV-infected, eHIV- = Exposed HIV-uninfected, uHIV- = Unexposed HIV-uninfected

Participants. A total number of 3 734 participants were included across the 22 included studies, of this 2 390 were HIV-infected. Of the 1 312 controls, 807 were HIV-exposed but uninfected and 505 were HIV-unexposed. According to the quality assessments, the majority of the studies (19/22) included participants who are representative of the patient populations they are meant to represent. The average mean age reported was 9.53 with a standard deviation of 2.19 for the studies who reported this data (7/22). The age range was 2 months – 17 years across the studies who reported this data (20/22).

Types of neuropsychological measures. Most of the included studies (18/21) made use of psychometrically sound neuropsychological test measures. These measures are standardized for use in children and adolescents and are widely used for assessing cognitive ability in this group. Given that standardized test measures were used, data were comparable between studies although different tests may have been used. Whilst extracting the data, every effort was made to analyse tests that are as similar as possible (i.e., selected WASI data for all studies that reported WASI data, etc.). If this was not possible, then the data was not entered into the meta-analysis.

Findings from the meta-analysis. Ten separate between-group comparisons were carried out for the meta-analysis and these ten comparisons consisted of the following cognitive domains: attention, executive function, general intellectual functioning, language, motor co-ordination, processing speed, verbal memory, visual memory, visual spatial ability, working memory. Each comparison sought to determine the effect of HIV on cognitive performance within that particular domain.

Table 2 present the results of the between-group comparisons for each cognitive domain. Statistically significant effects were found for 2 out of 10 domains, with executive function and processing speed showing significant group differences. When ranked according

to the effect size the top three domains are (ranked from largest effect size): working memory (MD = 16.46, 95% CI = -14.22 to 47.13, number of studies = 2, P = 0.12), processing speed (SMD = 9.36, 95% CI = 3.73 to 14.98, number of studies = 2, P = 0.00*) and executive function (SMD = 3.68, 95% CI = 1.35 to 6.02, number of studies = 4, P = 0.00*). Looking at the ESEs, it appears that working memory, processing speed and executive function are the domains with the largest between-group differences.

The results of the meta-analysis yielded negative effect sizes for the following domains: attention, language, general intellectual functioning, motor co-ordination and verbal memory. This negative effect indicates that the effect decreases the mean in the HIV-infected group. In other words; as scores in these domains increase in the control group it decreases in the HIV-infected group.

Findings from the systematic review. The 16 studies that were not entered into the meta-analysis were looked at qualitatively. With regards to significant differences between perinatally HIV-infected children and adolescents and HIV-uninfected controls (both exposed and unexposed), 3/15 studies explicitly reported differences in the domain of executive function (Angelini et al., 2000; Llorente et al., 2014; Smith et al., 2012)and one of the 15 studies explicitly reported a group difference for working memory (Smith et al., 2012). A few studies reported findings on components of executive function and working memory (for example; semantic fluency or attention) (Boivin, Busman, et al., 2010; Koekkoek et al., 2008), or on measures which encompasses executive function as part of the scales total scoring system (E.G: the KABC-II). There were a few studies who reported findings for processing speed (4/15) (Boivin, Busman, et al., 2010; Koekkoek et al., 2008; Llorente et al., 2004; Smith et al., 2012) and visual memory (3/15) (Fundaro et al., 1998; Koekkoek et al., 2008; Nichols et al., 2016). The remainder of the studies only reported findings for overall or global cognition (Boivin, Ruel, et al., 2010; Franklin et al., 2005; Martin et al., 2006; Nozyce

et al., 2006; Puthanakit et al., 2013; S. Y. Walker et al., 2013). See Appendix B for further details on the qualitative analysis for all of the included studies.

Table 2: Results from the meta-analysis. Domains ranked in order of largest to smallest effect size.

Comparison	Studies	Participants	Statistical method	Effect size estimate	p	I^2
Working Memory	2	95	Mean Difference (IV, Random, 95% CI)	16.46 [-14.22, 47.13]	.12	100%
Processing Speed	2	96	Mean Difference (IV, Random, 95% CI)	9.36 [3.73, 14.98]	.00*	0%
Executive Function	4	400	Std. Mean Difference (IV, Random, 95% CI)	3.68 [1.35, 6.02]	.00*	98%
Visual Memory	4	361	Std. Mean Difference (IV, Random, 95% CI)	2.71 [-2.31, 7.74]	.29	99%
Visual Spatial Ability	5	433	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-1.56, 1.97]	.82	98%
Attention	4	402	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-1.15, 0.13]	.12	84%
Language	2	70	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-2.18, 0.48]	.21	85%
General Intellectual Functioning	4	548	Std. Mean Difference (IV, Random, 95% CI)	-1.22 [-2.53, 0.10]	.07	97%
Motor Coordination	4	361	Std. Mean Difference (IV, Random, 95% CI)	-1.99 [-4.50, 0.52]	.12	98%
Verbal Memory	2	112	Std. Mean Difference (IV, Random, 95% CI)	-6.80 [-19.43, 5.83]	.29	98%

NOTES: * indicates a statistically significant effect at the p = .05 level.

DISCUSSION

This systematic review assessed the current state of scientific evidence on cognitive impairment in perinatally HIV-infected children and adolescents. In addition, we used meta-analytic techniques to rank the most important cognitive domains affected by perinatal HIV infection, with the aim of informing clinical practice and guiding development of future interventions to improve the cognitive well-being of this important population throughout their life trajectory.

Results from the meta-analysis revealed that children and adolescents with perinatally acquired HIV demonstrated significant impairments in executive function and processing speed relative to HIV-uninfected and unexposed controls. There is an increasing recognition in the research community that statistical significance only tells part of the story, and that effect size estimates can be a bit more informative, particularly with respect to under-powered studies with small samples. In medical research and in traditional meta-analytical approaches, the size of the effect is equal to the magnitude of the difference between the two groups of interest (Sullivan & Feinn, 2012) and can "be said to be the true measure of the significance of the difference" between the two groups (Coe, 2002). In recognition of the literature, and both the small sample sizes and number of studies, we decided prior to conducting this meta-analysis that it would be useful to estimate the strength of the association between HIV-infection and impairment in particular cognitive domains using the mean or standard mean difference ESEs.

Based on the results of this meta-analysis, large effects (ESE >= 0.8) of HIV status suggesting greater impairment in HIV-infected children and adolescents were observed for the following domains (ranked from largest to smallest effect size): working memory, processing speed, executive function, and visual memory. Small ESEs were observed for

visual spatial ability, attention, language, general intellectual functioning, motor coordination and verbal memory. The difference between the upper and lower limits of the confidence interval were greater than the actual effect estimate for all cognitive domains assessed. This lack of precision in the effect estimates reflects the small number of studies providing data for most of the domains. It could also potentially reflect methodological differences between the studies included in the meta-analysis, as suggested by the fact that substantial heterogeneity was observed for most of the domains in the effects reported by individual studies.

The Laughton et al. (2013) study found that HIV-infected children performed poorly in the cognitive domains of executive functioning (most notably with regards to processing speed, memory and attention), visual-spatial ability, visual memory, processing speed and planning/reasoning (Laughton et al., 2013a). Cohen (2015) found that HIV-positive children performed more poorly than controls in all cognitive domains, but most notably on general intellectual functioning, processing speed, attention and working memory (S. Cohen et al., 2015). A study conducted in South Africa found that even asymptomatic HIV-positive children performed more poorly on cognitive measure than controls, and once again, most notably on tests of general intellectual functioning, visual spatial ability, visual memory and semantic fluency (i.e.: executive functioning) (Hoare, Fouche, Spottiswoode, Donald, Philipps, Bezuidenhout, Mulligan, Webster, Oduro, Schrieff, et al., 2012).

The findings from these studies seem to consistently implicate working memory, executive function, processing speed and perceptual deficits in HIV-infected children and adolescents. Executive functioning emerges as one of the more prominent domains to be effected in this population, which is consistent with the finding in this review of significant differences in this domain. The vulnerability of executive function and processing speed to the effects of perinatal HIV infection was confirmed by the results of this meta-analysis, in

which these domains were determined to be relatively impaired in HIV-infected children and adolescents, with significant group differences observed in these cases. Impairments in working memory is also by this review with this domain obtaining the largest effect size. Although not ranked in the top three domains, this review also found that visual memory yielded a relatively large effect sizes (ESE > 0.8), as compared to other domains.

However, the results of this meta-analysis (with regards specifically to the ESEs) differ from previous findings in two important ways: 1) most studies found that general intellectual functioning was severely impaired and this review did not and 2) a large number of studies found that motor coordination was severely impaired and this review did not. In fact, the findings from this review and meta-analysis showed that general intellectual functioning and motor coordination were ranked 8th and 9th out of a total of 10 domains with regards to effect size. Reasons for the differences could be related to methodological differences and/or differences in focus areas with each studies research questions (which in turn will determine the methodology used). A more thorough comparison of the current findings to each of the included studies is provided in Appendix B. Individual studies may only be able to provide weak to moderate evidence, while this meta-analysis provides much stronger evidence since the results are pooled from 6 meta-analysed studies.

When judging the generalizability of the results of this review to populations from SSA, the quality of the included studies must be taken into account along with the demographic information of the participants included in the studies. Each of the included studies exhibited some methodological flaws as rated on the Down's and Black quality rating scale. Furthermore the geographical disparity in the scientific evidence base is notable. The majority of the 22 included studies (53%) occurred in developed countries. Very few studies (32%) occurred in SSA, where the burden of HIV disease is most prevalent. Overall, this

review identified that the scientific evidence needs further development both with regards to depth of knowledge as well as rigor of methodological design.

Our understanding of child and adolescent HIV-associated cognitive impairment is limited by multiple factors 1) the absence of appropriate control data in many studies, 2) the failure of many studies to focus specifically on perinatally acquired HIV, 3) the inclusion in some studies of seroreverters, 4) the fact that not all studies utilize standardized neuropsychological test measures, 5) the practice in some studies to include/collapse data from treatment naïve, treated and encephalopathy patients (ideally these groups should be separated for analysis purposes), and 6) the incomplete and inconsistent reporting of neuropsychological test result data or outcomes of statistical tests. Nevertheless, the strength of this review is that we were able to overcome many of these limitations by applying strict study inclusion criteria, by extracting as much data as possible from included studies, by using data presented to calculate means and standard deviations when these were not presented, and by excluding studies without appropriate control data from the meta-analysis.

Implications. This review revealed that significant cognitive differences between HIV-infected and HIV-uninfected children and adolescents are seen in the domains of executive function and processing speed. This review also revealed that the domains with the largest effect sizes were working memory, processing speed and executive function. This is in line with previous findings, and despite a paucity of methodologically sound studies in the field of child and adolescent HIV-associated cognitive impairment. With this in mind, future studies or interventions ought to primarily focus on these domains.

Strengths and Limitations. This review is the first systematic review and meta-analysis of child and adolescent HIV-associated cognitive impairment. This review successfully meta-analysed 6 studies in an attempt to rank cognitive domains according to

most impaired to least impaired. Given some of the methodological flaws identified in the included studies and based on the fact that 53% of the included studies were from developed countries and only 32% were from SSA in which the burden of HIV disease is most prevalent, one should exercise caution when generalizing these results to the context of SSA. However, and very importantly, what this review emphasizes is that this particular research field is very underdeveloped, and that more methodologically rigorous studies need to be conducted in this area, particularly in areas of the world where HIV is most prevalent, such as SSA. As far as we could deduce, the studies included in the meta-analysis were all unique samples without any overlap in study participants.

Conclusions

Based on the findings of this review, when considering which cognitive domains are most affected by the HIV-virus preference should be given to (and in order of most to least important): working memory, processing speed and executive function. Participants from studies conducted in high-income countries may have access to better healthcare, as compared to participants from low-income countries, like those in sub-Saharan Africa, and may therefore display better cognitive and functional outcomes. Therefore, caution should be exercised when generalizing these findings to the sub-Saharan continent (which bears the largest burden of the HIV disease) since only 32% of included studies were from SSA and that the size of the confidence intervals were relatively large for some of these findings.

Another finding of this chapter is that there are a lot of inconsistencies in the manner in which different researchers measure HIV-associated cognitive impairment, and no consensus criteria for the diagnosis of a spectrum of neurocognitive disorders

Appendix A

Appendix A: Quality assessment of the included studies.

Study ID	Reporting	Main outcomes	Patient characteristics	Principal confounders	Main findings	Random variability	Representative sample (recruitment)	Representative sample (participation)	Presentative setting	Data dredging	Follow-ups	Appropriate statistics	Accurate outcome measures	Internal validity	Different groups	Confounding adjustment
Angelini 2000	1	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0
Boivin 2010 a	1	1	1	0	1	1	1	1	1	1	0	1	1	0	1	1
Boivin 2010 b	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1
*Cohen 2015	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
Franklin 2005	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Fundaro 1998	1	1	1	0	1	1	1	1	0	0	1	1	1	1	1	0
Hoare 2015	1	1	1	0	1	0	1	1	1	0	0	1	1	1	1	1
*Hoare 2012	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0
*Kandawasvika 2015	1	1	1	0	1	1	1	1	1	0	0	1	1	1	0	0
*Keller 2004	1	1	0	0	0	1	1	1	0	0	0	1	0	0	0	0
Koekkoek 2008	1	1	1	0	1	0	1	1	1	0	1	1	1	1	0	0
Llorente 2012	1	1	1	1	1	0	1	1	1	0	0	1	1	1	1	0
Llorente 2004	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0
Martin 2006	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0
Nichols 2016	1	1	1	2	1	0	1	1	1	0	0	1	1	0	0	1
Nozyce 2006	1	1	1	0	1	0	1	1	1	0	0	1	1	1	0	0
Puthanakit 2013	1	1	0	0	1	0	1	1	1	0	1	1	1	1	1	0
*Ravindrin 2014	0	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0
Rice 2012	1	1	1	1	1	0	1	1	1	0	0	1	1	1	1	0
*Ruel 2012	1	1	1	0	1	0	1	1	1	0	0	1	1	1	1	0
Smith 2012	1	1	1	0	1	0	1	1	1	0	0	1	1	1	1	0
Walker 2013	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	0

NOTES: * = Denotes the studies included in the meta-analysis.1 = “YES”, the study has met this quality criteria, 0 = “NO” or “unable to determine”, the study has not met the quality criteria.
Since this checklist was designed for use for both RCT and non-RCT type studies, not all the items were applicable to the studies included in this review, namely items 4, 8, 9, 10, 14, 15, 19, 23, 24, 26, 27. Quality assessment ratings for each of the included studies were done by two independent raters (NP and TA).

Appendix B

Appendix B: Comparison of study findings to current meta-analysis results.

Study ID	Study main findings	Comparison of study findings to current meta-analysis results
Angelini 2000	Slow mental processing with deficit of selective attention, decreased IQ and impairment in executive function.	Consistent findings with regards to executive function. This review did not find that attention and IQ had major effects. Data from Angelini 2000 was not included in the meta-analysis of this review.
Boivin 2010 a	HIV+ children performed more poorly on measures of sequential processing, simultaneous processing and learning when compared to HIV- controls (controls data was published in a separate study and did not form part of this cohort).	Findings not consistent findings with this review. This review did not include the domain of learning. Data from Boivin 2010a was not included in the meta-analysis of this review.
Boivin 2010 b	Subtype A-infected children performed more poorly on KABC-II than those with subtype D-infected. Recombinant infected children performed similarly to subtype A-infected children.	Not applicable to the findings of this review, since we did not separate the HIV+ groups into HIV subtypes. Data from Boivin 2010b was not included in the meta-analysis of this review.
*Cohen 2015	HIV+ adolescents performed poorer on all cognitive domains compared to HIV- controls, but particularly on intelligence, information processing, and attention/working memory.	Consistent findings with regard to working memory. Data from Cohen 2015 was included in the meta-analysis of this review.
Franklin 2005	IQ means scores increased over a period of 6years in HIV+ adolescents (longitudinal study).	Findings not consistent with this review. Data from Franklin 2005 was not included in the meta-analysis of this review.
Fundaro 1998	The two groups (HIV+ and HIV-) obtained scores that were significantly different on the WISC-IV, copy version of the Rey complex figure and memory. HIV+ scored more poorly than HIV-.	Findings consistent with this review with regards to visual memory. Data from Fundaro 1998 was not included in the meta-analysis of this review.
Hoare 2015	HIV+ adolescents scored poorer global cognitive scores than HIV- adolescents.	Not applicable to this review since we looked at individual cognitive domains and not globally. Data from Hoare 2015 was not included in the meta-analysis of this review.
*Hoare 2012	HIV+ children performed more poorly on cognitive measure than controls especially on tests of general intellectual functioning, visual spatial ability, visual memory and semantic fluency (i.e.: executive functioning).	Consistent findings with regards to visual memory and executive function. Data from Hoare 2012 was included in the meta-analysis of this review.
*Kandawasvika 2015	HIV+ scored significantly lower than HIV-unexposed adolescents on measures of perceptual-	Findings not consistent with this review. Data from Kandawasvika 2015 was included in the meta-analysis of this review.

	performance. No significant differences between the groups on measures of verbal, quantitative and memory domains.	
*Keller 2004	HIV+ and control adolescents had similar performance on a panel of cognitive tests, except for spatial learning and memory.	Findings not consistent with this review. Data from Keller 2004 was included in the meta-analysis of this review.
Koekkoek 2008	HIV+ children and adolescents were significantly poorer on measures of intelligence, baseline speed, pattern recognition, shifting set and visuospatial memory as compared to age-appropriated norms.	Consistent findings with regards to visual memory only. Data from Koekkoek 2008 was not included in the meta-analysis of this review.
Llorente 2012	Statistically significant differences between HIV+ with and without a class C diagnosis and HIV- adolescents on unadjusted mean scores of executive function.	Not applicable to this review since we did not separate HIV+ without a class C diagnosis from whose with a class C diagnosis. Data from Llorente 2014 was not included in the meta-analysis of this review.
Llorente 2004	Results were separated according to ethnicity groups. HIV+ African American adolescent performed significantly lower than HIV+ European American adolescents on measures of processing speed and language.	Not applicable to this review since we did not separate groups according to ethnicity. Data from Llorente 2004 was not included in the meta-analysis of this review.
Martin 2006	IQ and PSI scores for HIV+ adolescents fell within the average range according to the Wechsler's qualitative classification system.	Findings are somewhat consistent with this review since we found that processing speed was least affected domain based on ESEs. Data from Martin 2006 was not included in the meta-analysis of this review.
Nichols 2016	HIV-infected youth have lower scores on measures of verbal learning and delayed visual memory compared to HIV-exposed but uninfected controls.	Findings are not consistent with this review. Data from Nichols 2016 was not included in the meta-analysis.
Nozyce 2006	Mean baseline cognitive scores for HIV+ adolescents were lower than that of the general population (on the WISC-IV and WPPSI-R).	Findings not consistent with this review. Data from Nozyce 2006 was not included in the meta-analysis of this review.
Puthanakit 2013	There were no significant cognitive differences between HIV+ early ART and HIV+ deferred ART. There were significant differences between HIV+ and HIV- controls.	Not applicable to this review since we did not separate HIV+ groups based on ART initiation. Data from Puthanakit 2013 was not included in the meta-analysis of this review.
*Ravindrin 2014	T-tests revealed that HIV-infected groups were more impaired on several neuropsychological measures than controls, specifically on tests of attention, language, verbal learning and memory, visuomotor function, fine motor performance, executive function, but not visual memory.	Findings both consistent and inconsistent with this review. Consistent with regards to executive function, but inconsistent with regards to visual memory. Data from Ravindrin 2014 was included in the meta-analysis of this review.

Rice 2012	Core language scores were comparable between HIV+ and HIV- exposed adolescents (not statistically different).	Findings not consistent with this review. Data from Rice 2012 was not included in the meta-analysis of this review.
*Ruel 2012	HIV+ adolescents had significantly poorer scores in the attention domain. HIV+ adolescents performed poorer than controls (taken from a separate cohort for comparative purposes) on the Kaufman global scores for sequential processing, simultaneous processing, planning/reasoning and total score.	Consistent findings with regards to executive function. Data from Ruel 2012 was included in the meta-analysis of this review.
Smith 2012	Cognitive functioning for HIV+ with and without class C diagnosis and HIV- but exposed adolescents performed in the average range on measures of general intellectual functioning.	Not applicable to this review, since we did not separate HIV+ groups according to whether or not they had a class C diagnosis. Data from Smith 2012 was not included in the meta-analysis of this review.
Walker 2013	On measures of IQ, memory, attention and fine motor coordination, HIV+ encephalopathy adolescents achieved lower scores than HIV+ non-encephalopathy adolescents.	Findings not consistent with this review. Data from Walker 2013 was not included in the meta-analysis of this review.

NOTES: * = Denotes the studies included in the meta-analysis. In comparing the findings of the included studies to the findings of this review we only considered the top 5 domains as ranked above since these were the domains that displayed the greatest difference between HIV+ and HIV+ and where controls performed better than HIV+.

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CHAPTER 4: HIV-ASSOCIATED COGNITIVE DISORDERS IN PERINATALLY INFECTED CHILDREN AND ADOLESCENTS: A NOVEL COMPOSITE COGNITIVE DOMAINS SCORE.

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Abstract

Accurate assessment of HIV-associated cognitive disorders in perinatally infected children and adolescents is challenging. Assessments of general intellectual functioning, or global cognition, may not provide information regarding domain-specific strengths and weaknesses, and may therefore fail to detect, impaired trajectories of development within particular cognitive domains. We compare the efficacy of global cognitive scores to that of composite cognitive domain scores in detecting HIV-associated neurocognitive disorders in a sample of perinatally HIV-infected children, and a demographically matched HIV negative control group, drawn from the Cape Town Adolescent Antiretroviral Cohort (CTAAC) study. All children were administered a comprehensive neuropsychological test battery. Using data from that test battery, we created 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. Within each domain, each test bore a high level of association with each of the other tests in that domain (Cronbach's $\alpha \geq .70$ for all domains). We found that composite domain scores calculated on whole-sample data were significantly higher than those calculated using control-sample data. Our comparison of a global cognitive score to composite domain scores suggested that the latter provided more detailed information (regarding strengths,

weaknesses, areas of impairment), and when compared to global scores, were more sensitive in detecting HIV-associated neurocognitive disorders, and were able to distinguish HIV-infected patients from uninfected controls. Hence, we recommend using this method of composite cognitive domains scores, rather than global aggregate scores, when assessing cognitive function in paediatric HIV. This method provides a convenient and relatively accurate assessment that might help with cross-cultural and cross-region comparisons as researchers try to detect cognitive impairment patterns in HIV-infected children and adolescents globally.

In this chapter, which addresses aim 2 of the thesis, I sought to statistically determine a method to accurately assess domain-specific HIV-associated cognitive impairment. Given the inconsistencies in measurement found in the previous chapter, a method which can be used in different setting and with differing assessment batteries is needed.

Accurate assessment of HIV-associated neurocognitive disorders in perinatally infected children and adolescents is challenging. Cognitive impairments present differently in children and adolescents than in adults (Tardieu et al., 2000). A recent systematic review and meta-analysis of the HIV-associated cognitive impairment in children and adolescents found both similarities and inconsistencies between the included studies' regarding cognitive performance in the different domains (N. Phillips et al., 2016). What is clear from the systematic review is that a global consensus is needed with regards to how HIV-associated cognitive impairment is assessed in children and adolescents and, consequently, making diagnoses of HIV-associated neurocognitive disorders (HIV-ND). A spectrum of neurocognitive disorders in HIV-infected youth have been recently published (Hoare et al., 2016b), which aims to address this issue of assessment and diagnosis, but further work is needed to expand on our understanding and improve diagnosis of these disorders. This approach to diagnosing HIV-ND is not without its limitations, as highlighted by Bearden and Meyer (2016) (Bearden & Meyer, 2016), however, some of these limitations could be addressed by applying a stringent methodological procedure when working with the data obtained from neuropsychological assessment. For example, reaching consensus on appropriate tests to include in the assessment of individuals and by prioritizing the cognitive domains which are most affected by HIV infection, as identified in the Phillips et al. meta-analysis.

The concept of cognitive impairment or deficit suggests a normal, or prior level of functioning, against which performance is measured (Lezak, 2004). This "normal" or

baseline may be the individual's own level of functioning prior to an event which may have caused cognitive impairment. However, in the case of perinatally HIV-infected children and adolescents, we are unable to determine their baseline functioning prior to the HIV infection. Based on the above findings using a whole sample mean score and SD to calculate Z-scores will erroneously inflate the composite scores obtained, thereby masking the effects of any real-world deficits which are potentially present.

The debate regarding whether or not to use composite scores (as opposed to raw scores) to determine outcomes of interest has been a long-standing one, both in the clinical trial and the neuropsychological literature (Freemantle, Calvert, Wood, Eastaugh, & Griffin, 2003; Goldberg, Gore, Barton, & Gurwitz, 2014; Montori et al., 2005).

Current research in the field of cognitive impairment in adult HIV increasingly uses global and/or composite cognitive domain scores (Alvarez-Tostado, Inozemtseva, Aguiñiga, López, & Matute, 2015; Baker et al., 2015; R. K. Heaton et al., 2015; Jacqueline Hoare, Jean-Paul Fouche, Nicole Phillips, John A Joska, Kirsten A Donald, et al., 2015; Jacqueline Hoare, Jean-Paul Fouche, Nicole Phillips, John A Joska, Robert Paul, et al., 2015; Judd et al., 2015; Linn et al., 2015; Milanini et al., 2016; Vance, Ross, & Downs, 2008). Although global composite scores provide statistical efficiency and an overall summary of impairment, important information may be missed. Assessments of general intellectual functioning, or global cognition, do not provide information regarding domain-specific strengths and weaknesses, and may therefore fail to detect, impaired trajectories of development within particular cognitive domains. For example, in the case of HIV-associated cognitive impairment a global composite cognitive score may appear to indicate average performance, but performance in one or two specific cognitive domains may be severely impaired and may be masked by unimpaired/average performance in the other domains. The global composite cognitive score assumes that all the components are equally weighted, but this might not

reflect functional competence. An example of this is in pharmacological randomised controlled trials (RCTs), where aggregated endpoints sometimes include a number of components for example change in symptoms, mortality rates and relapse rates. However, in some cases the mortality might only account for only a few of the final endpoints between all participants (Goldberg et al., 2014). In these cases, the aggregate score (or global score) assumes that all its components have a similar impact on the health of the individual, but this is not a true reflection of the real outcomes.

In neuropsychological research, the global score would provide an overall cognitive score, whereas the composite cognitive domain score provides a score for a specific cognitive function/domain such as executive function. To calculate the composite cognitive domain score, many researchers have placed tests together which in theory measure the same function within a particular domain (Wolinsky, Vander Weg, Howren, Jones, & Dotson, 2016). No evidence is provided for the statistical basis or strength behind this method.

Regarding the calculation of the *z*-score in order to derive the composite score, there seems to be no consensus as to which sources of data (means and standard deviations) should be used in the formula ($z = (x\text{-}M)/SD$). Some authors use the control sample data (Hoare, 2015; Linn et al., 2015) while others use the entire sample data (controls plus patients)(Annelies Van Rie et al., 2008). Then there are studies who use the publisher norms to create z-scores (R. K. Heaton et al., 2015; Judd et al., 2015), which may not be appropriate in the African setting since majority of test publisher norms are based on data from first world countries.

The formula for calculating *z*-scores is defined as follows: *x* is a raw score to be standardized, M is the mean of the control or normative sample and SD is the standard deviation of the control or normative sample (Iverson, 2011). If strictly adhering to the definition of z-score calculation, using a whole sample approach would, technically speaking,

render the calculated *z*-score invalid. Clinically, using a whole sample means and SD also has implications for making inferences about the characteristics of the sample or population of interest.

A child and adolescent-sensitive method for examining domain-specific patterns of HIV-associated cognitive impairment is needed. We aim to 1) determine, using statistical measures of association, which individual neuropsychological test measures might best be combined to form composite cognitive domain scores, 2) assess which source of data (uninfected controls, or controls plus patients) might be best to use in calculating standard scores for the composite cognitive domains and 3) compare the efficacy of global cognitive scores to that of composite cognitive domain scores in detecting HIV-associated neurocognitive disorders in a sample of perinatally HIV-infected children, and a demographically matched controls.

Methods

Design. This study was nested within the larger Cape Town Adolescent Antiretroviral Cohort (CTAAC) study, a longitudinal study investigating the health of perinatally HIV-infected children and adolescents established on antiretroviral therapy (ART). This analysis investigates the baseline cognitive performance of a subset of the perinatally HIV-infected children and adolescents enrolled into the larger CTAAC project. A subset of the CTAAC sample were included in the neuro sub-study and all of these participants completed a comprehensive neuropsychological test battery as previously described (Hoare, Fouche, Spottiswoode, Donald, Philipps, Bezuidenhout, Mulligan, Webster, Oduro, & Schrieff, 2012). The battery measures cognitive performance within the following cognitive domains: general intellectual function, attention, working memory, verbal memory, visual memory, visual spatial ability, language, motor coordination, processing speed and executive function. All study procedures were completed within the Department of Psychiatry and Mental Health of

the University of Cape Town at Groote Schuur Hospital. Extensively trained research assistants with many years of experience administered the comprehensive neuropsychological test battery to participants. All tests were translated into isiXhosa and back translated into English to ensure compatibility with the original test.

CTAAC was approved by the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (HREC REF: 056/2013). All participants completed informed assent, and caregivers informed consent, prior to enrolment, and study procedures adhered to the South African National Department of Health ethics code for research with minors.

Setting. CTAAC recruited children and adolescents from community health clinics in and around the Cape Town (South Africa) area. Demographically matched HIV-uninfected unexposed controls were recruited from community youth centres. The CTAAC participants are representative of the perinatally HIV-infected adolescents across Cape Town, and did not apply strict exclusion criteria, apart from excluding participants who had been on ART treatment for shorter than 6 months prior to study enrolment. The majority of participants were recruited from primary care. Participants were not selected based on disease stage, adherence or viral suppression

Participants. This study consisted of children and adolescents between the ages of 9 – 12 (WHO, 2013) years enrolled in the neuro sub-study of CTAAC. The neuro sub-study consisted of a sub-set of the larger CTAAC sample. Both males and females were enrolled. All HIV-infected participants were vertically infected with HIV, and had been on ARV for at least 6 months prior to their study enrolment. Participants who had previous severe psychiatric diagnoses, traumatic brain injuries or central nervous system infections (e.g. meningitis) were excluded from participation. Controls were frequency matched for age, gender and socioeconomic status (SES), and recruited form the same schools and

communities as the adolescents living with HIV to attempt to control for quality of education. All controls underwent rapid HIV-testing to confirm their HIV-negative status. All controls received both pre- and post-test counselling from study doctors of the larger study.

Data analysis. Data was captured, cleaned and analyses in SPSS 24. Measures of central tendency for age, gender, education, language race were calculated for all participants. Bloods were drawn in line with routine clinical care schedules to determine CD4 count and Viral load.

Using data from that test battery, as well as theoretical knowledge about the construct(s) each test is meant to test, we created 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, we conducted Cronbach's alpha tests on various combinations of neuropsychological tests to determine which neuropsychological tests had strong inter-relatedness (or internal consistency) within a specific domain. For the Cronbach's alpha tests we only used the total scaled scores of the tests, and/or subtests, for each of the individual neuropsychological tests. Scaled scores were used because they take into account the child's age, gender and the various developmental changes happening in the different age groups. To compute the individual test scaled scores, we used the individual test publisher norms. Where test publisher norms were not available (for example; for the HVLT) we converted the test raw score into a *z*-score.

A Cronbach's alpha value of 0.7 was considered high and deemed as an indication of good inter-relatedness between the tests (Tavakol & Dennick, 2011). The Cronbach's alpha tests were only done for domains in which there were more than one neuropsychological test measuring performance in that domain. The domains of language and visual spatial ability, each consisted of only one neuropsychological test from the battery, and thus Cronbach's

alpha values are not reported for these two domains. Tests from the larger battery which did not contribute well to the cognitive domains with regards to the Cronbach's alpha value were excluded from the individual composite cognitive domain scores.

To determine which source of data is best for the composite cognitive domain scores we calculated two sets of *z*-scores: 1) using only the control sample means and standard deviations, we converted all scaled and T-scores of the individual neuropsychological tests into *z*-scores, 2) using the whole sample (controls plus HIV-infected patients) means and standard deviation, we converted all scaled and T-scores of the individual neuropsychological tests into *z*-scores. In both instances, we used the test publisher norms to calculate the T-scores of the individual tests, before converting them into *z*-scores. From these two set of *z*-scores, we calculated control sample based global and composite cognitive domain scores and whole sample based global and composite cognitive domain scores. To calculate the global scores, we averaged the calculated *z*-scores for each test to yield one single score for each of the patients and uninfected controls. To calculate the composite cognitive domain scores, we averaged the scores of the test which comprised that domain (according to the Cronbach's alpha tests performed prior) to yield one single score for each domain for each of the patients and uninfected controls.

Then, to determine the differences in *z*-score calculations based on the control sample versus whole sample data, we ran a series of paired samples *t*-tests. With these *t*-tests we sought to demonstrate the significant differences between both global and composite cognitive domain scores when calculated on control sample data compared to those calculated using whole sample data (a population that consist of both HIV-positive and HIV-negative controls). In other words, we compared the same set of participants' scores calculated under two different conditions.

Furthermore, we then compared the efficacy of global cognitive scores to that of composite cognitive domain scores in detecting HIV-associated cognitive impairment in a sample of perinatally HIV-infected children by means of frequency counts to compare the number of true positives yielded in each case. For this comparison we dichotomised the global and composite domain scores (impaired versus unimpaired). Using a cut-off of 1 standard deviation below the control sample mean we categorised each participants' global aggregate score and individual composite cognitive domain scores as either impaired (if they were 1 standard deviation below the control means) or not impaired (above or equal to the control means). We ran a cross tabulation frequency count to determine the rate of true positives. The rates of impaired cases for the 10 composite cognitive domains were averaged across the domains, to yield one frequency value.

A total number of 249 participants were enrolled into the CTAAC neuro sub-study, of which 247 (203 HIV-infected + 44 controls) were included in this analysis. The two participants from the total enrolled were excluded because one participant was a pilot participant, and one had severe attention hyperactivity disorder (ADHD) and was unable to complete any of the neuropsychological test measures. Some of the participants who were included in this analysis, were unable to complete some of the neuropsychological tests because of severe cognitive impairment. For these participants, their composite cognitive domain scores were calculated based on only the tests which they were able to perform. For example, for attention, if the participant completed only the Children's Colour Trails Test (CCTT) 1 and was unable to perform the CCTT 2, their composite cognitive domain score for attention consisted of only the CCTT 1 *z*-score. In this way participants individual composite cognitive domains scores would not be unfairly lowered by the fact that they were "missing" a test score included in the calculation of that domain score.

Results

203 HIV-infected participants (median age 10. years) and 44 HIV-negative controls were tested; controls were well matched to the HIV-infected sample with regards to age, gender, race, education, and SES, Table 1. There were significant differences between HIV-infected participants and controls regarding home language and repeated grades at school. HIV-infected participants were more likely to have repeated school grades, Table 1. Regarding CD4 count and Viral Load, these biological markers of HIV were significantly correlated with only motor co-ordination ($r = -.15$, $p < 0.05$) and attention ($r = .17$, $p < 0.05$), respectively.

Table 2 presents the outcomes of the acceptable Cronbach's alpha testing procedures for each cognitive domain. The cognitive domains of general intellectual functioning, attention, working memory, visual memory, verbal memory, motor coordination, processing speed and executive function all achieved the threshold for acceptable internal consistency with Cronbach's $\alpha \geq 0.7$. It is notable that there is overlap in the domains (e.g., the score for CCTT 2 is part of the composite score for three different domains). This may mean that there is shared variance between the domains, however, each domain is calculated separately, and based on strong statistical support from the Chronbach alpha's, low scores on one particular test is unlikely to result in multiple domains being assessed as low since the scores of each domain are weighted for that particular domain. For example, a low score of the CCTT 2 will result in a low score for the attention domain, but not necessarily for the executive function (EF) domain because the other tests in the EF domain will add to the overall domain score.

Table 3 presents analyses supporting the use of normative (i.e. control) data for the *z*-score calculation to compute the composite cognitive domain score, as opposed to using whole sample data. The mean composite cognitive domain scores based on the whole sample data are statistically significantly higher than the scores based on the control sample data for all cognitive domains, except motor coordination. There was also a statistically significant

difference between the global aggregate scores calculated based on the whole sample means and the control means, such that the scores based on the whole sample means were higher. Because of the consequent danger of erroneous inflation of cognitive performance, we used the control-based *z*-scores in further analyses.

Table 1: Baseline characteristics

	Group		T-test	
Variable	HIV-infected N = 203	Controls N = 44	t	p
Age: M(SD)	10.37 (0.87)	10.38 (1.09)	.08	.94
Gender: M/F	100/103	20/24	.46	.65
Race: Black African/Coloured/White/Other	186/17/0/0	44/0/0/0	-1.99	.05
Home Language: isiXhosa/English/Afrikaans/Other	138/6/12/2	42/0/0/2	-2.35	.02*
Education[a]	3.19 (1.13)	3.39 (1.35)	1.02	.31
Repeated any grades: Y/N	121/82	18/26	-2.28	.02*
SES[b]	2	2	-1.29	.19
CD4 count: M(SD)	952.66 (496.45)	N/A	N/A	N/A
Viral Load: M(SD)	5231.37 (32300.66)	N/A	N/A	N/A
Cognitive domains: means (SD)				
General intellectual function	-.55 (.78)	.00 (.79)	4.12	.00*
Executive function	-.45 (.62)	-.01 (.59)	4.15	.00*
Motor coordination	.03 (.99)	.00 (.91)	-.18	.86
Attention	-.39 (.92)	-.00 (.92)	2.55	.01*
Working memory	-.46 (.61)	-.00 (.63)	4.40	.00*
Visual spatial ability	-.35 (.89)	-.00 (1.00)	2.31	.02*
Visual memory	-.49 (.87)	-.00 (.98)	3.31	.00*
Language	-.38 (.102)	-.00 (1.00)	2.21	.03*
Verbal memory	-.52 (1.26)	.00 (.84)	3.37	.00*
Processing speed	-.55 (.63)	.00 (.68)	5.13	.00*

NOTES: a: Education was measured as the number of years of completed schooling. b: SES = Socioeconomic status was measured using the ASSET index. A score of 2 indicates that majority of households fell into the R1.00 – R5000.00 per annum income bracket. N/A: Not Applicable. * Indicates a significant difference at the $p<0.05$ level.

Table 2: Cronbach's alpha values for establishing cognitive domain composite scores.

Cognitive domain	**Neuropsychological test/s**	**Intra-test information[a]**	**Cronbach's alpha**
General intellectual function	WASI[b] vocabulary, similarities, block design and matrix reasoning subtests	42 (0-80), 13 (0-71), 26 (0-48), 35 (0-35)	.76
Attention	CCTT[c] 1 and 2	1 (0-120)*, 1 (0-120)*	.83
Working memory	WISC[d] Digit Span backward, CCTT 1 and 2, NEPSY naming, inhibition and switching	8 (0-16), 1 (0-120)*, 1 (0-120)*, 80 (0-360)*, 80 (0-360)*, 80 (0-360)*	.72
Verbal memory	HVLT[e] total, delayed recall and recognition subtests	12 (0-12), 12 (0-12), 24 (0-12)	.79
Visual memory	RCF[f] 3-minute and 30-minute delayed recalls subtests	18 (0-36), 18 (0-36)	.80
Visual spatial ability	RCF copy	18 (0-36)	--
Language	BNT[g]	16 (0-16)	--
Motor coordination	NEPSY FTT[h] dominant and non-dominant	4 (0-150)*, 4 (0-150)*	.84
Processing speed	WISC Symbol Search and Coding, NEPSY naming, inhibition and switching	60 (0-60), 140 (0-140), 80 (0-360)*, 80 (0-360)*, 80 (0-360)*	.73
Executive function	NESPY naming, inhibition and switching, WASI matrix reasoning and similarities, CCTT 2, VFLU category and phonetic	80 (0-360)*, 80 (0-360)*, 80 (0-360)*, 35 (0-35), 13 (0-71), 1 (0-120)*, 1 (0-120)*, 2 (0-60), 3 (0-60)	.73

NOTES: a: The intra-test information is presented as "number of test items (total raw score range)". The intra-test information is presented in the same order the neuropsychological tests are presented in the second column of the table. b: Weschler Adult Scale of Intelligence, c: Children's

Colour Trails Test, d: Weschler Intelligence Scale for Children-IV, e: Hopkins Verbal Learning Test, f: Rey Osterich Complex Figure, g: Boston Naming Test, h: Fingertip Tapping Test. * = indicates timed tasks where the number in parentheses is the maximum time allowed for the task.

Table 3: Paired samples t-test for global composite scores and composite domains for the HIV-infected group only calculated under two different conditions.

	Composite scores		Difference between means	
Variable	[a]Control calculation M(SD)	[b]Whole sample calculation M(SD)	t	p
Global composite	-.38 (.49)	-.02 (.46)	-94.55	.00**
Domain composite				
GIF[c]	-.54 (.78)	-.09 (.74)	137.43	.00**
Attention	-.39 (.92)	-.07 (.91)	129.99	.00**
WM[d]	-.46 (.61)	-.07 (.61)	299.35	.00**
VerbM[e]	-.53 (1.26)	-.07 (.89)	18.41	.00**
VisM[g]	-.49 (.86)	-.09 (.87)	142.80	.00**
VSA[h]	-.36 (.89)	-.07 (.99)	40.30	.00**
Language	-.39 (.98)	-.07 (.99)	1004.97	.00**
MC[i]	.03 (.99)	.01 (.94)	-6.95	.00**
PS[j]	-.55 (.63)	-.09 (.64)	259.71	.00**
EF[k]	-.45 (.62)	-.06 (.57)	78.59	.00**

NOTES: All composite scores are presented as Means (Standard Deviation). a: These set of *z*-scores were calculated using the means and standard deviation of the control sample only. b: These set of *z*-scores were calculated using the means and standard deviation of the whole sample which includes HIV-infected and HIV-uninfected controls. c: General Intellectual Functioning, d: Working Memory, e: Verbal Memory, f: Visual Memory, g: Visual Memory, h: Visual Spatial Ability, i: Motor Coordination, j: Processing Speed, k: Executive Function. ** indicates a significant difference between the *z*-scores calculated using the control means and the *z*-scores calculated using the whole sample means with the Bonferroni correction applied α = p-value/number of comparisons = 0.05/11 = 0.004.

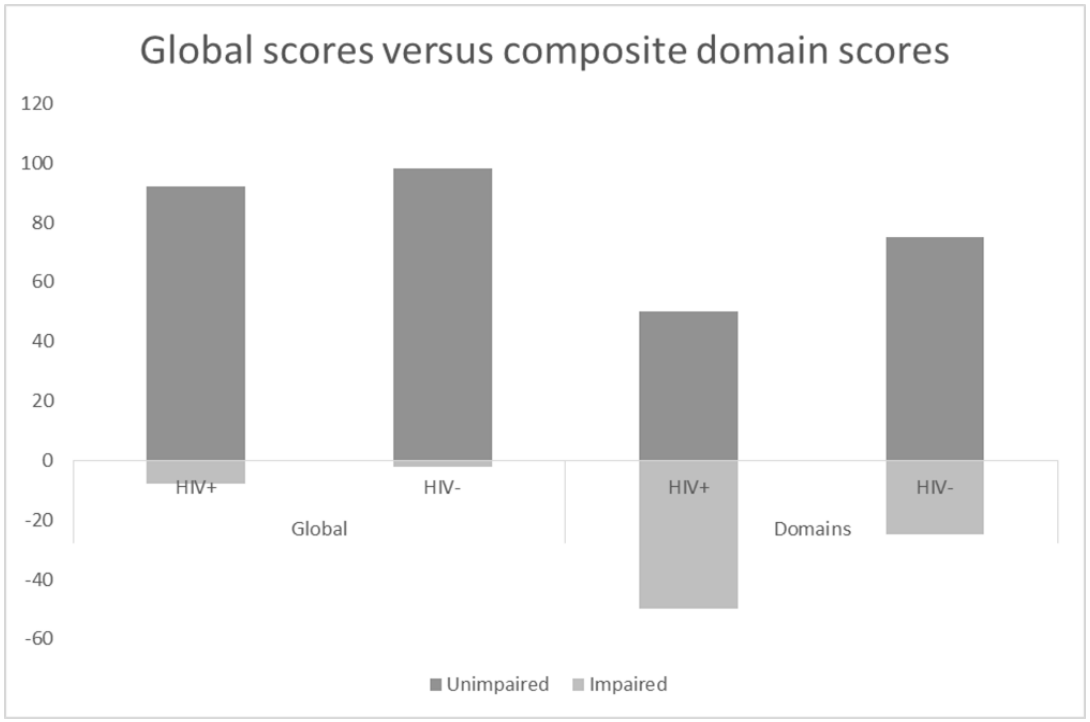
Table 4 present the comparison between the global aggregate score and the composite cognitive domains regarding their efficacy in detecting HIV-associated cognitive impairment. The outcomes of this comparison suggested that the composite cognitive domain scores provided more detailed information (regarding strengths, weaknesses, areas of impairment), and when compared to global scores, were more sensitive in detecting HIV-associated cognitive impairment, and were able to distinguish HIV-infected patients from uninfected controls. For the HIV-infected group, 17 participants were classified as impaired when looking at the global aggregate score and 102 were classified impaired when looking at the composite cognitive domain scores. For the control group, 1 participant was classified as impaired when looking at the global aggregate score and 11 were classified impaired when looking at the composite cognitive domain scores. The composite cognitive domain score provides an easy way of detecting which domains are impaired and in which domains the children and adolescents' strengths lie. For example; where children and adolescents' global aggregate score suggests that their overall cognitive functioning is average, this same individual may have impairments in attention and visual memory which are masked in the calculation of the global score. The youth HAND classification is based on whether or not the adolescent is "impaired" on one or two or more cognitive domains (Hoare et al., 2016b). This type of classification is not possible when examining the global aggregate score alone. Furthermore, the composite cognitive domains scoring system correctly identified 75% of the controls as not impaired, as opposed to 98% when examining the global score. This finding supports the similar rates of cognitive impairment found in the Hoare et al (2016) study. The global score over estimates the number of controls without any cognitive impairment and might therefore, fail to detect subtle cognitive differences between controls and HIV-infected children and adolescents.

Table 4: Efficacy of global aggregate scores compared to composite cognitive domain scores in detecting HIV-associated cognitive impairment.

	Impaired in the HIV-infected group (N = 203)	Impaired in the control group (N = 44)	t	p
Global cognitive score	17 (8%)	1 (2%)	-4.21	.00**
Average across domains[a]	102 (50%)	11 (25%)	-3.75	.00**

NOTES: For both the global aggregate score and the composite cognitive domains we used 1 SD below the mean as a cut-off for impairment such that participants scoring 1 or more SDs below the mean were classified as impaired. a: This variable presents a frequency count of how many participants for each of the groups were classified as "impaired" in two or more domains when examining the composite cognitive domains. ** = indicates significance at the $p<0.01$ level.

Figure 1: Efficacy of global aggregate scores compared to composite cognitive domain scores in detecting HIV-associated cognitive impairment.



Discussion

The purpose of this study was to test and describe a novel method for the accurate measurement of HIV-associated neurocognitive disorders in perinatally infected children and adolescents. The study has demonstrated three important aspects of cognitive deficit measurement in perinatally HIV-infected children and adolescents: 1) applying a methodologically sound statistical test to determine which neuropsychological tests demonstrate better internal consistency within a specific cognitive domain results in a composite score which is more true to the real world cognitive ability of the individual 2) composite cognitive domain scores calculated using whole-sample data were significantly higher than those calculated using control-sample data, and this might provide an inflated sense of the children and adolescents' cognition and 3) comparison of a global cognitive scores to composite domain scores suggested that the latter provided more detailed information (regarding strengths, weaknesses, areas of impairment), and when compared to global scores, were more sensitive in detecting HIV-associated cognitive impairment, and were able to distinguish HIV-infected patients from uninfected controls.

The use of cognitive domain specific composite scores has two major advantages: it becomes easier to determine what the individual's strengths and weaknesses are, and it enables one to detect the variance (or changes) in cognitive impairment, both between different domains and over time. We propose that the calculation of the composite score should be backed by tests of internal consistency with a Cronbach's alpha value of .70 or higher to strengthen the validity of the composite score obtained, thereby more accurately measuring cognitive performance within that domain.

As mentioned in the introduction, measurement of impairment requires a comparison to a prior level of functioning (Lezak, 2004), which is difficult to do in the case of perinatally HIV-infected children and adolescents, since we're unable to determine their baseline

functioning prior to the HIV infection. Based on the above findings using a whole sample mean score and SD to calculate Z-scores will erroneously inflate the composite scores obtained, thereby masking the effects of any real-world deficits which are potentially present.

Given the inconsistency within the literature regarding the calculation of *z*-score we have calculated the *z*-scores using both the whole sample means and SD, and the control sample means and SD. Running a paired samples *t*-test on the difference between the two versions of the *z*-score revealed highly significant differences between the scores such that *z*-scores calculated using the whole sample means and SD were higher than those calculated using the control means and SD.

Children from low to middle income countries (LMICs), like South Africa, are at high risk for cognitive, social and behavioural problems compared to children of high income countries (HICs) (Bornstein & Putnick, 2012; Grantham-McGregor et al., 2007; Liddell & Rae, 2001; S. P. Walker et al., 2011). This risk is perpetuated by the cycle of poverty which majority of these children find themselves in (Heckman, 2008; Heckman & Masterov, 2007). For this reason, using HICs established norms is inappropriate for data collected in LMICs. Since there are no published neuropsychological performance norms for South Africa, or even sub-Saharan Africa, using data from a demographically matched control samples is likely the most accurate "normative data" to use in this context and setting. In the case of perinatally HIV-infected children and adolescents a control (or normative sample) should ideally be matched for age, gender and other demographic identifiers (for example; SES, education, etc) who are HIV-uninfected, but recruited form the same community/schools. There is emerging literature that HIV-uninfected but exposed children and adolescents may display subtle deficits in overall cognition, motor coordination and language as compared to their unexposed counterparts (Kerr et al., 2014; Annelies Van Rie et al., 2008) and may therefore not be an appropriate control for comparisons.

In this study we found that the composite cognitive domains scores results in more true positives than the global cognitive score, when comparing it to the Hoare et al (2016) classification. For this study we constructed the composite cognitive domains using Cronbach's alpha because we wanted to construct domains using various neuropsychological tests and which showed good internal consistency (or reliability) between the tests. A recent study conducted by Hermetet-Lindsay and colleagues (Hermetet-Lindsay et al., 2017) created a composite cognitive functioning score using an exploratory factor analysis, which determines the validity of the factors entered into the model. When utilising standardized neuropsychological tests, one can be certain that the items of the individual tests have good validity and then in this case, when combining scores from the different tests to create a composite score, would not require re-validation of the test items. The composite score itself requires confirmation that the tests included in the score have good inter-relatedness (i.e.: reliability) and would therefore warrant a Cronbach's alpha analysis. The outcome of a factor analysis essentially results in a global cognitive score. A global score cannot determine what the patients' cognitive strengths and weaknesses are, and these are important for determining appropriate interventions for treatment. In addition, one singular score in unable to pick up variances between the different facets of overall cognitive functioning, and these variances are important for tracking the changes in cognitive impairment over time in a cohort like perinatally HIV-infected children and adolescents. Cognitive deficits in children and adolescents may vary over time and along their normal adolescent developmental trajectory. Also, the different cognitive domains may develop, and in the case of HIV-infection, deteriorate at different rates. A method that is both child-sensitive and time-sensitive for examining and classifying these deficits will enable researchers and clinicians for treat children and adolescent in real-time with specifically targeted and appropriate strategies.

In the systematic review and meta-analysis that found both similarities and inconsistencies regarding cognitive performance in the different domains (N. Phillips et al., 2016) for some of the comparisons standard mean differences were used to determine the effect size, and the reason for this is that the various studies included in these comparisons made use of different neuropsychological test measures. Another possible reason for the consistencies across studies is the fact that some studies made use of domain score and others made use of global aggregate scores (these were not entered into the meta-analysis). The method proposed here would enable researchers from different settings, contexts, and with differing test batteries to accurately compare findings in order to determine patterns of cognitive impairment in perinatally HIV-infected children and adolescents.

We recommend using this method of composite cognitive domains scores, rather than global aggregate scores, when assessing cognitive function in pediatric HIV. This method provides a convenient, standardized, and relatively accurate assessment that researchers across all settings and contexts might use. Ultimately, employing the method might help with cross-cultural and cross-region comparisons as researchers try to detect cognitive impairment patterns in HIV-infected children and adolescents globally. This method could also help to potentially develop a standardised neuropsychological test battery for use and comparison in different populations

Conclusion

We propose a novel method for the accurate measurement of cognitive impairment in perinatally HIV-infected children and adolescents that: 1) carefully and statistically considers the test measures used to assess deficit within a specific cognitive domain, 2) as far as possible makes use of a control sample means and SD for the *z*-score calculations of the domain specific composite scores and 3) measures deficits and strengths as opposed to an overall performance (i.e.: domain specific measurement). Researchers can apply this method

to their own data, to develop cognitive domains based on their unique test batteries and appropriately normed for their cohorts.

The extent to which these cognitive impairments cause significant functional problems has yet to be determined.

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CHAPTER 5: YOUTH PERINATAL HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS: ASSOCIATION WITH FUNCTIONAL IMPAIRMENT.

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Abstract

Context

Relatively little is known about associations between cognitive and functional impairment in perinatally HIV-infected children and adolescents.

Objectives

To determine whether cognitive impairment is associated with measures of functional impairment, and to assess the relative risk of having functional impairment in the presence of cognitive impairment.

Methods

HIV-infected children and adolescents and HIV-uninfected controls from the Cape Town Adolescent Antiretroviral Cohort (CTAAC) were included. Functional impairment was assessed by the Columbia Impairment Scale (CIS), Child Behavior Checklist (CBCL) and the Vinelands Adaptive Behavior-II scale (VABS2). We then assessed associations between degree of cognitive impairment and functional impairment. Finally, we used relative risk analyses to determine the risk of having functional impairment if cognitive impairment was present.

Results

Degree of cognitive impairment correlated strongly with decreased function: CIS, $r = .13$, $p = .05$; CBCL, $r = -.17$, $p = .01$; VABS2, $r = -.28$, $p < .001$; repeated grades, $r = .26$, $p < .001$.

Finally, the presence of cognitive impairment was associated with increased risk of functional impairment: 3.47 (CIS); 1.71 (CBCL); 2.17 (VABS2); 2.97 (repeated grades). Repeated grades was strongly associated with cognitive impairment and functional impairment as measures by the CIS, CBCL and VABS2.

Conclusions

Asking children and adolescents about school performance and whether or not they have repeated a grade at school could be a helpful screening question for assessing potential functional impairment. Having a repeated grade at school also correlates strongly with cognitive impairment and could potentially form part of a screening tool for neurocognitive impairment in perinatal HIV.

To diagnose HIV-associated cognitive disorders requires information regarding both the youth's cognitive abilities and functional abilities. In this chapter, which addresses aim 3 of the thesis, I set out to assess HIV-associated functional impairment, as it relates to cognitive disorders.

HIV-associated functional impairment (e.g., in scholastic/academic or social functioning) may be caused by cognitive impairment secondary to the viral infection, especially when cognitive deficits arise from dysfunction within fronto-striatal brain circuitry (R. K. Heaton, Marcotte, Mindt, Sadek, Moore, Bentley, McCutchan, Reicks, Grant, et al., 2004). Hence, associations between cognitive impairment and functional impairment in HIV-infected individuals are important to detect, describe, and track over time, particularly when clinicians are concerned about ways in which to rehabilitate impairments in everyday functional abilities.

Functional impairment is defined by Winters et al. as "specific deficits in multiple domains of functioning developing subsequent to a disorder" (Winters, Collett, & Myers, 2005). The presence of such impairment in children and adolescents is a marker of struggles to adapt to the challenges of novel situations. Moreover, when such impairment remains formally undiagnosed (and therefore untreated), there is the risk of continuing difficulty throughout adulthood, with associated economic costs to the family and the wider community (R. K. Heaton, Marcotte, Mindt, Sadek, Moore, Bentley, McCutchan, Reicks, Grant, et al., 2004).

Therefore, it is important to accurately characterize the current real-world functioning of HIV-infected children and adolescents during routine healthcare visits. An ideal assessment of functional impairment would involve detailed observation of the individual in social, familial, and academic settings (Antinori et al., 2007). However, such assessment alongside already lengthy neuropsychological testing would place enormous pressure on the

capacity of healthcare systems, particularly in low-resource settings that carry the highest burden of HIV infection (Katz, Ehrenkranz, & El-Sadr, 2018). The most time- and cost-efficient ways to measure functional impairment involve administration of standardized questionnaires that gather information from patients themselves and/or from their close relatives (Antinori et al., 2007).

In adults, the most widely-used standardized measures of functional impairment (e.g., the Sheehan Disability Scale (Sheehan & Sheehan, 2008) (SDS)) assess the ability to perform activities of daily living (ADLs; e.g., medication management (R. K. Heaton, Marcotte, Mindt, Sadek, Moore, Bentley, McCutchan, Reicks, Grant, et al., 2004)). These measures are difficult to adapt for use in children and adolescents, because, for instance, younger people often require some assistance from parents or caregivers in completing the most important or complex daily tasks (e.g., they are typically not solely responsible for managing their medication). In other words, the types of everyday activities that children and adolescents are expected to accomplish without help are different from those expected of adults.

The purpose of the present study was to determine whether an existing set of standardized child-focused measures accurately assess functional impairment as it relates to HIV-associated cognitive impairment. We used data from a sample of perinatally HIV-infected South African children and adolescents to 1) determine the associations between degree of cognitive impairment and scores on four different measures of functional impairment, and 2) determine the relative risk of having functional impairment in the presence of cognitive impairment, which we classified using the youth HIV-associated diagnostic criteria established Hoare et al.(2016)(Hoare et al., 2016a).

Methods

Study design, setting and participants.

Participants were recruited from community health clinics as part of the Cape Town Adolescent Antiretroviral Cohort (Brittain et al., 2018) (CTAAC). We enrolled 249 participants into this cross-sectional sub-study of CTAAC. Of that number, 205 were HIV-infected and 44 were HIV-uninfected frequency-matched controls. Controls were matched for age, gender and socio-economic status (SES). The seronegative status of participants in the latter group was confirmed by rapid antibody testing prior to participation.

All study procedures were administered within the University of Cape Town's Department of Psychiatry and Mental Health.

The CTAAC study is ethically approved by the Human Research Ethics Committee of the Health Sciences Faculty at the University of Cape Town (HREC REF: 051/2013). All study procedures adhered to the ethical guidelines for conducting research with children and adolescents as set out by the South African National Department of Health and the Declaration of Helsinki. Children and adolescents signed informed assent forms before participating, and parents/caregivers signed informed consent for both their own and their child's participation.

Measures.

Functional impairment. The parent-rated version of the 13-item Columbia Impairment Scale (CIS) (Bird, Shaffer, Fisher, & Gould, 1993) measures perceived impairment within the following domains: interpersonal relationships, psychopathology, schoolwork, and use of leisure time. Parents are asked to rate, by responding to a particular statement (e.g., "How much of a problem would you say he/she has with: his/her behaviour at school"), how much of a problem their child has within a particular domain of functioning. Ratings are made on a Likert-type scale, with response options being *no problem, a very small problem, some*

problem, a moderate problem, or *a very bad problem*. Parents also have the option of answering *not applicable* or *don't know*.

The Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001) is one of the most widely used and psychometrically sound measures for assessing child behavioral and emotional problems and psychopathology (Albores-Gallo et al., 2007; Rescorla, 2005). This 113-item instrument provides parent-reported information on the child's overall competencies and problems, as well as internalizing and externalizing behaviours. For each item, the parent is asked to rate how accurately a given statement (e.g., "Acts too young for his/her age") describes the child, with response options ranging from 0 (*not true*) through 1 (*somewhat or sometimes true*) to 2 (*very true or often true*).

The parent/caregiver-rated version of the Vineland Adaptive Behaviors Scale - 2nd edition (VABS2 (S. Sparrow, D. V. Cicchetti, & D. A. Balla, 2005)) is used frequently in clinical settings. Parents are asked to rate, by responding to each of more than 200 items (e.g., "Holds spoon, fork, and knife correctly"), whether their child displays appropriate adaptive functioning. Ratings are made on a Likert-type scale, with response options ranging from 0 (*never*) through 1 (*sometimes or partially*) to 2 (*usually*). Parents also have the option of answering N/O (*no opportunity)* or *DK (don't know)*.

Supplement 1 provides further details on the CIS, CBCL, and VABS2.

Previous studies suggest that repeating a school grade is an indicator of functional impairment in the school domain (Biederman et al., 2004). Hence, we asked parents/caregivers the following yes/no question regarding the child's academic performance: "Has he/she repeated any grades at school?"

Cognitive functioning. We used a comprehensive neuropsychological test battery comprised of several individual standardized cognitive tests used commonly used in assessment of HIV-infected children and adolescents. The battery measured performance in the domains of general intellectual functioning (IQ), motor coordination, processing speed, attention, working memory, visual memory, verbal memory, visual-spatial ability, language, and executive function (Hoare, Fouche, Spottiswoode, Donald, Philipps, Bezuidenhout, Mulligan, Webster, Oduro, & Schrieff, 2012).

Procedure.

A parent/caregiver completed the questionnaires described above, thus providing information about the child participant's everyday functioning. Each child participant was administered the neuropsychological test battery by a trained research assistant.

Statistical analysis.

We completed all statistical analyses using SPSS (Arbuckle, 2010) (version 25, IBM, Armonk, New York 10504-1722,United States), with a 2-tailed alpha of 0.05 unless otherwise noted.

Deriving outcome variables. For the CIS, the main outcome variable was a total score, calculated by summing the individual item scores. For the CBCL, we captured all responses into the proprietary scoring software and thereby generated a Total Competence T-score as the main outcome variable. For the VABS2, two independent assessors (NP and BM) scored and checked all responses by hand, and then derived the main outcome variable, an overall adaptive behavior composite score comprised of independent scores for functioning in the domains of communication, daily living, and socialization. Both the CBCL and VABS2 derive total standardized scores which take into account the participants age and gender. The repeated grades question yielded dichotomous outcome scores (coded 1 for "yes" and 0 for "no").

For the neuropsychological test battery, we calculated a composite score for each participant for each cognitive domain, using a previously-published method(N. J. Phillips et al., 2018). Next, we applied the youth HIV-associated neurocognitive disorder diagnostic criteria(Hoare et al., 2016a) to each participant's neuropsychological profile in order to classify each as having either a major neurocognitive disorder (major ND), a minor neurocognitive disorder (minor ND), or no cognitive impairment (No ND). Although the usual application of these diagnostic criteria involves drawing on data from both cognitive performance and functional ability, in this instance we used cognitive data only to avoid the risk of false positive associations when conducting subsequent correlational analyses. Hence, here we defined major ND as being cognitive performance of > 2 *SD* below the mean in at least two domains, minor ND as being cognitive performance of > 1 *SD* below the mean in at least two domains, and No ND as being all other cognitive performance.

Preliminary analysis. We undertook this analysis because the standardized functional impairment measures (CIS, CBCL, and VABS2) have not been validated for use in our local context, and thus we sought some assurance that they were suited for this purpose. First, a series of Confirmatory Factor Analyses (CFAs) sought to determine whether, within our sample, these measures retained the same factor structure as reported in their respective test manuals. Second, internal consistency analyses (computed using Cronbach's alpha coefficient) assessed the reliability of each measure within our sample.

Association of functional measures with degree of cognitive impairment. A series of bivariate nonparametric point-biserial correlational analyses measured, within the HIV-infected group only, the magnitude of association between cognitive diagnosis (categories as described above) and each of the three standardized measures of functional impairment. A Pearson's chi-squared test calculated the association between score on the repeated grades question and cognitive diagnosis.

Calculating relative risk ratios. First, we used published cut-off scores (CBCL and VABS2) or a median split (CIS) to categorize participants' score on each of the standardized measures as either *impaired* and *not impaired*. Then, for each of those three dichotomous variables, and the repeated grades question, we computed the statistic describing the risk of having functional impairment if one had been diagnosed as being cognitively impaired (either major ND or minor ND) relative to having a diagnosis of no cognitive impairment.

Results

Sample characteristics. 247 participants were included in this analysis. Data for two participants were excluded. One was a pilot participant and the other had severe ADHD and was unable to complete any of the neuropsychological test measures. The participants ranged in age from 9-12 years. The group of HIV-uninfected controls was matched to the group of perinatally HIV-infected participants on major sociodemographic characteristics, and hence there were no significant between-group differences in terms of age, sex, education, and home language (see Table 1). Regarding scores on functional impairment measures, analyses detected significant between-group differences on the CBCL and repeated-grades outcome variables only.

Application of the youth HIV-associated neurocognitive disorder diagnostic criteria suggested that, within the HIV-infected group, 8 participants could be classified as major ND, 98 as minor ND, and 97 as no cognitive impairment. Within the control group, 1 participant could be classified as major ND, 10 as minor ND, and 33 as no cognitive impairment. This means that slightly more than half of all HIV-infected participants had a neurocognitive disorder.

Table 1: Sample Characteristics, and Scores on Measures of Functional and Cognitive Impairment (N = 247).

Variable	HIV-infected (*n* = 203)	HIV-negative (*n* = 44)	*t*	*p*	CI	ESE
Age: *M* (*SD*)	10.39 (0.88)	10.38 (1.09)	-0.05	.957	-0.311 to 0.295	.009
Sex: male/female	100/103	20/24	0.46	.649	-0.126 to 0.202	--
Education[a]: *M* (*SD*)	3.21 (1.12)	3.39 (1.35)	0.93	.356	-0.203 to 0.562	.154
Race: Black African/Other	186/17	44/0	1.99	.047*	0.001 to 0.166	--
Home language: isiXhosa/Other	184/19	42/2	1.04	.301	-0.043 to 0.140	--
CD4 count: *M* (*SD*)	952.66 (496.45)	N/A	N/A	N/A	N/A	N/A
Viral load[b]: median	0.00	N/A	N/A	N/A	N/A	N/A
CIS Total: *M* (*SD*)	5.20 (6.63)	3.73 (4.79)	-1.39	.163	-3.553 to 0.603	.231
CBCL Total Competence: *M* (*SD*)	37.70 (7.77)	41.16 (7.91)	2.65	.009**	0.887 to 6.049	.444
VABS2 Adaptive Behavior Composite: *M* (*SD*)	95.19 (22.95)	95.23 (11.14)	0.01	.991	-7.034 to 7.113	.002
Repeated any grades: yes (%)	120 (59)	18 (40)	-2.22	.027*	-0.344 to (-0.020)	--
Neurocognitive disorder[c]: impaired (%)	95 (46.8)	8 (18.2)	-3.58	<.001**	-0.505 t0 (-0.146)	--

Note. [a]The highest level of completed education (i.e., highest grade passed), in years. [b]Median value was lower than detectable levels. [c]Classified according to the youth HIV-associated neurocognitive disorders classification system recently published by Hoare et al (2016). CIS = Columbia Impairment Scale; CBCL = Child Behavior Checklist; VABS2 = Vinelands Adaptive Behaviour Scale - 2nd Edition; 95% CI = confidence interval; ESE = effect size estimate (in this case, Hedges' *g*, due to the large difference in group sample sizes).
*$p < .05$. **$p < .01$.

Preliminary analysis. Results of the Kaiser-Meyer-Olkin (KMO) test of sampling adequacy and Bartlett's test of sphericity (see Table 2) suggested the data were suited to application of CFAs. We applied a varimax rotation to all three CFAs, with factors extracted based on eigenvalues greater than 1.

For the CIS Total Score variable, the analysis confirmed the presence of four factors (interpersonal relationships, psychopathology, schoolwork, and use of leisure time), a result consistent with that reported by the test manual. For the CBCL Total Competence variable, the analysis confirmed the presence of three factors (internalizing, externalizing, and total problems), a result inconsistent with that reported by the test manual (there, the authors report the presence of four factors: internalizing, externalizing, total problems, and total competence). For the VABS2, the analysis confirmed the scale was unidimensional, a result consistent with that reported by the test manual. Table 2 presents a basic summary of the CFA analyses, while Supplement 2 presents more detailed information.

Regarding internal consistency reliability, although the Cronbach's alpha value for the CIS (0.63) was quite low, values for the CBCL and the VABS2 were excellent (0.92 and 0.97, respectively).

Major Analyses: Functional-cognitive associations and relative risk ratios. Analyses detected significant associations between degree of cognitive impairment and scores on three of the four measures of functional impairment (CBCL Total Competence, VABS2 adaptive behavior composite, and the repeated grades question; see Table 3). For each of these measures, greater functional impairment was significantly associated with a higher degree of cognitive impairment. Moreover, the association between CIS Total Score and degree of cognitive impairment tended strongly toward statistical significance, also in the predicted direction.

Given these strong associations, we expected that the results of the relative risk analyses would confirm that HIV-infected children and adolescents with cognitive impairment would be at increased risk of functional impairment. This expectation was confirmed. Analyses suggested that those classified as cognitively impaired by the youth HIV-associated diagnostic criteria (i.e., either major ND or minor ND) were at (a) three times higher risk for having CIS- or repeated grades-defined functional impairment, and (b) more than double the risk for having CBCL- or VABS2-defined functional impairment (see Table 4).

Table 2: Confirmatory Factor Analyses (CFA) for CIS, CBCL and VABS2 (N = 247)

Measure	Factors extracted	KMO value	Bartlett's test *p*	Goodness-of fit test	
				χ^2	p
CIS Total	4	.592	<.001**	59.913	.002**
CBCL Total Competence	3	.847	<.001**	576.601	<.001**
VABS2 Adaptive Behavior Composite	1	.908	<.001**	60.235	<.001**

Note. KMO = Kaiser-Meyer-Olkin measure of sampling adequacy; CIS = Columbia Impairment Scale; CBCL = Child Behavior Checklist; VABS2 = Vinelands Adaptive Behaviour Scale - 2nd Edition. *$p < .05$. **$p < .01$. ***$p < .001$.

Table 3: Correlation Matrix: Associations between the measures of functional impairment and youth HIV-associated neurocognitive disorders classification (N = 203).

	CIS	CBCL	VABS2	Repeated grade	NCD-HIV
CIS	--	-.16 (.02)*	-.12 (.08)	.14 (.03)*	.13 (.05)
CBCL	-.16 (.02)*	--	.30 (< .001)***	-.31 (< .001)***	-.17 (.10)*
VABS2	-.12 (.08)	.30 (< .001)***	--	-.26 (< .001)***	-.28 (< .001)***
Repeated grade	.14 (.03)*	-.31 < .001)***	-.26 (< .001)***	--	18.29 (< .001)***
Neurocognitive disorder	.13 (.05)	-.17 (.01)*	-.28 (< .001)***	.26 (< .001)***	--

Note. For analyses involving the CIS, CBCL, or VABS2, the Spearman's ρ correlation coefficient, resulting from a nonparametric point-biserial correlation, is presented, with the associated *p*-value in parentheses. For the analysis involving the repeated grades question and the NCD-HIV variable, the Pearson χ^2 statistic is presented, with the associated p-value in parentheses. CIS = Columbia Impairment Scale; CBCL = Child Behavior Checklist; VABS2 = Vinelands Adaptive Behavior Scale - 2nd Edition. *$p < .05$. **$p < .01$. ***$p < .001$.

Table 4: Relative Risk: Odds of being functionally impaired if diagnosed with an HIV-associated neurocognitive disorder (N = 203).

Measure	Relative risk	Percentage at risk for NCD	Risk estimate	95% CI
CIS	Increased	59.9	3.47	1.58 to 7.63
CBCL	Increased	51.2	1.71	0.95 to 3.08
VABS2	Increased	59.7	2.17	1.18 to 3.99
Repeated grade	Increased	57.5	2.97	1.65 to 5.34

Note. CIS = Columbia Impairment Scale; CBCL = Child Behavior Checklist; VABS2 = Vinelands Adaptive Behavior Scale - 2nd Edition; CI = 95% confidence interval. CIS was dichotomized at the median, which was 3 for this sample.

Discussion

The purpose of this study was to determine whether, in a sample of perinatally HIV-infected South African children and adolescents, degree of cognitive impairment was associated with functional impairment. Specifically, we measured associations between degree of cognitive impairment (as captured by the youth HIV-associated diagnostic criteria; Hoare et al., 2016) and each of four measures of functional impairment: the Columbia Impairment Scale (CIS), Child Behavior Checklist (CBCL), Vinelands Adaptive Behavior Scales - 2nd edition (VABS2), and a dichotomous variable reflecting whether or not the child had repeated a grade in school. We then assessed the child/adolescent's relative risk of being functionally impaired if s/he had been classified as being cognitively impaired.

The CIS, CBCL, and VABS2 were developed in high-income countries (HICs), and their original validation used a standardization sample of English first-language individuals. Although they are used frequently in South African clinical practice and research studies, they have not been formally validated for use in the local context. Hence, we sought to determine if, when administered to a sample of children and adolescents from a low- and middle-income country (LAMIC) and without English as a first language, they (a) displayed the same factor structure as reported by their developers, and (b) were internally consistent.

Confirmatory factor analyses indicated that the current CIS data conformed to the 4-factor structure reported in the instrument's test manual. That positive result is offset by the fact that (a) the CIS internal consistency coefficient was quite low, and (b) the association between CIS score and degree of cognitive impairment did not reach the threshold of statistical significance. Together, these results suggest that, in this sample of perinatally HIV-infected South African children and adolescents, the CIS is relatively unreliable and might be less-than-optimally sensitive to subtle associations between everyday functioning and cognitive impairment. Hence, one might evaluate this scale as being less appropriate than

others when seeking a measure of functional impairment suitable to the LAMIC context of perinatal HIV.

CBCL-related analyses suggested that, within our sample, the distribution of data on the scale might be classified into three main factors (internalizing, externalizing, and total problems). In contrast, the standardization manual suggests the instrument has a four-factor structure, with total competence added to the three we detected. The absence of this total competence factor is of concern given that on the CBCL it is the subscale meant to measure of everyday ability to function. The CBCL is used frequently in different cultural and language contexts, and, consistent with the current findings, its authors report good internal consistency for various language versions of this scale. The findings from this study suggest that although the CBCL may display varied psychometric properties in different contexts, the underlying constructs of the scale are robust enough to still be clinically relevant.

CBCL Total Competence scores correlated strongly with the presence of cognitive impairment, and relative-risk analyses suggested that HIV-infected cognitively impaired participants were almost twice as likely to score below the CBCL clinical cut-off as those without cognitive impairment. Together, these data suggest that the items contained within the CBCL Total Competence subscale are sensitive to activities of daily living that are reliant on intact cognitive functioning.

VABS2-related analyses suggested that, within our sample, this scale retained its author reported factor structure and displayed good internal consistency. Although few studies report on cross-cultural use of the VABS2, studies using samples with different medical and psychological conditions suggest, consistent with the current findings, that the scale's psychometric properties are quite resistant to application across different contexts (de Bildt, Kraijer, Sytema, & Minderaa, 2005; Perry, Flanagan, Geier, & Freeman, 2009). Of

further note here is that VABS2 scores correlated strongly with the presence of cognitive impairment, and that relative-risk analyses suggested that HIV-infected cognitively impaired participants were more than twice as likely to score below the clinical cut-off on this subscale as those without cognitive impairment. Together, these data suggest that VABS2 adaptive behavior composite is useful in describing everyday activities that rely on intact cognitive functioning.

Scores on the repeated grades variable correlated strongly and significantly with the presence of cognitive impairment, and relative-risk analyses confirmed that those with either major or minor neurocognitive disorders were almost three times as likely to have repeated a grade as those without any cognitive impairment. One very important incidental finding is that scores on the repeated-grades variable correlated significantly with those on the CIS, CBCL, and VABS2 outcome variables (i.e., those participants who had repeated a grade were more likely to have their parents report higher levels of functional impairment). This piece of data demonstrates the usefulness of this question in assessing general functional impairment in school-aged children and adolescents. Together, these results suggest that this question may be a good, quick (albeit crude) screening question for functional impairment related to cognitive impairment.

Although functional impairment is not inextricably related to academic impairment, it is true that, in children and adolescents, performance in the school domain is often severely affected by difficulties in everyday adaptive skills. For example, in a study of youths diagnosed with Obsessive-Compulsive Disorder (OCD), the most common disorder-related functional impairments involved concentrating at school and completing homework assignments (Piacentini, Bergman, Keller, & McCracken, 2003). Similarly, Valderhaug and Ivarsson (2005) reported that, in a sample of Swedish and Norwegian children and

adolescents, the school domain was one of the those most affected by OCD-related functional impairment (Valderhaug & Ivarsson, 2005).

The post-apartheid South African basic education system is designed to address past inequalities (e.g., through policies to ensure basic education for all, regardless of race, gender, or socioeconomic status). Hence, the school curriculum has undergone a number of reforms since the dawn of democracy in 1994 (Bantwini, 2010). In the context of this paper, one particularly noteworthy aspect of these reforms is that the South African National Department of Basic Education periodically lowers the pass mark requirements within public schools (Nkosi, 2018). At present, the pass mark is set at 30% in three out of seven subjects, and at least 40% in the other four subjects, one of which must be the home language (Africa, 2013). Even in the presence of these relatively meagre requirements, there are policies set in place to promote scholars to the next grade even if they do not meet the pass mark for all their subjects (Africa, 2013). Hence, it is quite difficult for a scholar to repeat a grade, and thus, when a repeat is recommended, it speaks to the degree of the child's academic (and other) struggles at school.

The current study is limited by the fact that we were unable to verify the self-reported information given in response to the repeated grades question. This variable, or any similar question asking about academic functioning, requires more in-depth investigation and understanding before we accept it as a reliable source of information regarding whether an HIV-infected child or adolescent is at risk for functional impairment. A second limitation is that all the measures used to assess functioning rely on self-report, and it may be that parents/caregivers could have under- or over-reported problems with everyday functioning. A plethora of literature, starting with the work of Cronbach and Meehl (Cronbach & Meehl, 1995) highlights the weaknesses of self-report measures, particularly with regard to issues of construct validity. Emerging research is moving towards multi-modal methods of assessment

in order to achieve more accurate estimation of the constructs under investigation (McDonald, 2008). A third limitation is that the current study is cross-sectional, thus limiting inferences we can make about causal associations between functional impairment and cognitive disorders.

Summary and conclusion

In resource-limited settings such as South Africa, it is difficult to accurately assess functional impairment (including academic struggles) that might accompany HIV-associated neurocognitive disorders in children and adolescents. Although administering standardised questionnaires is considered appropriate in the absence of observational assessments, if such administration is to deliver valid and practically useful data then administrators need to have adequate time and proper training, and the questionnaires themselves must be psychometrically appropriate for use in the context. Unfortunately, neither time nor training are feasible given the high burden of patient numbers at the various community-level clinics, and few research studies have investigated the cross-cultural transfer of these instruments' psychometric properties. Hence, one particularly useful finding from the current study is that repeating a grade at school may provide a quick but accurate insight into the presence of cognitive and/or functional impairment, and may indicate whether further in-depth observation/testing is warranted. More studies looking specifically at the link between HIV-related functional impairment and school performance is needed.

Given that half of adolescents living with HIV in this study have a NCD despite being stable on ART, highlights the continued significant risk that HIV exerts on the CNS. Screening for these NCDs in all adolescents living with HIV, should be a routine part of clinical care, given the functional impairment demonstrated here.

Supplement 1

Additional information on measures of functioning: CIC, CBCL and VABS2.

The Columbia Impairment Scale (CIS)

The parent-rated version (Bird et al., 2008) of the CIS (a 13-item Likert-type scale) was used to measure the child's global functioning level. It measures impairment within the following domains: interpersonal relationships, psychopathology, schoolwork, and use of leisure time. Parents are asked to rate, by responding to different statements, how much of a problem their child had within different areas of functioning. An example of one such statement is, "How much of a problem would you say he/she has with: his/her behaviour at school". Parents were required to rate their child as having no problem, a very small problem, some problem, a moderate problem, or a very bad problem with each of the statements/scenarios given. Parents also had the option to answer not applicable or don't know.

The instrument's developers report that it has a test-retest reliability of 0.89, and that it also has good validity. They also report that the parent-rated version of the questionnaire has better psychometric properties than the child self-rated version; the former is therefore recommended for both clinical and research purposes. This scale has not been used in published South African studies. It is, however, listed on the Mental Health Screening and Assessment Tools for Primary Care toolkit, released by the American Academy of Pediatrics (2010), as a psychometrically good measure of child global functioning, taking into account cultural considerations.

Child Behaviours Checklist (CBCL)

This 113-item instrument (Achenbach & Rescorla, 2001) is one of the most widely used and psychometrically sound measures for assessing child behavioural and emotional problems

and psychopathology (Albores-Gallo et al., 2007; Rescorla, 2005). In this study, it was used to measure internalizing and externalizing problems experienced by the child. It was also used to measure total problems experienced by the child, as well as the child's total competence.

Parents were asked to rate items according to how much each given statement applied to their children: 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true). Examples of some statements are: "Acts too young for his/her age" and "Can't concentrate, can't pay attention for long."

The scale developers report test-retest reliability coefficients of 0.95-1.00, and internal consistency reliability of 0.78-0.97. These figures hold for translated versions of the CBCL; the instrument has been translated into more than 70 languages, and is used globally (Albores-Gallo et al., 2007). This scale has been used successfully used to measure child behaviour problems in South African children (Shields, Nasaden, & Pierce, 2004).

Vinelands Adaptive Behaviours Scale 2nd edition (VABS2)

The version of the VABS2 used for this study is the parent/caregiver rated version on which parents are asked to rate their child's ability on a likert scale (2 = usually, 1 = sometimes or partially, 0 = never, DK = don't know, N/O = no opportunity)3. All VABS2 were individually and manually scored and checked by two independent assessors (NP and BM). For ages 7 through 90 the adaptive behaviour composite score is comprised of functioning in the domains of communication, daily living and socialization.

The authors of the scale report that the overall reliability of the subdomains estimates are moderate to high, with reliability tending to be higher for younger children and for adults aged 72 – 90 years, and lower for adolescents and young adults. The authors report reliability

coefficients for different age ranges. The age ranges and associated reliability coefficients for this study are: ages 6-11 years with a reliability of .97 and ages 12-18 years with a reliability of .95.

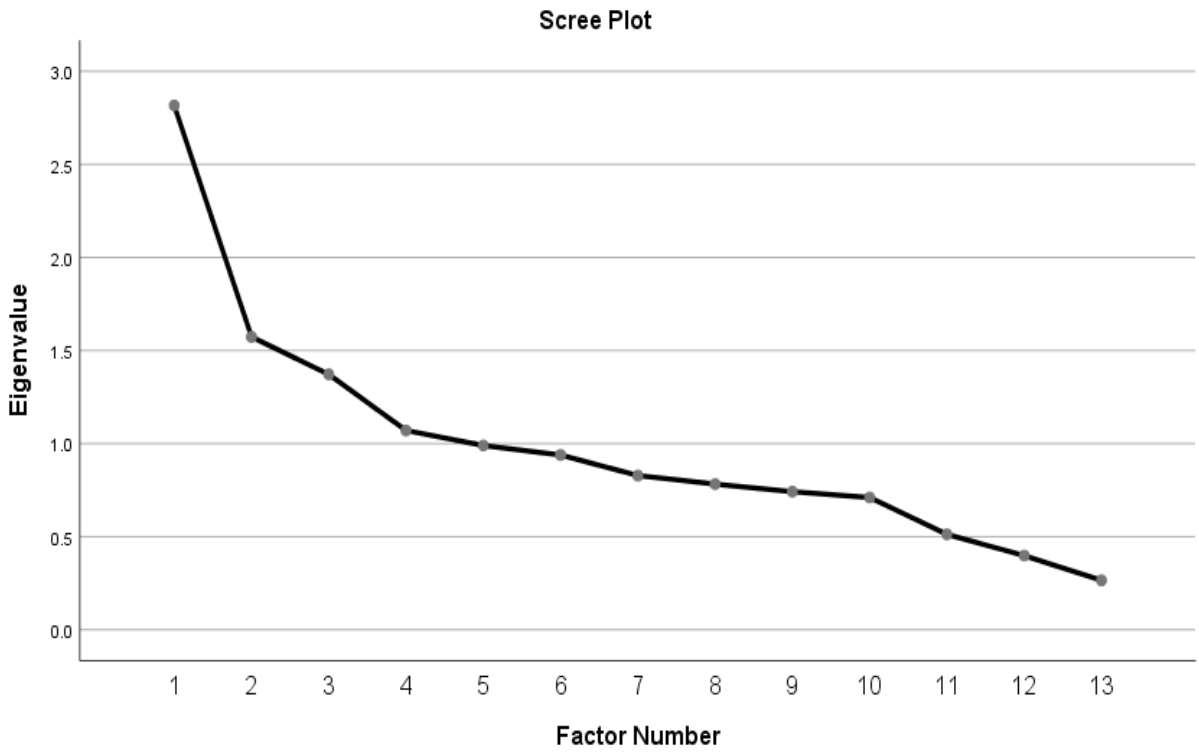
VABS2 Domains and Subdomains	Content
Communication Domain	
Receptive	How the individual listens and pay attention, and what he or she understands.
Expressive	What the individual says, how he or she uses words and sentences to gather and provide information.
Written	What the individual understands about how letters make words, and what he or she reads and writes.
Daily Living Skills Domain	
Personal	How the individual eats, dresses, and practices persona hygiene.
Domestic	What household tasks the individual performs.
Community	How the individual uses time, money, the telephone, the computer, and job skills.
Socialization Domain	
Interpersonal Relationships	How the individual interacts with others.
Play and leisure	How the individual plays and uses leisure time.
Coping skills	How the individual demonstrates responsibility and sensitivity to others.
Motor Skills Domain	
Gross	How the individual uses arms and legs for movement and coordination.
Fine	How the individual uses hands and fingers to manipulate objects.
Adaptive Behaviour Composite	
Adaptive behaviour composite	A composite score. For individuals aged 0 – 6 years the composite score includes the communication, daily living skills, socialization and motor skills domains. For individuals aged 7 - 90 years the composite score includes the communication, daily living skills and socialization domains only.
Maladaptive Behaviour Domain (optional)	
Maladaptive behaviour index	A composite score of internalizing, externalizing and other types of problem behaviour that may interfere with the individual's adaptive functioning.
Maladaptive behaviour critical items	More severe maladaptive behaviours that may provide clinically important information.

Supplement 2

Additional data for the Confirmatory factory analysis for the CIS, CBCL and VABS2.

Columbia Impairment Scale (CIS)

The factorability of 13 items were considered for the CIS. Factors which yielded an Eigenvalue of >1 were considered as factors and thus, a total number of 4 factors were extracted for the CIS as determined by scree plot. These factors correspond with the author reported subscales of the CIS, namely: interpersonal relationships, psychopathology, schoolwork, and use of leisure time.



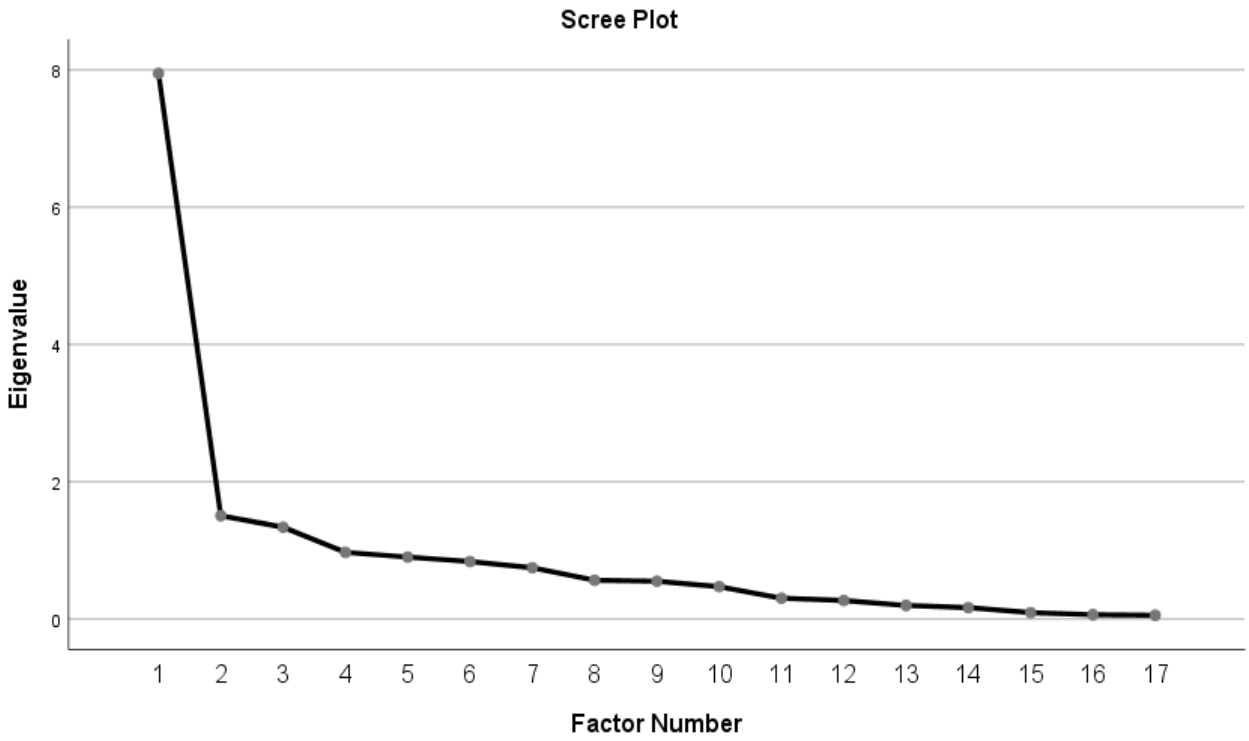
CIS item	Factor 1	Factor 2	Factor 3	Factor 4	Communalities
Problems getting along with male caregiver.	**.72**	**-.69**			.11
Problems with feeling nervous or afraid.	**.72**	**.69**			.44
Problems getting along with female caregiver.	**.61**	-.10	.11	-.20	.99
Problems with feeling unhappy or sad.	.24		.10	.24	.14
Problems getting along with other child own age.	.18		.14		.45
Problems with behaviour at school.			**.61**	.25	.14
Problems with behaviour at home.	.33		**.54**	-.20	.40
Problems with getting along with siblings.	.34		**.53**		.99
Problems with school work.	.14	.10	**.52**		.42
Problems with getting involved with activities like sport or hobbies.	.10		.19	-.15	.07

CIS item	Factor 1	Factor 2	Factor 3	Factor 4	Communalities
Problems getting along with other adults.	.41	-.15		**.45**	.07
Problems with having fun.				.36	.32
Problems with getting into trouble.	.19			.25	.45

Factor correlation	1	2	3	4	%Variance explained
1	--	.27	.23	.01	15.32
2	.27	--	.25	.18	8.03
3	.23	.35	--	.07	10.16
4	.01	.18	.07	--	5.01

Child Behaviours Checklist (CBCL)

The factorability of 17 items (corresponding to the 17 subscales of the CBCL) were considered for the CBCL. Factors which yielded an Eigenvalue of >1 were considered as factors and thus, a total number of 3 factors were extracted for the CBCL as determined by scree plot. These factors correspond with the author reported subscales of the CBCL, namely: Total problems, internalizing problems, externalizing problems.



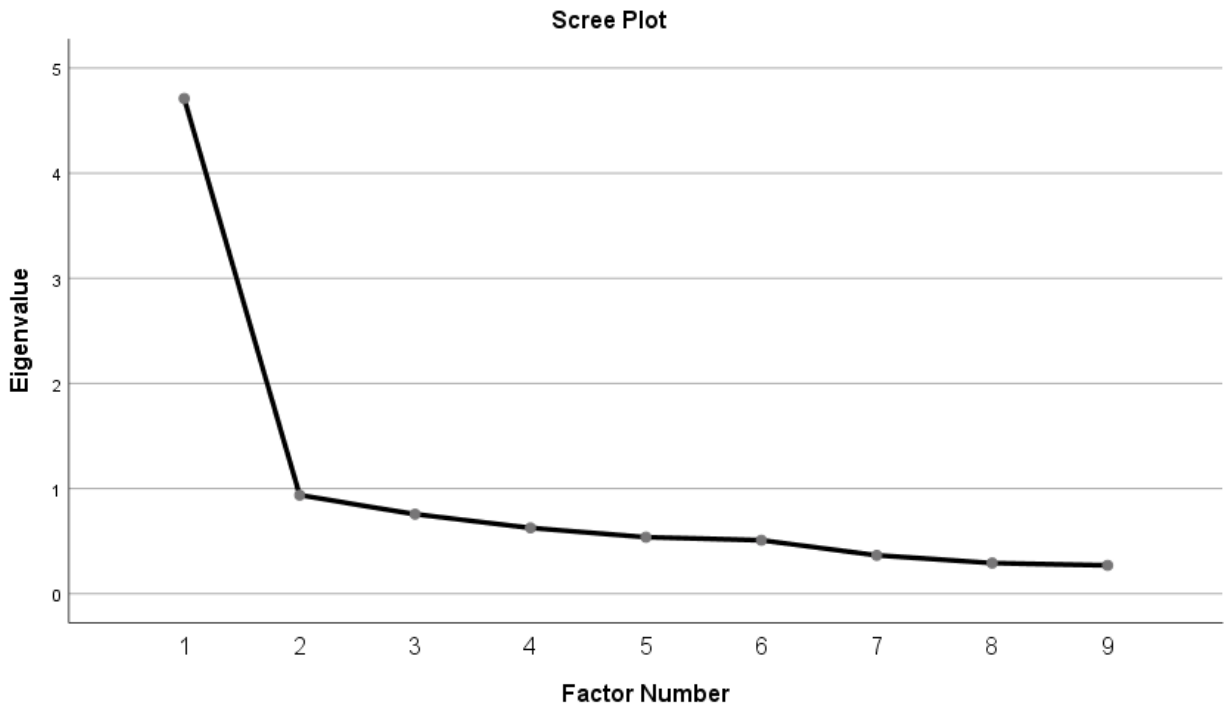
CBCL item	Factor 1	Factor 2	Factor 3	Communalities
Activities				.01
Social			-.10	.02
School	-.25	-.16	-.20	.14
Anxious or depressed	.59		.50	.62
Withdrawn or depressed				.01
Somatic complaints	.85	-.52		.99
Social problems	.71	.11	.38	.67
Thought problems	.64		.41	.58
Attention problems	.61		.53	.67
Rule breaking behaviour	.71	.43		.69
Aggressive behaviour	.74	.28	.35	.77
Affective problems	.67		.39	.61
Anxiety problems	.53		.53	.58
Somatic problems	.77	-.51		.86

CBCL item	Factor 1	Factor 2	Factor 3	Communalities
Attention deficit	.66	.12	.45	.66
Oppositional defiant problems	.65	.20	.41	.64
Conduct problems	.84	.52		.99

Factor correlation	1	2	3	%Variance explained
1	--	-.35	.29	37.98
2	-.35	--	-.22	7.21
3	.29	-.22	--	10.88

Vinelands Adaptive Behaviour Scale 2nd edition (VABS2)

The factorability of 9 items (corresponding to the 9 subscales of the VABS2) were considered for the VABS2. Factors which yielded an Eigenvalue of >1 were considered as factors and thus, a total number of 1 factor was extracted for the VABS2 as determined by scree plot. This factor correspond with the author reported subscale of the VABS2, namely: VABS composite score for overall adaptive functioning.



VABS2 item	Factor 1	Communalities
Receptive communication	.32	.11
Expressive communication	.81	.69
Written communication	.83	.69
Personal daily living	.62	.39
Domestic daily living	.53	.29
Community daily living	.66	.44
Interpersonal relationships socialization	.70	.49
Play and leisure socialization	.78	.62
Coping skills socialization	.71	.51

Factor correlation	1	%Variance explained
1	--	47.11

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CHAPTER 6: SCREENING FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS IN PERINATALLY INFECTED ADOLESCENTS: Y-IHDS VALIDATION.

Phillips, N. J., Thomas, K. G. F., Myer, L., Sacktor, N., Zar, H. J., Stein, D. J. & Hoare, J. (2019). *AIDS*, 33(5): 815-824.

Abstract

Context

Perinatal HIV-infection has adverse cognitive consequences into adolescence. However, there are no screening tools that assess risk for HIV-associated neurocognitive disorders in adolescent populations. Such screening tools are needed urgently for clinical care in resource-poor settings with a high prevalence of HIV.

Objective

To investigate the performance of the International HIV Dementia Scale (IHDS) as a screening tool for HIV-associated neurocognitive disorders in perinatally HIV-infected adolescents.

Design

This study is a quantitative, quasi-experimental design.

Methods

Perinatally HIV-infected adolescents aged 9-12 years were recruited from community health clinics into the Cape Town Adolescent Antiretroviral Cohort (CTAAC); matched HIV-negative controls from the same communities were enrolled. Each participant completed the IHDS and a comprehensive neuropsychological battery. The adult version of the IHDS was

performed, except for two minor modifications. We evaluated the diagnostic validity of this modified instrument, the youth-IHDS (y-IHDS), using a four-step process that included sensitivity and specificity calculations, and generating receiver operating characteristic (ROC) curves. Validity was measured against the youth HIV-associated diagnostic criteria.

Results

At a cut-off score of ≤10, the y-IHDS demonstrated good sensitivity (94%) but poor specificity (24%) for detecting all forms of neurocognitive disorders, with an acceptable area under the curve (AUC) value of 0.695.

Conclusions

The y-IHDS requires minimal resources and is based on a screening tool for adult HIV-associated cognitive disorders that is already widely-used globally. Hence, this brief, cost-efficient, and valid screening tool may be a useful addition for clinicians working in resource-poor contexts where adolescent HIV is highly prevalent.

Accurate assessment of HIV-associated cognitive and functional impairment can be time-consuming and places enormous pressure of the healthcare system, especially in low-resourced areas. In this chapter, which addresses aim 4 of the thesis, using findings from the previous two chapters I set out to validate a screening tool for detecting the risk of HIV-associated cognitive impairment, as such a tool has not yet been validated for use in children and adolescents.

Perinatally-acquired HIV remains a global health concern even in the era of antiretroviral therapy (ART), Africa is particularly severely affected, with 1.8 million perinatally infected children and adolescents globally (HIV.gov, 2018; Organisation, 2013). Current WHO HIV guidelines recommend universal access to ART(Organization, 2016a). For infected children and adolescents, this means increased life expectancy, and the potential for social, economic, and cultural contributions throughout adulthood.

However, the extent of these contributions and the associated quality of life is tempered by risk for disease-associated cognitive impairment (R. K. Heaton, Marcotte, Mindt, Sadek, Moore, Bentley, McCutchan, Reicks, & Grant, 2004; Organization, 2016b). HIV-associated cognitive impairment persists despite earlier and better ARV access (R. Heaton et al., 2010). Cognitive impairments are associated with mental health problems (e.g., anxiety and depression) and with diminished adaptive functioning (e.g., poor self-care and social communication) (R. K. Heaton, Marcotte, Mindt, Sadek, Moore, Bentley, McCutchan, Reicks, & Grant, 2004) (N. Phillips et al., 2016; Jana L Wachsler-Felder & Charles J Golden, 2002). Hence, persistent and undiagnosed HIV-associated cognitive impairment in children and adolescents has long-term consequences for their academic, occupational, and socioeconomic achievement.

The gold standard for assessing cognitive function, and detecting impairment, is administering a comprehensive neuropsychological battery. Such administration is rarely feasible as a first-line option in low-and middle-income countries (LMICs). Neuropsychological batteries are time-consuming to administer, require specialist training and knowledge to interpret, rely on expensive materials, and hence are not feasible in the already burdened healthcare systems in LMICs. Brief, valid screeners could address these issues, and might assist in ensuring that appropriate specialist assessment and intervention is provided for those at risk of being cognitively impaired (Bloch et al., 2016). Hence, cognitive screening is an essential part of service delivery for this vulnerable group (T. J. Barber et al., 2014).

This study aimed to validate a modified version of the International HIV Dementia Scale (IHDS), as a cognitive screening test for HIV-infected children and adolescents. The IHDS is an easy-to-use and widely employed screening tool that has good psychometric properties in HIV-infected adults (Joska et al., 2011; Sacktor et al., 2005).

Methods

Study design, setting and participants. This was a cross sectional study of children enrolled in the Cape Town Adolescent Antiretroviral Cohort (CTAAC) (Brittain et al., 2018). Perinatally HIV-infected children and adolescents (n=203) were recruited from community health clinics. Inclusion criteria were being between 9-12 years of age, having acquired HIV vertically, having been stable on ART for more than 6 months, and having no history of central nervous system conditions or serious head injury. Age-matched uninfected controls (n=44), from similar socioeconomic backgrounds, were recruited from a local youth clinic.

The CTAAC study was approved by the Human Research Ethics Committee of the University of Cape Town's Faculty of Health Sciences (HREC REF: 051/2013). Parents gave informed consent for their own participation and for their child to participate, and children and adolescents provided informed assent.

Measures and procedures. All study procedures were completed in private rooms within the University of Cape Town (UCT) Department of Psychiatry and Mental Health. Each participant was administered a comprehensive neuropsychological test battery by trained research assistants. All tests (including the y-IHDS) were translated into isiXhosa and back-translated into English to ensure compatibility with the original. The neuropsychological test battery assessed performance within various cognitive domains and included the following tests, among others: the Wechsler Abbreviated Scale of Intelligence (WASI); the Digit Span, Symbol Search, and Digit Symbol-Coding subtests of the Wechsler Intelligence Scale for Children (WISC); the Inhibition and Fingertip Tapping subtests of the NEPSY; and the Children's Colour Trails Test (CCTT) (see Hoare and colleagues (Hoare, Fouche, Spottiswoode, Donald, Philipps, Bezuidenhout, Mulligan, Webster, Oduro, & Schrieff, 2012) for full description).

Each participant also completed the modified version of the IHDS, the y-IHDS (youth-IHDS). Administration followed standard procedures for adults with two exceptions: Adolescents were allowed to practice the words and motor tasks until they were able to complete them correctly at least once before they proceeded with the timed tasks and were asked a yes/no question about whether or not they had ever repeated a grade at school. The y-IHDS is not without limitations, even when administered in adult populations (Haddow, Floyd, Copas, & Gilson, 2013), but of particular note is that sensitivity and specificity may be improved by the addition of screening questions which may tap into cognitive impairment (Joska et al., 2011). To this end, we asked the children and adolescents if they had ever

repeated a grade at school, with responses coded as either *yes* or *no*. Repeating a grade at school has been shown to be an indicator of functional impairment in the school domain (Biederman et al., 2004) and is also associated with cognitive impairment more generally (Nicole Phillips, 2018). We refer to this modified version of the y-IHDS (i.e., a version that features increased practice opportunity on the verbal memory and motor tasks, and that includes the repeated-grades question) as the youth-IHDS (y-IHDS).

The y-IHDS took approximately 3-5 minutes to complete and was administered by trained research assistants. Supplement 1 provides English and isiXhosa test administration guidelines for the instrument. Supplementary videos 1 and 2 demonstrate English and isiXhosa administrations of the instrument.

Parents of the adolescent participants completed measures related to their child's functioning. Here, we analyzed data from two of those measures (the Vinelands Adaptive Behaviour Scale–II (VABS2) (S. S. Sparrow, D. V. Cicchetti, & D. Balla, 2005) and the Child Behaviour Checklist (CBCL)) (Achenbach & Ruffle, 2000) to assess functional impairment in adolescents. Parents also completed basic questionnaires regarding their child's performance at school.

Statistical analysis. We captured all data from the neuropsychological test battery and from the y-IHDS into SPSS (version 25, Armonk, IBM). We used the same software to complete all inferential statistical analyses, with α set at .05 and confidence intervals at 95%.

Calculating variables. Using data from the neuropsychological test battery, we created 10 composite cognitive domain scores (one each for general intellectual functioning, motor coordination, processing speed, attention, working memory, visual memory, verbal memory, visual-spatial ability, language, and executive function) using our previously described theoretical-statistical method (N. J. Phillips et al., 2018). Briefly, we grouped test

outcome variables based on theory regarding the cognitive function they assessed, and then tested the inter-relatedness (internal consistency) of the variables within each group using Cronbach's alpha correlation coefficient. Only those groups with alpha values > .70 were retained. Eight participants were unable to complete some of the neuropsychological tests due to severe cognitive impairment. For these participants, individual composite scores were calculated based on the tests they were able to complete. We scored the y-IHDS as follows: Total score = ((Items 2 +3 + 4) – (Item1)) (see Supplement 1). This scoring of the y-IHDS takes into account school performance. Regarding the behavioural data, adolescents were classified as having functional impairment if either their VABS2 Total score or CBCL Total Competence score was lower than the manual-based cut-off score for impairment.

Descriptives. Regarding descriptive statistics, we conducted between-group comparisons on sociodemographic, cognitive and behavioural data in order to provide an overview of the sample.

As a first step in our inferential analyses, we conducted bivariate correlational analyses (using the Spearman rho's co-efficient for non-normally distributed data) to determine the magnitude of association between y-IHDS score and scores within each composite cognitive domain.

y-IHDS validation process. Next, we followed a four-step process to validate the y-IHDS:

1. We applied the youth HIV-associated neurocognitive disorder diagnostic criteria(Hoare et al., 2016b) to each participant's neuropsychological profile to screen for HIV-associated neurocognitive disorders and to classify each as having either a major neurocognitive disorder (major ND), minor neurocognitive disorder (minor

ND), or no impairment (no ND). The criteria draw on the adolescent's cognitive performance and functional ability, with the taxonomy structured as follows: major ND = performance of >2SD below the mean in two separate cognitive domains, plus the presence of functional impairment; minor ND = performance of >1SD below the mean in two separate cognitive domains, with or without functional impairment; and No ND = no cognitive impairment.

2. We performed a series of cross-tabulations (i.e., y-IHDS *x* youth HIV-associated neurocognitive disorders diagnosis) at various y-IHDS cut-off scores (i.e., 8, 9, 9.5, 10, and 10.5) to determine the ratio of true positives versus false positives, and false negatives versus true negatives.
3. Based on the frequencies obtained at the previous step, we calculated sensitivity and specificity values for each cut-off score using a MedCalc application (https://www.medcalc.org/calc/diagnostic_test.php).
4. We constructed receiver operating characteristic (ROC) curves using the youth neurocognitive disorders classification as the state variable, plotted against the y-IHDS raw scores for major ND, minor ND, and all HIV-associated neurocognitive disorders or impairments.

Between-group comparison. After calculating the optimum cut-off score on the y-IHDS, we used independent-samples *t*-tests to determine if there were significant differences in cognitive performance (estimated using composite cognitive domain scores) between those HIV-infected children and adolescents scoring at or above that cut-off point and those scoring below.

Results

Descriptives. Demographic and clinical characteristics of the adolescents are described in Table 1. Analyses detected no significant between-group differences with regard to age, sex, language, or years of education. However, significantly more participants in the HIV-infected group had repeated at least one grade at school. Regarding the VABS2, there were no significant between-group differences. There was a significant difference seen on the CBCL total competence scores, with the controls displaying better total competence than the HIV-infected group.

Table 2 presents the cognitive data. Analyses detected significant between-group differences for y-IHDS total scores, as well as for score in every cognitive domain except motor coordination. In each case, the healthy control group outperformed the HIV-infected group.

The series of bivariate correlational analyses detected significant positive associations between y-IHDS score and performance in each cognitive domain, except attention (i.e., higher y-IHDS scores were correlated with overall better cognitive performance; see Table 3.)

Table 1: Summary of sample characteristics.

Variable	**HIV-infected (n = 203)**	**Controls (n = 44)**	**t**	**p**	**ES[f]**	**95% CI**
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
VABS[b]: M (SD)	95.19 (22.95)	95.23 (11.14)	0.02	.991	0.002	-7.03 to 7.11
CBCL[c] Competence: M (SD)	37.70 (7.77)	41.16 (7.91)	2.65	.009**	0.444	0.89 to 6.05
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

NOTES: a: number of years of completed formal schooling. b: Vinelands Adaptive Behaviour Scale – II; 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: Summary of sample cognitive domain performance.

Variable	**HIV-infected (n = 203)**	**Controls (n = 44)**	**t**	**p**	**ES[f]**	**95% CI**
y-IHDS[d]: M (SD)	9.33 (1.51)	10.11 (1.15)	3.83	< .001***	0.603	0.44 to 1.48
Cognitive domain: M (SD)						
General intellectual function	-0.54 (.78)	0.00 (.79)	-4.18	< .001***	0.691	0.29 to 0.80
Attention	-0.39 (.92)	0.00 (.92)	-2.55	.013*	0.424	0.08 to 0.69
Motor Coordination	0.02 (.99)	0.00 (.91)	0.13	.862	-0.02	-0.35 to 0.29
Visual memory	-0.49 (.87)	-0.00 (.98)	-3.31	.001**	0.55	0.19 to 0.77
Verbal memory	-0.56 (.67)	-0.00 (.68)	-5.02	.009**	0.834	0.13 to 0.91
Working memory	-0.35 (.89)	0.00 (1.00)	2.32	< .001***	0.385	0.29 to 0.69
Language	-0.38 (1.02)	-0.00 (1.00)	-2.20	.028*	0.374	0.04 to 0.71
Visual spatial ability	-0.52 (1.26)	0.00 (.84)	-2.62	.022*	0.434	0.05 to 0.65
Processing speed	-0.56 (.67)	-0.01 (.68)	-5.02	< .001***	0.819	0.35 to 0.78
Executive function	-0.48 (.67)	0.01 (.60)	-4.42	< .001***	0.744	0.27 to 0.70

Table 3: Correlations of y-IHDS scores with neuropsychological gold standard test measures within the HIV-infected group (N = 203).

Correlation of y-IHDS raw score		
General intellectual function	.383	< .001***
Attention	.040	.540
Motor coordination	.291	< .001***
Visual memory	.300	< .001***
Verbal memory	.416	< .001***
Working memory	.280	< .001***
Language	.266	< .001***
Visual-spatial ability	.331	< .001***
Processing speed	.395	< .001***
Executive function	.422	< .001***

NOTE: Nonparametric bivariate correlations were conducted because 67% of all variables were not normally distributed according to the Shapiro-Wilk test of normality. *$p < .05$. **$p < .01$. ***p < .001.

y-IHDS validation. Based on the youth neurocognitive disorder criteria, we classified 7 participants as having a major ND, 96 as minor ND, and 144 as no ND (or no impairment). Using those classifications, we created the cross-tabulations shown in Table 4 and hence examined the ability of the y-IHDS (at cut-off scores of 8, 9, 9.5, 10, and 10.5, where in each case a score at or below the cut-off indicated impairment) to discriminate between (a) major ND and non-impaired participants, (b) minor ND and non-impaired participants, and (c) any form of ND (major or minor) and non-impaired participants. A y-IHDS cut-off score of ≤9 yielded the best balance between sensitivity and specificity, table 4. However, the cut-off score of ≤10 yielded the best sensitivity (but had poor specificity) and is therefore regarded as the best value for cut-off for the y-IHDS.

Follow-up ROC analyses indicated that, at each the preferred cut-off value of ≤10, the y-IHDS was significantly better than chance at discriminating major ND, minor ND, and any form of ND from no impairment (see Figures 1, 2, and 3). Although the AUC value was acceptable in each case, the strongest of those values (0.859, $p < .001$) was associated with the ability of the instrument to discriminate major ND from no impairment. The ROC for the y-IHDS to screen for any form of ND yielded an AUC of 0.695 ($p = .001$) and for minor ND the AUC was 0. 682 ($p < .001$).

Between-group comparison. Finally, an independent-samples *t*-test detected significant performance differences in each cognitive domain (except attention) between HIV-infected adolescents with y-IHDS scores ≤10 and those with scores >10 (see Table 5).

Table 4: Sensitivity and specificity of the y-IHDS for Major ND, Minor ND and all forms of cognitive impairment (CI) at various cut-off points (N = 247).

Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
y-IHDS ≤ 8						
Control vs. Major	71.43	73.61	11.63	98.15	2.71	0.39
Control vs. Minor	50.53	73.61	55.81	69.28	1.91	0.67
Control vs. CI	51.96	73.61	58.24	68.39	1.97	0.65
y-IHDS ≤ 9						
Control vs. Major	100.00	50.69	8.97	100.00	2.03	0.00
Control vs. Minor	75.79	50.69	50.35	76.04	1.54	0.48
Control vs. CI	77.46	50.69	52.67	76.04	1.57	0.44
y-IHDS ≤ 9.5						
Control vs. Major	100.00	48.61	8.64	100.00	1.95	0.00
Control vs. Minor	77.89	48.61	50.00	76.92	1.52	0.45
Control vs. CI	79.41	48.61	52.26	76.92	1.55	0.42
y-IHDS ≤ 10						
Control vs. Major	100.00	24.31	6.03	100.00	1.32	0.00
Control vs. Minor	93.68	24.31	44.95	85.37	1.24	0.26
Control vs. CI	94.12	24.31	46.83	85.37	1.24	0.24
Control vs. Major	100.00	23.61	5.98	100.00	1.31	0.00
Control vs. Minor	93.68	23.61	44.72	85.00	1.23	0.27
Control vs. CI	94.12	23.61	46.60	85.00	1.23	0.25

NOTE: Shaded rows indicate the cut-off score with the best sensitivity values. PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio.

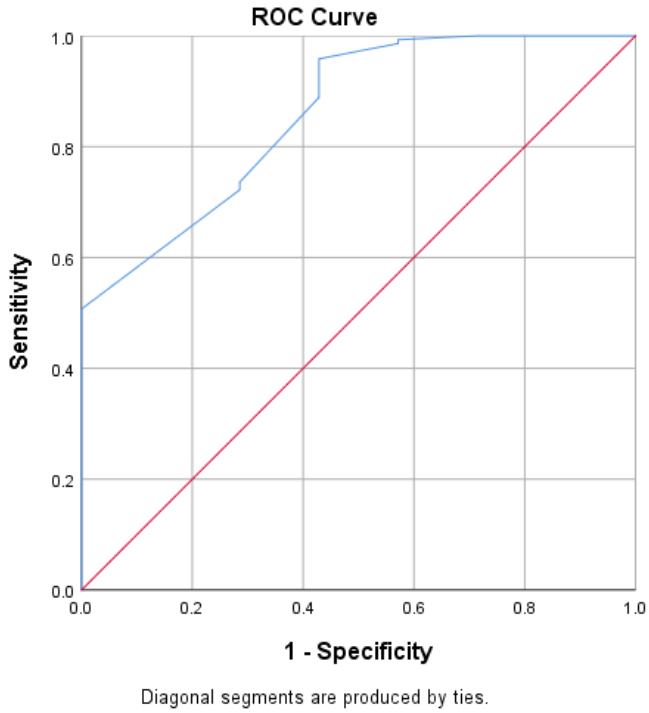

Figure 1. Receiver operating characteristic (ROC) curve for diagnostic ability of the y-IHDS to screen for Major ND (N = 247). Here, the area under the curve (AUC) value = .859, with 95% CI = 0.728 to 0.989.

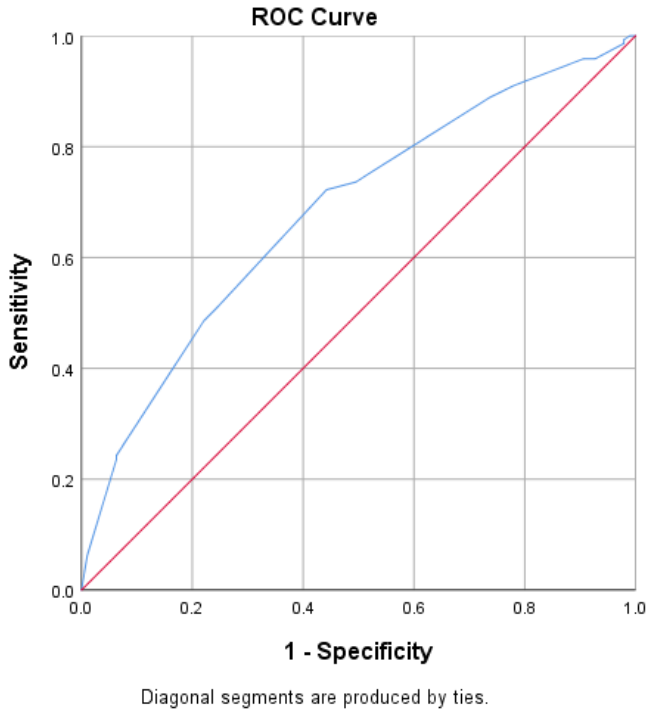

Figure 2. Receiver operating characteristic (ROC) curve for diagnostic ability of the y-IHDS to screen for Minor ND (*N* = 247). Here, the area under the curve (AUC) value = .682, with 95% CI = 0.615 to 0.750.

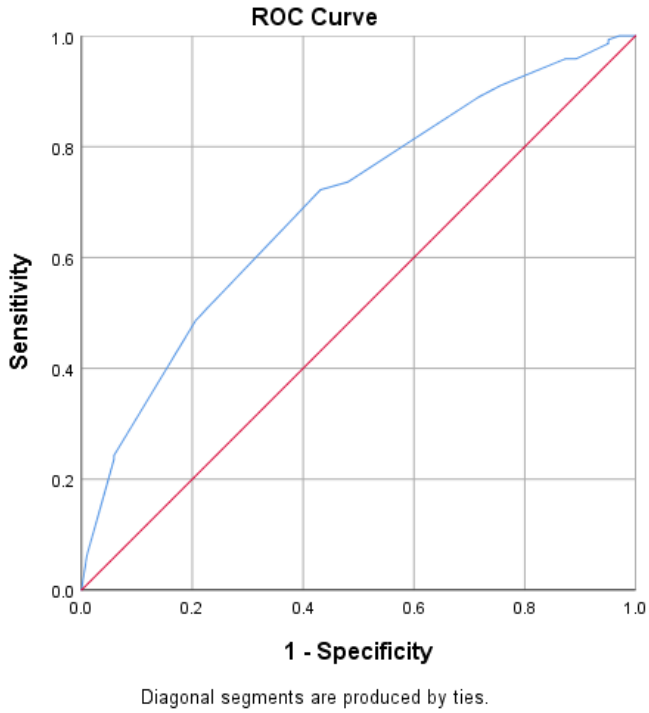

Figure 3. Receiver operating characteristic (ROC) curve for diagnostic ability of the y-IHDS to screen for all form of HIV-associated cognitive impairment (*N* = 247). Here, the area under the curve (AUC) value = .695, with 95% CI = 0.629 to 0.760.

Table 5: Cognitive differences between HIV-infected participants, when separated into groups based on the recommended y-IHDS cut-off score (i.e., ≤10) (N= 203)

Cognitive domain	MD[a]	*t*	*p*
General intellectual functioning	0.583	3.963	< .001***
Attention	-0.184	-1.019	.309
Motor coordination	0.806	4.342	< .001***
Visual memory	0.355	2.125	.035*
Verbal memory	1.219	5.210	< .001***
Working memory	0.237	1.978	.049*
Language	0.895	3.050	.003**
Visual spatial ability	0.517	3.046	.003**
Processing speed	0.561	4.517	< .001***
Executive function	0.547	4.357	< .001***

NOTE: a: Mean Difference.
*p < .05. **p < .01. ***p < .001.

Discussion

This study aimed to validate an adapted version of the International HIV Dementia Scale (the Youth IHDS, or y-IHDS) as a cognitive screening test for HIV-infected children and adolescents. Our analyses found that, at a cut-off score of ≤10, the instrument had good sensitivity but low specificity in discriminating children and adolescents with HIV-associated cognitive impairment from those with unimpaired function, but also displayed high negative predictive ratios, suggesting that the y-IHDS as a screening tool correctly excludes participants without cognitive impairment.

Our validation process encompassed four steps. At the first step, we found that 46% of HIV-infected participants could be classified as displaying either a major (3%; *n*=7) or a minor (43%; *n*=88) ND. The proportions of participants with either a minor or major ND are slightly lower to those previously found in a smaller cohort(Hoare et al., 2016b) comparable to the CTAAC sample. Although it may seem that the rates of major ND are declining, subtle or minor forms of neurocognitive impairment may go undetected, and therefore a validated quick screening tool for all forms of, neurocognitive impairment encompassing major and minor ND, is needed.

Of note is that 18% of HIV-negative controls (*n*=8) were classified as having a minor neurocognitive disorder, consistent with prior reports (Hoare et al., 2016b). The relatively high rate of minor neurocognitive impairment in controls may be a result of socioeconomic disadvantage resulting in, for instance, malnutrition and a lack of stimulating home environments (Grantham-McGregor et al., 2007). Of that group of 144, 103 had some form of functional impairment without any cognitive impairment. In these cases, their functional impairment could be caused by factors other than their cognitive ability (for example; behavioural problems or ADHD).

At the second validation step, we found that at the lowest y-IHDS cut-off score (i.e., 8) the rate of true positives was lower than that of false positives. At higher cut-off scores, (i.e., 9, 9.5, 10, and 10.5), however, the rate of true positives was higher than that of false positives. Screening tools should be optimized to minimise false negative and false positive results. Considering the rates of cognitive impairment we observed in this cohort, it becomes important to minimize the rates of false negatives when screening for neurocognitive disorders. High rates of false negatives would provide an incorrect representation of the extent of the problem in real-world terms. High false negatives also mean that there is the potential to miss cases who need further intervention. Reducing false positives is also important in a low resource setting as it is not feasible to conduct full neuropsychological testing on individuals who may not require it.

We found that a cut-off of 9 produced the best balance between sensitivity and specificity, but that a cut-off of 10 gave higher sensitivity. We recommend using the cut-off of ≤10 because the associated NPV value is 85%, which means at this cut-off we can correctly exclude cases of no cognitive impairment. In the public health context of SA (and other low-resource settings), the ideal is to reduce false negatives and identify as many true positive cases as possible because in the long-term public health costs of false negatives is potentially higher than the cost of assessing false positive cases (Franchini, Pieroni, Passino, Emdin, & Molinaro, 2018). In this case, we could therefore accept a screening tool with high sensitivity and relatively poor specificity.

In a setting like South Africa, where the rates of HIV-associated neurocognitive disorders are high, one would rather run the risk of over screening as opposed to under screening and possibly missing cases which require further assessment and intervention. A high sensitivity of at least 80% is recommended for screening (Sacktor et al., 2005),

therefore, based on these results and taking into account the high rates of all forms of HIV-associated cognitive impairment and the high NPVs, a cut-off score of ≤10 is suggested as optimal so as not to falsely exclude cases.

For the fourth and last step in the validation process, our ROC analyses findings suggest that using a y-IHDS cut-off score of ≤10 yields a moderate diagnostic accuracy for detecting all forms of cognitive impairment and minor ND. Furthermore, using a y-IHDS cut-off score of ≤10 yields a high diagnostic accuracy for detecting major ND. These findings also demonstrate that the y-IHDS can discriminate between two groups (Zweig & Campbell, 1993) (in this case between no impairment and having a form of cognitive impairment).

Overall, these results suggest that the use of the y-IHDS could be valuable in both clinical practice and research. Specifically, our results suggest that y-IHDS is a valid screening tool for neurocognitive disorders in HIV-infected children and adolescents. Early detection of HIV-associated neurocognitive disorders, using an instrument such as the y-IHDS, should be combined with early initiation of ARVs (WHO Treat All policy has been implemented by 70% of low- and middle-income countries (Ford, Vitoria, & Doherty, 2018)) and other elements of a multidisciplinary interventions approach to optimize long-term health, and minimize occupational health and safety risks, of infected children and adolescents (Dobroszycki et al., 2017; Flynn, 2018).

The current findings are especially relevant to clinicians working in low-resource settings with high HIV prevalence rates. The benefits of having an effective screening tool that can be administered by lay professionals and that can detect the risk of all forms of HIV-associated cognitive impairment may enable rapid screening and referral of children and adolescents, and alleviate pressure on already overburdened healthcare systems (Cysique, Murray, Dunbar, Jeyakumar, & Brew, 2010). Of particular note here is that administration,

scoring, and interpretation of the y-IHDS does not require specialist training. It takes a maximum of 5 minutes to administer and score and requires only minimal resources (a paper and pen).

The fact that higher numbers of HIV-infected participants compared to the HIV-uninfected controls were included for logistical reasons related to the larger study, may be seen as a study limitation; however, these groups were well matched, and the types of analyses performed here are not sensitive to unequal sample sizes or unequal variances between the groups. A limitation is that although all the measures on the neuropsychological test battery were translated and back-translated into isiXhosa and administered in the participant's preferred language, we did not validate this battery. However, these tests were selected based on their widespread usability in adolescents in low-resource settings, taking into consideration their reported psychometric properties (Hoare et al., 2016b). We also took steps to ensure that the battery was administered in accordance with the International Test Commission Guidelines(Bartram, 2001).

More research into possibly adding cognitive screening questions to the y-IHDS will strengthen the findings here and may possibility produce a tool which is even more suited to screening for HIV-associated cognitive impairment in children and adolescents. Adding cognitive screening questions to the IHDS has been shown to improve the sensitivity and specificity in adult populations (Gouse, Casson-Crook, Decloedt, Joska, & Thomas, 2017a).

In conclusion, this study shows that the y-IHDS, at a cut-off score of ≤10 may be a useful and quick screening tool to assess the risk of all forms of HIV-associated neurocognitive disorders in perinatally infected children and adolescents. We recommend that the instrument be considered for addition to The Western Cape Consolidated Guidelines for HIV Treatment (HIV/AIDS/STI/TB Directorate, 2015) for children and adolescents

(Provincial Government of the Western Cape Department of Health, 2015). Although these guidelines recommend neurocognitive screening as part of the monitoring process for children and adolescents, the recommended tool only assesses neurodevelopment in children up to the age of 6 years. In contrast, the y-IHDS can be administered to children aged 9 years and older and is suited for use throughout adolescence.

Supplement 1

Youth International HIV Dementia Scale (y-IHDS)

Blue script – read this as it appears to the patient
Black script – administrator notes, do not read this to the patient

Today we are going to be doing a quick activity which will give us really useful information. Some parts of the tasks will be easy, others parts will be difficult. You are not expected to get everything right. Just try to do the best you can.
I'm going to time some parts of the tests and write the answers down.
If you don't understand something, please ask me to explain it again.
Do you have any questions? (answer any questions the participant might have without going into too much detail about what the y-IHDS entails)
Which hand do you use most of the time? (make a note of the patient's dominant hand) For all these tasks we are going to use your opposite hand (point to the patient's non-dominant hand) Okay, let's get started.

y-IHDS English

1. Screen for cognitive/functional impairment.
Have you ever repeated a grade at school? (please circle appropriate)

YES = 1 point
NO = 0 points

Memory registration – read words to patient at 1 word per second.
I am going to read four words to you: dog, hat, bean, read. Please repeat the words back to me. (do this until the participant recalls all four words).
Good. I am going to ask you to repeat these words again later.

2. Motor speed – demonstrate finger tapping of non-dominant hand as follows: open and close the first finger and thumb as widely as possible.
Please can you do the same with your first two fingers of your non-dominant hand like this (show), you need to do it as widely and as quickly as possible (do this until the patient gets it correct).
Good. Now I am going to time you. When I say go, tap your first two fingers as widely and as quickly as possible. Ready? (wait for ready signal from patient)
Go! (start timer and count the number of correct taps and assign scores according to scale below)

4 points = 15+ correct taps in 5 seconds
3 points = 11-15 correct taps in 5 seconds
2 points = 7-10 correct taps in 5 seconds
1 point = 3-6 correct taps in 5 seconds
0 points = 0-2 correct taps in 5 second ___ / 4

3. Psychomotor speed – demonstrate the hand sequence of non-dominant hand as follows: clench hand in fist on flat surface, then put hand flat on surface with palm down, then put hand perpendicular to flat surface on the side of the 5th digit.
Please can you do the same with your non-dominant hand like this (show), you need to do it as quickly as possible (do this until the patient gets it correct).
Good. Now I am going to time you. When I say go, do the hand movements as quickly as possible. Ready? (wait for ready signal from patient)
Go! (start timer and count the number of correct sequences and assign scores according to scale below)

4 points = 4 correct sequences in 10 seconds
3 points = 3 correct sequences in 10 seconds
2 points = 2 correct sequences in 10 seconds
1 point = 1 correct sequences in 10 seconds
0 points = unable to perform correct sequences in 10 seconds ___ / 4

4. Memory recall – ask patient to recall the words given at the start, if the participant cannot recall the words a semantic clue can be given as follows: animal (for dog), piece of clothing (for hat), vegetable (for bean) and colour (for red).
Please can you tell me the four words I gave you at the start of this task? (count the number of correct words recalled without prompting and assign scores according to the scale below)

4 points = all 4 words recalled without prompting
3 points = 3 words recalled without prompting
2 points = 2 words recalled without prompting
1 point = 1 words recalled without prompting
½ point = for each word recalled after prompting with semantic clue
0 points = unable to recall any words with and/or without prompting ___ / 4

Total score: _____

y-IHDS scoring: Add items 2 to 4 and subtract item 1 to give a total score out of 12 points.
For example: (item 2 + item 3 + item 4) - (item 1)
Patients scoring 10 or less should be evaluated for further possible cognitive impairment/disorder.

Youth International HIV Dementia Scale (y-IHDS)

Umbhalo oblue/ozuba - funda oku njengoko kubonakala kwisigulana.

Umbhalo omnyama – amanqaku kumlawuli; musa ukusifundela oku isigulane

Namhlanje sizakwenza umsebenzi ngokukhawulweza ozakusinika ulwazi olulunceda nyani. Ezinye iinxalenye zalomsebenzi zizakuba lula, ezinye iinxalenye zizakuba nzima. Awulindelekanga uchane yonke into. Zama nje ukwenza konke onako ukukwenza.

Ezinye zeenxalenye zovavanyo ndiza kuzimisela ixesha kwaye ndibhale iimpendulo phantsi.

Ukuba kunento ongayiqondiyo, nceda undibuze ukuze ndikucacisele kwakhona.

Ingaba unombuzo? (phendula nawuphi na umbuzo asenokuba nawo umthabathi-nxaxheba ngaphandle kokungena nzulu kwiincukacha malunga noko kuqukwa yi y-IHDS)

Sesiphi isandla osisebenzisa rhoqo? (Chaza ngokubhala phantsi esona sandla asisebenzisa rhoqo) Kuyo yonke le misebenzi, siza kusebenzisa esi sandla ongasisebenzisi rhoqo (Khomba esi sandla isigulane esingasisebenzisi rhoqo).

Kulungile ke, masiqalise.

y-IHDS isiXhosa

1. Screen for cognitive/functional impairment.

Wawukhe waphinde ibanga? (please circle appropriate)

Ewe = 1 amanqaku
Hayi = 0 amanqaku

Memory registration – fundela isigulane igama elinye kumzuzwana ngamnye.

Ndizakufundela amagama amane: inja, umnqwazi, imbotyi, bomvu. Nceda undiphindele lamagama ngokuvakalayo. (yenza oku de isigulane siwakhumbule omane amagama)

Kulungile ke. Ndizakucela uwaphinde lamagama kwakhona ngelinye ixesha kamva.

2. Motor speed – bonisa ukubethaniswa kweminwe yesandla angayisebenzisi rhoqo ngokulandelayo: vula uze uphinde uvale ucikicane nobhontsi kakhulu kangangoko unako.

Ndicela wenze ngokufanayo ngeminwe yakho emibini yokuqala yesandla ongayisebenzisi rhoqo ngoluhlobo (mbonise), kufuneka uvule kakhulu nangokukhawulezisa kangangoko unako (yenza oku de isigulane sikwenze ngokuchanekileyo).

Kulungile. Ngoku ndizakubekela ixesha. Xa ndisithi qalisa, bethanisa iminwe yakho emibini yokuqala ngokuvulekileyo nangokukhawuleza kangangoko unako. Ingaba ukulungele? (lindela umqondiso obonisa ukuba isigulane sikulungele)

Qalisa! (qalisa ixesha elibalayo uze ubale ukubethana kweminwe okuchanileyo, uze wabele amanqaku ngokwesikali esingezantsi)

4 amanqaku = 15 + yokubethana okuchanileyo ngemizuzwana e5

3 amanqaku = 11-15 yokubethana okuchanileyo ngemizuzwana e5

2 amanqaku = 7-10 yokubethana okuchanileyo ngemizuzwana e5

1 inqaku = 3-6 yokubethana okuchanileyo ngemizuzwana e5

0 amanqaku = 0-2 yokubethana okuchanileyo ngemizuzwana e5 ___ / 4

3. Psychomotor speed – bonisa isigulane iintshukumo ngokulandelelanayo kwisandla angasisebenzisi rhoqo ngokulandelayo: shwabanisa isandla sibelinqindi phezu kwendawo ethe tyaba (eflet), wolule impama yesandla phezu kwendawo ethe tyaba (eflet), ubeke isandla ngecala kwindawo ethe tyaba ngecala likacikicane.

Ndicela wenze ngokufanayo ngeminwe yakho emibini yokuqala yesandla ongasisebenzisi rhoqo ngoluhlobo (mbonise), kufuneka wenze ngokukhawulezisa kangangoko unako (yenza oku de isigulane sikwenze oku ngokuchanekileyo)

Kulungile. Ngoku ndizakubekela ixesha. Xa ndisithi qalisa, yenza iintshukumo zesandla ngokukhawuleza kangangoko unako. Ukulungele? (lindela umqondiso obonisa isigulane sikulungele)

Qalisa! (qala ixesha elibalayo uze ubale ulandelelwano oluchanekileyo uze wabele amanqaku ngokwesikali esingezantsi)

Amanqaku amane (4) = 4 yolandelelwano oluchanekileyo ngemizuzwana e10

Amanqaku amathathu (3) = 3 yolandelelwano oluchanekileyo ngemizuzwana e10

Amanqaku amabini (2) = 2 yolandelelwano oluchanekileyo ngemizuzwana e10

Inqaku elinye (1) = 1 yolandelelwano oluchanekileyo ngemizuzwana e10

Iqanda /Akukho nqaku (0) = akakwazanga ukwenza ulandelelwano oluchanekileyo ngemizuzwana e10 ___ / 4

4. Memory recall/Inkumbulo – cela isigulane siphinde amagama amane ebesiwanikwe ekuqaleni, ukuba isigulane asiwakhumbulo amagama, ungamnika intluva ngoluhlobo: isilwanyana (endaweni yenja), into enxitywayo/impahla (endaweni yomnqwazi), imifuno (endaweni yembotyi) nombala (endaweni yobomvu).

Ingaba ungakwazi ukundichazela lamagama mane bendikuchazele wona ekuqaleni kwalomsebenzi? (bala amaqama aye wawakhumbula ngaphandle kokumphembelela uze wabele amangqaku ngokwesikali esingezantsi)

Amanqaku amane (4) = ukuba uwakhumbule omane (4) amagama ngaphandle kokuncediswa

Amanqaku amathathu (3) = amagama amathathu (3) awakhumbule ngaphandle kokuncediswa

Amanqaku amanini (2) = amagama amabini (2) awakhumbule ngaphandle kokuncediswa

Inqaku elinye (1) = igama elinye (1) alikhumbulileyo ngaphandle kokuncediswa

Isiqingatha (½) senqaku = ngegama ngalinye alikhumbulileyo emveni kokuba aye wanikwa intluva

Iqanda /Akukho nqaku (0) = ukuba akakwazanga ukukhumbula igama ngokunokwakhe kwaye/okanye encediswa ngentluva ___ / 4

Amanqaku ewonke:

_____

y-IHDS ukunikwa kwamanqaku: Dibanisa u 2 ukuya ku 4 uthabathe u 1 akunike isiphumo samanqaku angaphakathi ku 12.

For example: (item 2 + item 3 + item 4) - (item 1)

Izigulane ezifumana amanqaku angu 10 okanye ngaphantsi, kufuneka ziphononongelwe ukuphazamiseka kwendlela yokucinga (cognitive impairment/disorder).

Video 1 and 2: y-IHDS administration videos in English and isiXhosa

https://drive.google.com/open?id=1xt_SzYqU_YTHOcDfUqHffxHMafr2SbDb

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CHAPTER 7: SUMMARY AND CONCLUSION

This thesis has addressed three major issues in the field of paediatric NeuroAids, locally and globally; namely: 1) how to accurately assess cognitive impairment in a manner which is both child and adolescent sensitive, 2) how to assess functional impairment related to HIV-associated cognitive impairment and 3) how to quickly and accurately screen for the risk of HIV-associated neurocognitive disorders in perinatally HIV-infected youth. The systematic review and meta-analysis found that cognitive domains most severely impaired are that of executive function, working memory and processing speed. The composite cognitive domain scores were more accurate in their assessment of the youth's real-world cognitive ability, than a global cognition score. Cognitive impairment was significantly associated with three out of four measures of functional impairment and all four measures of functional impairment were associated with an increased risk of having functional impairment in the presence of cognitive impairment. The y-IHDS displayed a high sensitivity for screening for NCD at a cut-off score of ≤10 (which represents a cut-off score lower than that recommended for adults) and is suitable for cognitive screening in children and adolescents.

Using standardized instruments to assess cognitive function may eliminate some confounders, however, these instruments have not been validated for use in the low to middle income settings. Low- and middle-income countries are dependent on cognitive measures which are imported from high-income countries and these measures are then applied to our context and populations with little to no contextual adaptations (Mwaura & Marfo, 2011). Using control or comparison data which is "generally representative, is representative of none" according to Shuttleworth-Edwards (2016), who extensively highlights the pitfalls of standard IQ testing in a

multicultural setting, like South Africa (Shuttleworth-Edwards, 2016). In addition to a lack of appropriate norming data, many researchers have long recognized the need for assessments which are fair both cross culturally and cross socio-economic status (Ardila, 1995; Carter et al., 2005; Hackman & Farah, 2009; Jukes & Grigorenko, 2010; Rosselli & Ardila, 2003; Sirin, 2005).

Some experts in the field may argue that global deficit scores (GDS) are preferred over domain scores (Blackstone et al., 2012; C. Carey et al., 2004; C. L. Carey et al., 2004; Woods et al., 2004). The GDS encompasses the number and severity of cognitive deficits, giving more weight to areas with impairment and less to areas within normal performance range (C. L. Carey et al., 2004). This approach may be suited to adult who have already attain full cognitive ability before the HIV insult. However, this method may not be appropriate for perinatally HIV-infected children and adolescent who are still in the developmental phase of their cognition. Using the GDS system in children and adolescent will only provide a picture of their deficits and not their strengths (or domains which are less affected by the virus).

The method used to derive the composite cognitive domains scores in chapter 4 of this thesis provides a method which, in the absence of culturally and socio-economically fair standardized instruments, may most accurately assess cognitive impairment. This method, which can be applied in various settings and using varying neuropsychological test batteries, encompasses both the youth's age and developmental level, as well as provides a detailed picture of the child or adolescents cognitive functioning in different domains. This publication is openly accessible, and researchers are encouraged to use this method, or similar, to assess HIV-associated cognitive impairment in their unique settings.

HIV-associated NCD have consequences for overall functional impairment (Hoare et al., 2016b). There are no HIV-specific measures of functioning available to

assess functioning in children and adolescent infected with the virus. We are thus reliant on instruments which measure general functioning in childhood and adolescence. The relationship between these measures of functioning and cognitive impairment have, until now, been under-studied. In chapter 5 of this thesis a strong and significant association between various gold standard measures of functional impairment (in the case of the CBCL, VABS2 and repeated grades) and the degree of cognitive impairment was found. I also found that the participants had an increased risk of having functional impairment (on all measures of functional impairment; CIS, CBCL, VABS2 and repeated grades) when they also had cognitive impairment which was assessed using the youth HIV-associated neurocognitive diagnostic criteria (Hoare et al., 2016b). These measures also displayed good psychometric properties within our sample, as shown in both the confirmatory factor analyses to confirm the factor structure of each measure and Cronbach's alpha tests for internal consistency. These findings suggest that the CIS, CBCL, VABS2 and repeated grades are appropriate for assessing functional impairment within our sample. There is also further evidence for assessing repeated grades at school as a quick assessment of possible risk for cognitive and functional impairment in perinatally HIV-infected children and adolescents.

The pinnacle of this thesis is the validation of a quick screening tool for risk of NCD in HIV-infected children and adolescents, namely; the Youth International HIV Dementia Scale (y-IHDS). Chapter 6 of this thesis shows that the y-IHDS is suitable for screening for cognitive impairment in children and adolescents, and as noted above, this brief (3-5 minute) and valid screening tool could alleviate the assessment burden in low-resourced healthcare systems. Rapid and accurate screening might assist in ensuring that appropriate specialist assessment and intervention is provided for those at risk of being cognitively impaired (Bloch et al., 2016). Hence, cognitive

screening should be made an essential part of service delivery for this vulnerable group (T. J. Barber et al., 2014).

The findings of this thesis will be shared with the South African Western Cape Government Department of Health (DoH) and Department of Education (DoE). This will provide useful information to all government employees associated with both healthcare and education about the extent of HIV-associated cognitive and functional impairment in children and adolescents. Sharing these findings will also facilitate the rollout of the use of the y-IHDS in health and education settings to accurately screen for HIV-associated cognitive impairment in children and adolescents. Youth who are screened as having a high risk of cognitive impairment, can then be referred for further clinical assessment and appropriate health and educational interventions can be put in place for these individuals.

The y-IHDS, while suitable and valid in its current state, could be improved by adding cognitive screening questions. This could help to increase both the sensitivity and specificity of the tool. We have started to address this by including 5 cognitive screening YES/NO type questions to the end of the y-IHDS. The questions are as follows:

1. Have you been more forgetful compared to other children in your class or your friends? For example: you can't remember things/stuff like your classmates can.
2. Are you more easily distracted compared to other children in your class or your friends? For example: you cannot pay attention for very long like your classmates can.

3. Have you noticed that you think more slowly compared to other children in your class or your friends? For example: it takes you longer to find a solution to a problem than it normally would take your classmates.
4. Have you noticed that your hands are clumsy, compared to your classmates/friends? For example: you drop things more.
5. Do you move slower than your classmates/friends? For example: you can't get up fast, or it takes you longer to do thing/stuff.

These questions have been adapted for administering to children and adolescent from a paper recently published by Gouse et al. (Gouse, Casson-Crook, Decloedt, Joska, & Thomas, 2017b). This adaptation of the y-IHDS is currently being administered to participants in the longitudinal arm of the CTAAC study. This provides us with longitudinal data to test the rate of deterioration/stability/improvement of NCD in adolescents and also a way to test the sensitivity and specificity of the adapted y-IHDS in the same sample of children. We have also partnered with Prof Lucie Cluver and this adaption to the y-IHDS is being administered to participants in her HIV-infected adolescent cohort in the Eastern Cape. Having data from adolescents living in the Eastern Cape will provide us with an opportunity to compare the patterns of HIV-associated cognitive impairment in adolescents from different geographical locations in South Africa.

At the time of submitting this thesis my primary supervisor, Prof Jackie Hoare, was awarded a new NIH R01 grant titled: Improving Assessment for Neurocognitive Impairment Among Perinatally HIV Infected Youth (NASA). I have been appointed as the research project manager for this study. This study aims to validate a tablet-based screening tool, called NeuroScreen, for cognitive impairment in HIV-infected

adolescents. This work allows us to further our research into new and improved ways for screening for HIV-associated cognitive impairment in adolescents.

We are currently also brainstorming ideas for a potential new study which will focus on assessing real-world and practical functional impairment in HIV-infected adolescents. The current self-report measures we have available to us are general in their focus and are not HIV-specific. In other words, these measures do not assess the adolescents' ability to manage their HIV (e.g.: medication management, remembering and attending clinic appointments, managing stigma, etc). Assessing HIV-related functioning is important in this cohort as HIV is a chronic condition the adolescent will be required to manage into adulthood.

Limitations

This study has a number of limitations. First, the study is cross-sectional and thus unable to describe the long-term outcomes of HIV on cognitive and functional impairment in perinatally infected children and adolescents. Second, there are no published neuropsychological tests norms for sub-Saharan Africa, all our analyses of the neuropsychological test performances were compared against our own HIV-uninfected control group, which in the absence of standardized norms is likely the most accurate "normative data" for our specific context. Third, although all the measures on the neuropsychological test battery were translated and back-translated into isiXhosa and administered in the participant's preferred language, we did not validate this battery. However, these tests were selected based on their widespread usability in adolescents in low-resource settings, taking into consideration their reported psychometric properties. Fourth, all measures related to the child/adolescents' functional impairment are self-report (parent-rated). Numerous

studies have reported on the problems related to making clinical diagnoses on the basis of self-reported measures, as noted in earlier chapters. Lastly, a smaller number of control participants were included in this study compared to higher numbers of HIV-infected participants. This is due to logistical reasons related to the larger study within which this study was nested. Fortunately, the types of analyses performed in chapters 4-6 are not sensitive to potential violations to heterogeneity of variance.

Recommendations for clinical practice and future research

Several important clinical issues should be considered as a result of this research. Perinatally infected children and adolescents need comprehensive, multidisciplinary and coordinated care that includes screening for HIV-associated neurocognitive disorders and overall functional problems, as found in this study. Children and adolescents presenting with risk factors such as low CD4, high viral load, failing first line ART and scholastic difficulties should be offered cognitive screening with the y-IHDS as part of routine HIV care and referrals should be made to supportive services or formal assessments where appropriate (Laughton et al. 2013).

HIV-infected children and adolescents are likely to face future physical and psychological health consequences related to the cognitive and functional impairment (Domek 2009). Care of perinatally HIV-infected youth needs to take into account the fact that their parents are also HIV-infected, and this case, the compounded effects of HIV and HIV stigma on the family, surpasses that of all other chronic conditions. In instances where youth are orphaned by HIV, their primary caregivers are often extended family members or foster homes, integration into the new family and education around HIV may be needed. Practical solutions around screening for HIV-associated neurocognitive disorders and functional impairment should go hand-in-hand with the scale-up of ARV accessibility in South Africa. These include mental

health services, community education, school-based programs, collaboration with the Department of Education, and strengthening families to provide a safe and secure home environment for HIV-infected children and adolescents (Domek 2009). Together with offering these services to HIV-infected youth, education around the effects of HIV on the cognitive and functional impact the virus has on them needs to be given to teachers, clinic staff and allied healthcare professionals who are most frequently in contact with these youths. Integrating maternal, neonatal, child health and nutrition services, including family planning is recognized as a key strategy to reduce child and adolescent HIV morbidity and mortality, and to control the HIV epidemic (Lindegren et al. 2012).

Regarding future research, an update is recommended for the systematic review and meta-analysis of cognitive impairment in perinatally infected children and adolescents. Systematic reviews may become out of date as new research is published. It is recommended by Cochrane that reviews are updated at least every two years (Green & Higgins, 2005).

There is a lack of longitudinal cohort studies designed to assess the long-term outcomes of HIV on cognitive functioning in HIV infected older children and adolescents. The CTAAC study is a longitudinal study which is currently in the late stages of collecting 3-year follow up data. The baseline data for the CTAAC study are presented in this study, and planning is underway to investigate the longitudinal outcomes of this cohort with regards to cognitive impairment.

Research into scale validation and neuropsychological test norms are very much needed in South Africa, and sub-Saharan Africa at large. Specifically, validation of functional impairment measures and research into the cross-cultural fairness of neuropsychological tests within the South African context.

More can be done to improve the sensitivity and specificity of the y-IHDS. A recent study into the validation of the IHDS for use in adults showed that both the sensitivity and specificity of the tool could be improved by the addition of cognitive screening questions (Gouse et al., 2017a). This is already being addressed as part of the 3-year follow-up data collection on the CTAAC project as mentioned above.

The quality of life of HIV-infected children and adolescents can be greatly improved by both cognitive and functional rehabilitation programs. While pharmacological interventions, like cART, offer better immunological stability, there remains unanswered questions regarding its neuroprotective ability against cognitive decline (Ellis et al., 2011). Some early clinical trials testing the effects of neuro-enhancing drugs have found only small effects (McMahon et al., 1997; N. Sacktor et al., 2001). The inherent problem with interventions that focus only on pharmacological treatment of cognitive impairment, is that it is dependent on and confounded by nonadherence (Hinkin et al., 2001). Successful neuro-rehabilitative interventions should employ multimodal strategies.

An area of increased focus is that of cognitive and behavioural rehabilitation. Cognitive rehabilitative programs are classed as either restorative or compensatory (Weber, Blackstone, & Woods, 2013). There is a paucity of studies looking specifically at neuro-rehabilitation in HIV-infected children and adolescents. New research has shown that even HIV-uninfected but exposed children are at risk for cognitive impairment (M. E. Rice & Harris, 2005), and this cohort could possibly also benefit from rehabilitation programs. Future research should focus on improving the quality of life of HIV-infected and affected individuals, given their extended life expectancy due to greater ARV coverage (Judd et al., 2018).

Conclusion

This work is highly relevant to South Africa, and other low- and middle-income parts of the world, where prevalence of perinatal HIV is high. The findings of this thesis provides low-resourced countries with methods to explore HIV-associated cognitive impairment in youth is a context appropriate manner, and provides high-resourced countries with a perspective which would enable them to tailor their measure for cross-cultural applicability. This study has made four important contributions to the field of child and adolescent neuroAids. First, a systematic review and meta-analysis provides a summary of literature (up to October 2016) regarding HIV-associated cognitive impairment in perinatally infected children and adolescents. Second, a child- and adolescent-sensitive method for assessing cognitive impairment in various cognitive domains is statistically tested and shown to be more accurate than global assessments. This method can be easily applied in different settings and with differing neuropsychological test batteries. Third, the associations between functional impairment and cognitive impairment are established, as well as showing that children and adolescents with HIV-associated cognitive impairments are at increased risk for also having functional impairment. It also provides evidence for assessing school performance as a measure for possible functional and cognitive impairment. Fourth, and finally, a screening tool to screen for the risk of HIV-associate cognitive disorders in perinatally infected children and adolescents is validated. The y-IHDS requires minimal resources and is based on a screening tool for adult HIV-associated cognitive disorders that is already widely-used globally. Hence, this brief, cost-efficient, and valid screening tool may be a useful addition for clinicians and allied healthcare professionals working in resource-poor contexts where adolescent HIV is highly prevalent. In South Africa, adding the y-IHDS to the Western Cape Consolidated Guidelines for HIV Treatment for children and adolescents would greatly improve our

accuracy when referring youth for neuropsychological assessment and treatment. Accurately screening for HIV-associated neurocognitive disorders in this vulnerable group could also help to alleviate public health burden but ensuring that youth at risk are identified early on so that interventions may be implemented where appropriate. Given that the y-IHDS can be administered by a wide range of healthcare and allied professionals also somewhat alleviates burden on the HIV-specific healthcare workforce. The y-IHDS should be tested and validated in other sub-Saharan African countries so that it may be incorporated into their own unique healthcare systems as well.

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