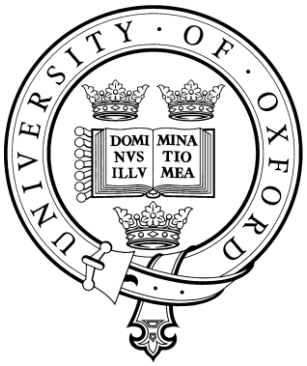
Exploring the relationship between HIV and executive function in adolescents, and testing the feasibility of a music intervention aiming to improve executive function in HIV-positive adolescents in rural South Africa



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A thesis submitted for the degree of Doctor of Philosophy

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Abstract

Executive function (EF) is an umbrella term for a group of related yet distinguishable cognitive functions responsible for flexibly controlling and directing attention and behaviour. EF is important in the top-down control of decision-making and the ability to direct attention towards the fulfilment of long-term goals. EF, particularly in emotive contexts, is still developing during adolescence. EF may also be affected negatively by various threats to optimal EF development, including depression and HIV infection. Immature or suboptimal EF may predispose to risk-taking behaviour, including risky sexual behaviour and substance use, which in turn increases the risk of HIV transmission and poorer health and socioeconomic outcomes.

I have three major hypotheses which are explored in this thesis. Firstly, I hypothesise that there is a relationship between HIV and poorer EF in adolescents. Secondly, I hypothesise that poorer EF is associated with increased risky sexual behaviour and substance use in adolescents, and lower adherence to treatment in HIV-positive adolescents. Thirdly, I propose that musical training, particularly group drumming, is a feasible and acceptable intervention to enhance EF and mood in HIV-positive adolescents.

The thesis begins with an introduction to the relevant concepts and background literature (Chapter 1) before presenting a systematic review and meta-analyses of EF in HIV-affected children and adolescents globally (Chapter 2). It then shifts to the region of interest, rural South Africa, and presents the validation of a tablet-based EF assessment tool (Chapter 3) followed by a cross-sectional study assessing the relationship between EF and risk-taking behavioural outcomes, including behaviourally acquired HIV, in late adolescent females (Chapter 4). Finally, musical training is explored as a potential intervention to improve EF. A literature review on musical training and EF, and the potential socio-emotional effects of group drumming (Chapter 5) provides the background to a feasibility trial assessing the feasibility and acceptability of a group drumming intervention aiming to improve EF in HIV-positive adolescents in rural South Africa (Chapter 6). The thesis concludes with a general discussion chapter which integrates the findings and considers potential future directions (Chapter 7).

Study 1 found evidence for EF deficits in perinatally acquired HIV; evidence was limited for behaviourally acquired HIV. Study 2 found that the OCS-EF is a valid and feasible tool for measuring EF reliably amongst adolescents in rural South Africa. Study 3 found that EF is only weakly associated with certain risky behavioural outcomes, and that adolescents with

behaviourally acquired HIV may only have limited EF deficits relating to verbal working memory. Study 4 found that a group drumming programme is a feasible and acceptable intervention amongst HIV-positive adolescents in rural South Africa, with promising effects on psychosocial wellbeing, including mood, but no effects on EF.

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List of abbreviations

ADHD
attention-deficit/hyperactivity disorder, 92
ART
antiretroviral therapy, 38
AUDIT
Alcohol Use Disorders Identification Test, 230
BBB
blood-brain barrier, 39
BHIV
behaviourally HIV-infected, 44
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EF
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HDSS
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HPTN
HIV Prevention Trials Network, 24
HSV-2
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LFK index
Luis Furuya-Kanamori index, 58
LMICs
low- and middle-income countries, 42
MRC
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MSPSS
Multidimensional Scale of Perceived Social Support, 229
NGO
non-governmental organisation, 217
OCS-EF
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PHIV
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PHU
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PTSD
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standardised root mean squared residual, 128

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ToC
Theory of Change, 208
Wits
University of the Witwatersrand, 109

Declaration

I, Kirsten Rowe, declare that this thesis is my own work completed for the degree of a Doctor of Philosophy at the University of Oxford. Some of the work in this thesis is currently under review for potential publication in peer-reviewed journals. A list of manuscripts (in preparation or undergoing peer review for publication) associated with this body of work is provided on page 26. I have permission from the co-authors to publish this work in my thesis. The contributions of collaborators on each study are listed on page 25.

Chapters 3 and 4 contain secondary data analysis from the HPTN 068 study. Permission to use this data for these analyses was provided by the HIV Prevention Trials Network (HPTN).

I have no conflicts of interest to declare.

Statement of contributions

Study 1

Dr Ruta Buivydaite (RB), Dr Torben Heinsohn (TH) and Dr Mana Rahimzadeh (MR) were my co-reviewers for this systematic review. I screened all records for inclusion; TH and MR each screened half the records for inclusion independently. MR and TH helped me select the final studies for inclusion. RB, MR and TH checked the data extraction tables. RB and I did independent quality assessments on all included studies and resolved discrepancies together.

Studies 2 and 3

Dr Audrey Pettifor was the principal investigator on the HIV Prevention Trials Network 068 (conditional cash transfer) study which the data for Studies 2 and 3 came from and conceptualised the original parent study. Professors Kathleen Kahn and Stephen Tollman, directors at the MRC/Wits Agincourt Research Unit where the data was collected, assisted with the initial conceptualisation of Study 3. Professors Nele Demeyere and Gaia Scerif selected, and Dr Mihaela Duta developed the tasks for inclusion in the Oxford Cognitive Screen – Executive Function version used in Studies 2 and 3.

Study 4

My music collaborators, Doctors Andeline dos Santos and Sonkanise ka Nkosi, helped me to develop the core components of the music intervention. Sonkanise also helped to train the fieldworkers to facilitate the group drumming intervention. Dr Alecia Nickless, statistician, assisted with the statistical analysis plan. Ms Julia Ruiz Pozuelo,

DPhil student, performed the data analysis in parallel with me as an independent analyst to minimise the risk of bias and error for trial publication.

Manuscripts associated with the thesis

1. Executive function in HIV-affected children and adolescents: a systematic review with meta-analyses (submitted)
2. Validation of OCS-EF, a tablet-based executive function assessment tool for use in low- and middle-income countries, amongst late adolescent females in the HPTN 068 cohort (submitted)
3. The relationship between executive functioning, risky behaviour and HIV in adolescent females from the HPTN 068 study (submitted)
4. The AHEAD Study: a randomised controlled feasibility trial of a group drumming programme aiming to improve executive function in HIV-positive adolescents (in preparation)

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Chapter 1: Background

Chapter outline:

1.1. Introduction

1.2. Adolescence

1.3. Executive function and its relevance

- 1.3.1. What is executive function?
- 1.3.2. What predicts executive function in children and adolescents?
- 1.3.3. Why is executive function important?
- 1.3.4. Can executive function be changed?

1.4. HIV and executive function

1.5. HIV and adolescence

1.6. Research gap

1.7. Research hypotheses

1.8. Overview of chapters

1.1. Introduction

This thesis focuses on the relationship between executive functioning (EF) and HIV in adolescents and the development and testing of a music intervention aiming to enhance EF in HIV-positive adolescents in rural South Africa. EF includes a group of cognitive processes that are important for self-control and focusing attention. EF enables people to plan and regulate their behaviour including the suppression of temporary impulses to achieve long-term goals. Poorer EF during adolescence may be associated with the development of psychological disorders (e.g. depression). Poorer EF may also predispose to risky sexual behaviour and substance use. Risky sexual and substance use behaviour may increase the risk of acquiring or transmitting

HIV in high prevalence communities or contexts. Poorer EF may thus be associated with an increased risk of HIV infection during adolescence. Many of these negative behavioural outcomes (e.g. substance use disorder) may in turn influence EF negatively which can lead to vicious reinforcing cycles. Better EF is associated with superior health and socio-economic outcomes.

EF is still maturing during adolescence and may thus be more malleable to improvement with interventions to promote EF development through positive neuroplasticity. Various factors may influence the development of EF positively or negatively during adolescence. HIV infection is one of the factors that may influence EF development negatively. HIV is often associated with other risk factors for poorer EF including psychological disorders and living in low socio-economic status (SES) households. These risks may be magnified in low-income contexts e.g. rural South Africa where there are multiple threats to optimal EF development (see section 1.3.2). HIV-positive adolescents, particularly in low-income contexts, thus comprise a vulnerable population at heightened risk of poor outcomes. They therefore need supportive interventions to improve EF, and hopefully their outcomes more broadly. Group musical training, particularly group drumming, may be one such intervention.

The rest of this chapter will consider adolescence as a key period for intervention, EF and its relevance in adolescence, how HIV infection might influence EF development, and the theoretical and epidemiological background to HIV in adolescence. It will then describe the research gap, thesis hypotheses and an overview of the thesis chapters.

1.2. Adolescence

In this thesis, I focus on adolescence because it is a critical period of development. It is a time of enormous biological, psychological and social change beginning with the onset of puberty. It represents the transition from childhood to adulthood during which there is growing autonomy and independence from one's family of origin. Relationships with peers and partners become increasingly valued with their opinions generally mattering the most. Adolescence is a period of exploration when people generally become sexually active and may start using alcohol and other substances. Adolescence plays a vital role in determining the future life trajectories of individuals during adulthood and the trajectories of their offspring, the next generation (G. C. Patton et al., 2018; G. C. Patton et al., 2016). It is a period of heightened risk for acquiring HIV, particularly amongst adolescent females in sub-Saharan Africa, and a period during which many psychological and substance use disorders emerge; however, it also represents a period of opportunity for intervening to improve outcomes for this generation and the next generation (Davidson, Grigorenko, Boivin, Rapa, & Stein, 2015; G. C. Patton et al., 2016). Intervening during adolescence represents an investment in human capital development for the future (*World Development Report 2007: Development and the Next Generation*, 2007).

There is a move to extend the definition of adolescence, which the World Health Organisation currently defines as 10-19-years-old, to include the 10-24-year-old age group (Kinghorn, Shanaube, Toska, Cluver, & Bekker, 2018; Sawyer, Azzopardi, Wickremarathne, & Patton, 2018). In this thesis, I adopt this extended definition. From a cognitive neuroscience perspective, brain maturation continues into the twenties

(Tamnes et al., 2017) and 20-24-year-olds, late adolescents, continue to face unique health threats that are different from children and adults, particularly with regards to HIV (Daniels, 2017; Kinghorn et al., 2018).

Adolescents are a vulnerable group prone to high-risk sexual and substance use behaviour because of ongoing underlying neural changes affecting cognitive development. The frontal lobes, including the prefrontal cortices which are important for EF, undergo protracted development (increased axonal myelination with increased white matter density; synaptogenesis and synaptic pruning with decreased grey matter density) throughout adolescence into early adulthood (Blakemore & Choudhury, 2006). EF is thus still developing during this important period of brain maturation (Casey, Getz, & Galvan, 2008; Kuhn, 2006; Luna, 2009; Sowell, Trauner, Gamst, & Jernigan, 2002; Steinberg, 2005; Tau & Peterson, 2010).

1.3. Executive function and its relevance

1.3.1. What is executive function?

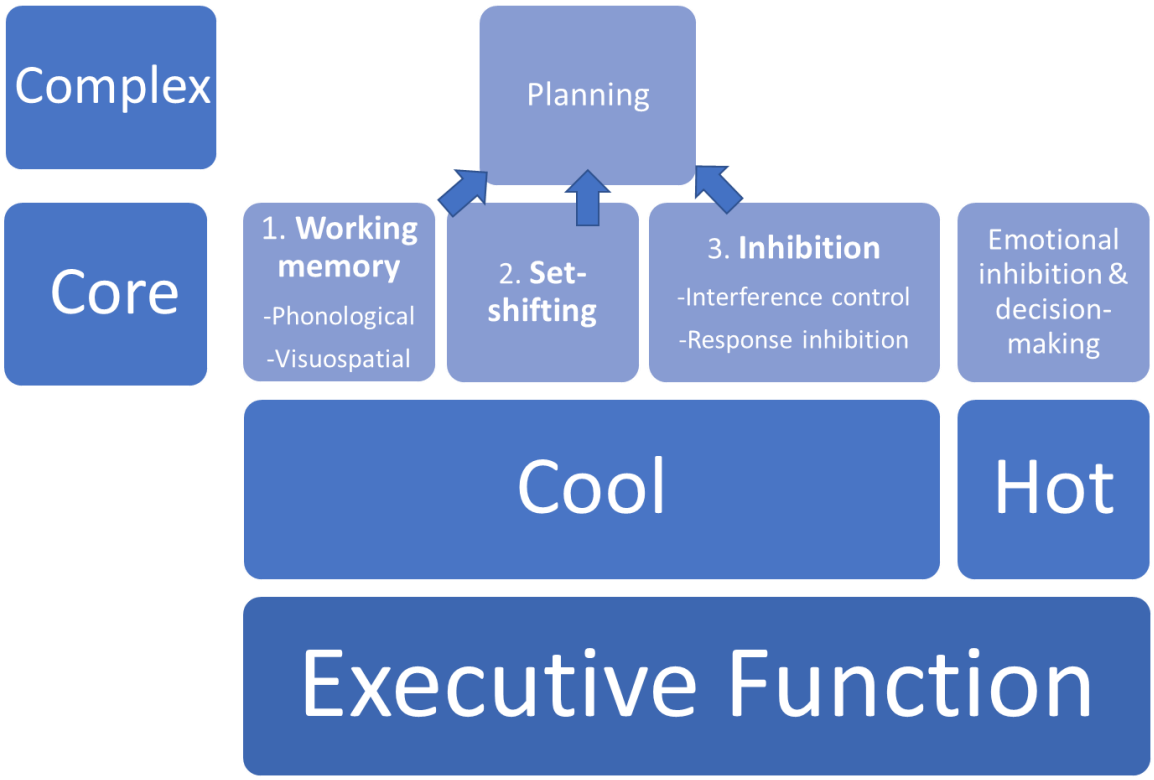


Figure 1. An overview of executive function

EF is a group of control processes in the brain which regulates cognition and behaviour. The components of EF are thought to be unified in preschool-aged children and differentiate during the transition to adolescence (C. Hughes, Ensor, Wilson, & Graham, 2010; Shing, Lindenberger, Diamond, Li, & Davidson, 2010; Wiebe, Espy, & Charak, 2007). Three separable core EF components of inhibition (inhibitory control), working memory, and set-shifting (task switching) emerge during adolescence (Diamond, 2013; Li et al., 2015; Miyake et al., 2000). Inhibition includes response inhibition (the ability to inhibit prepotent or automatic responses) and interference control (the ability to ignore a distractor or interfering stimulus) (Diamond, 2013).

Working memory involves maintaining (storage) and manipulating (processing) information that is held in mind (Baddeley, 2010). Set-shifting involves shifting from one previously learned rule or behavioural pattern to a new, different rule or pattern. These EF components are related yet distinguishable (Miyake & Friedman, 2012; Miyake et al., 2000). These core EF components contribute to higher-order or complex EF such as planning, sequencing, problem-solving and adapting behaviour in response to new information (Diamond, 2013). A distinction can also be made between EF in emotionally neutral contexts ("cool EF"), generally mediated by the dorsolateral prefrontal cortex, and EF in emotionally charged contexts or situations ("hot EF"), generally mediated by the orbitofrontal cortex (Poon, 2017; Philip David Zelazo & Carlson, 2012). See Figure 1 for an overview of EF.

The various components of EF develop at different rates during childhood and adolescence with hot EF having a more prolonged developmental course (Blakemore & Choudhury, 2006; Casey & Caudle, 2013; Prencipe et al., 2011). Self-regulation, particularly in emotionally charged contexts (hot EF), is still maturing during adolescence, while sensation seeking and sensitivity to social reward peak (Albert, Chein, & Steinberg, 2013; Botdorf, Rosenbaum, Patrianakos, Steinberg, & Chein, 2017; Steinberg et al., 2017). According to the dual systems model (see Figure 2), the imbalance between these two systems (sensation seeking and self-control) during adolescence predisposes adolescents to risk-taking behaviour. Adolescents are thus more likely to engage in risky sexual behaviour and substance use, particularly in the

presence of peers (Knoll, Magis-Weinberg, Speekenbrink, & Blakemore, 2015; Shulman et al., 2016).

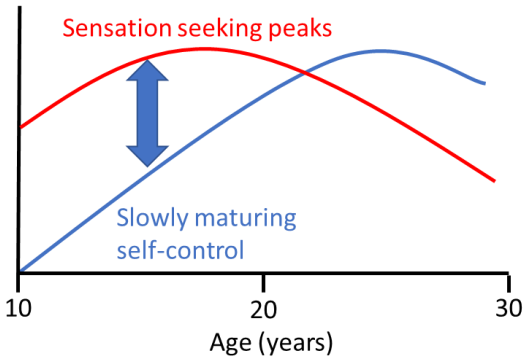


Figure 2. Figure demonstrating Steinberg's dual systems model of adolescent risk-taking which explains how adolescent risk-taking results from the mismatch between sensation seeking which peaks during adolescence and immature self-control which is still maturing slowly throughout adolescence and only reaches maturity in the mid-twenties. Figure adapted from (Steinberg et al., 2017).

The successful development of EF (top-down processes) is necessary to achieve resilience and to avoid emotionally driven or impulsive behaviour (bottom-up processes). This will help avoid the associated risks that may otherwise emerge during adolescence e.g. HIV, depression, and substance use disorders (see Figure 3).

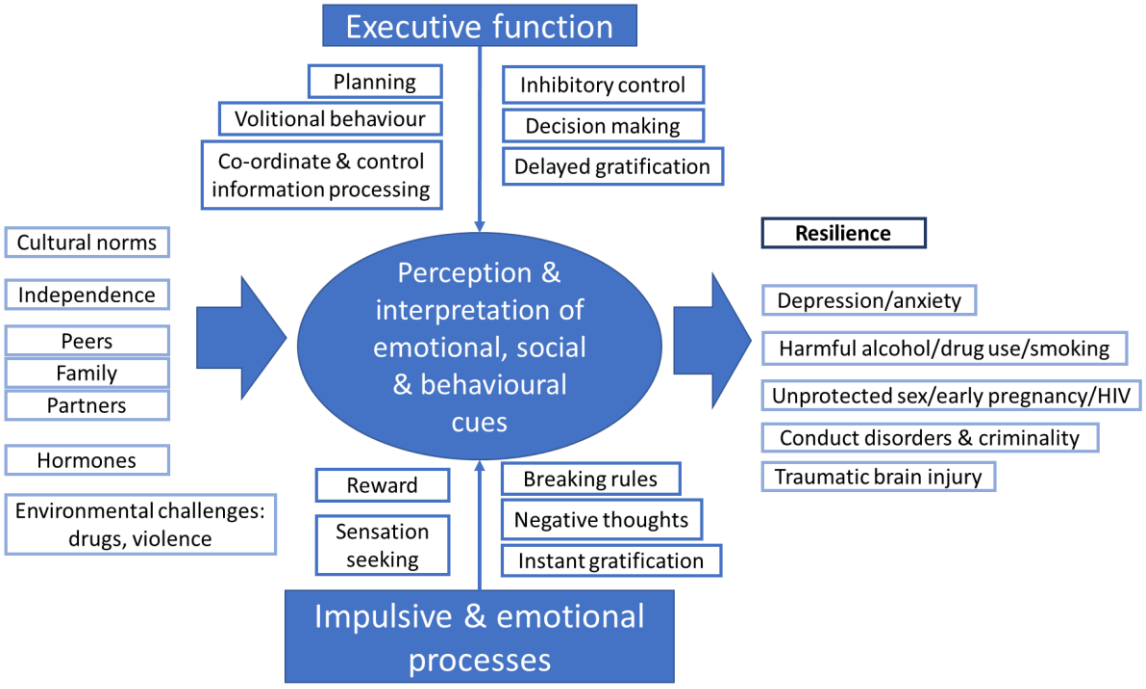


Figure 3. Diagram demonstrating the interaction between top-down processes involving executive function and self-control, and the bottom-up impulsive and emotionally driven processes in the regulation of the biological, psychological and social challenges of adolescence (left of the diagram). It shows a range of potential outcomes (right of the diagram) with the desired outcome being resilience. Figure adapted from (Davidson et al., 2015).

The relationship between EF and risky behaviour in adolescents is explored in Study 3 (chapter 4) and Study 4 (chapter 6) of this thesis.

1.3.2. What predicts executive function in children and adolescents?

EF is predicted by genetic and environmental factors and their interplay (Deater-Deckard, 2014; van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011). Maternal EF predicts child EF, likely due to genetic[1] and environmental mechanisms (Cuevas et al., 2014; Naomi P. Friedman et al., 2008). Many perinatal factors which may be more common in the context of HIV-affected pregnancies (e.g. intrauterine growth

[1] Executive function was found to be highly heritable in twin studies in the US (Friedman et al., 2008).

restriction, preterm birth, excessive alcohol exposure in utero, maternal antenatal anxiety, postnatal depression) may be associated with poorer child EF later in childhood or adolescence (Buss, Davis, Hobel, & Sandman, 2011; Desmond et al., 2012; Dos Reis et al., 2015; Kingdon, Cardoso, & McGrath, 2016; Pearson et al., 2016; Peltzer, Rodriguez, & Jones, 2016; Taylor & Clark, 2016; Tideman, Maršál, & Ley, 2007). Early life stress during childhood (e.g. low household SES (Hackman & Farah, 2009), malnutrition (J. F. Cohen, Gorski, Gruber, Kurdziel, & Rimm, 2016; Kar, Rao, & Chandramouli, 2008; Koss et al., 2010), child abuse (Watts-English, Fortson, Gibler, Hooper, & De Bellis, 2006), exposure to trauma (DePrince, Weinzierl, & Combs, 2009), early institutional care (Bos, Fox, Zeanah, & Nelson, 2009), and caregiver depression (C. Hughes, Roman, Hart, & Ensor, 2013)) has been associated with poorer child EF (Loman & Gunnar, 2010) and a higher risk for later depression and anxiety (Schiavone, Colaianna, & Curtis, 2015). Depressive disorders, common in HIV-positive adolescents (Judd et al., 2016; Kim et al., 2015), are often associated with poorer EF (Rubin & Maki, 2019; Semkovska et al., 2019). Childhood disease, including HIV and cerebral infections, may also be associated with poorer EF (Anderson, Anderson, Grimwood, & Nolan, 2004; John et al., 2008; Phillips et al., 2016).

Clinical disorders may affect EF components differentially depending on the specific disease process and the timing of the insult relative to their developmental stage. Earlier brain insults are generally associated with poorer outcomes, particularly if they occur during “critical periods” of frontal lobe development (Jacobs, Harvey, & Anderson, 2007). Skills emerging at the time of the insult tend to be more vulnerable

than already established skills (Anderson et al., 2010). A recent meta-analysis examining EF in adults with behaviourally acquired HIV found larger effect sizes for working memory than for inhibition and set-shifting suggesting that HIV infection might be associated with a particular pattern of EF deficits (K. A. Walker & Brown, 2018). In this thesis, this is explored with reference to perinatally acquired HIV and HIV acquired behaviourally during adolescence.

1.3.3. Why is executive function important?

EF predicts important outcomes including: academic achievement (Best, Miller, & Naglieri, 2011); occupational outcomes and income status (Miller, Nevado-Montenegro, & Hinshaw, 2012; Moffitt et al., 2011); obesity (Koike, Hardy, & Richards, 2015; Schlam, Wilson, Shoda, Mischel, & Ayduk, 2013); substance use and even future criminal behaviour (Moffitt et al., 2011). Better EF may be protective against depression, a major course of morbidity which may be independently associated with more risk-taking, lower adherence and poorer outcomes (Agoston & Rudolph, 2016; Davidovich et al., 2016; Mellins et al., 2009; Murphy, Durako, et al., 2001; Murphy, Wilson, Durako, Muenz, & Belzer, 2001).

Poorer EF is highly relevant in the context of HIV treatment and the prevention of transmission. It has been associated with increased sexual risk-taking behaviour (Rosenberg et al., 2018) and decreased adherence to treatment (Garvie et al., 2017) which is likely to worsen disease control. Outcomes associated with EF in adolescents are explored further in this thesis.

1.3.4. Can executive function be changed?

EF may be amenable to intervention in populations with EF deficits (Philip David Zelazo & Carlson, 2012). The hope is that improved EF will contribute to better outcomes; however, improved EF on behavioural tasks may not transfer to improved EF in daily life and/or be sufficient to result in behavioural change. Various activities and programmes have been assessed as potential interventions to enhance EF development in children. Some of the interventions include computerised cognitive training (Holmes, Gathercole, & Dunning, 2009; Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009), aerobic physical activity (Alvarez-Bueno et al., 2017; Kamijo et al., 2011), martial arts (Lakes & Hoyt, 2004), musical training (Bergman Nutley, Darki, & Klingberg, 2014; Moreno et al., 2011), mindfulness practices (Smalley et al., 2010), and classroom curricula (Diamond, Barnett, Thomas, & Munro, 2007). Similarly, interventions to rehabilitate or improve EF in children with diseases associated with EF deficits have been tested with varying degrees of success (Bangirana et al., 2009; Cerrillo-Urbina et al., 2015; Klingberg et al., 2005). The potential malleability of EF using interventions in HIV-affected children and adolescents is explored in this thesis in Study 1 (Chapter 2), a systematic review and Study 4 (Chapter 6), a feasibility trial.

1.4. HIV and executive function

HIV-1, the main subtype globally, is a neurotropic virus which enters the central nervous system (CNS) early after infection. It infects macrophages and microglia, immune cells in the CNS, and may be associated with neurocognitive impairment (Dunfee et al., 2006). Before antiretroviral therapy (ART) was available, more severe

forms of HIV-associated neurocognitive disorder (HAND), e.g. HIV encephalopathy in infants and children and HIV-associated dementia in adults, were more common (Cooper et al., 1998; Epstein et al., 1986). Now that ART is available, these severe forms are less common but milder forms of neurocognitive impairment, e.g. mild neurocognitive disorder or asymptomatic neurocognitive impairment, persist and are common (Clifford & Ances, 2013; Dunfee et al., 2006; Saylor et al., 2016). In a South African study, 45% of perinatally HIV-infected adolescents had neurocognitive impairment (Hoare et al., 2016). Host genetic factors may influence susceptibility to HAND with the CCR5wt/delta-32[2] genotype being protective (K. K. Singh et al., 2003).

The aetiology of HAND in adolescents is likely multifactorial with various biological, psychological and social factors playing a role (Crowell, Malee, Yogev, & Muller, 2014). Proinflammatory cytokines and toxic effects of viral proteins may facilitate HIV crossing the blood-brain barrier (BBB). HIV can have a direct neurological impact through triggering ongoing neuroinflammation which may persist despite ART. Macrophage, microglial and potentially astrocyte activation results in the release of chemokines that may affect neuronal function adversely. These inflammatory processes may result in excitotoxic neuronal injury with impaired synapse formation (Crowell et al., 2014). Plasma markers of residual systemic inflammation have also been associated with aspects of neurocognition in HIV-positive children and adolescents (Eckard et al., 2017; Kapetanovic et al., 2014). There may be residual symptoms from static, irreversible CNS insults before the adolescent started ART

[2] CCR5, C-C chemokine receptor type 5, is a protein on the surface of certain white blood cells that HIV uses to enter the cell.

(Crowell et al., 2014). There may also be incomplete CNS virological suppression. There may even be viral escape with ongoing viral replication in the CNS despite adequate ART with plasma virological suppression (Chahroudi, Wagner, & Persaud, 2018) or compartmentalisation with a genetically distinct virus in the CSF compared to the plasma (Dahl et al., 2013; Sturdevant et al., 2012). Finally, ART neurotoxicity may contribute to HAND. Efavirenz, one of the most commonly used antiretrovirals and still part of first-line ART in South Africa, is potentially neurotoxic with neuropsychiatric side effects being common (Ciccarelli et al., 2011; Treisman & Kaplin, 2002). All these pathophysiological mechanisms have the potential to disrupt normal cognitive development in children and adolescents with HIV.

Neuroimaging studies are helping to define structural and functional brain abnormalities associated with HIV infection. Adult studies suggest that cortico-striatal networks, particularly fronto-striatal, may be the most vulnerable to HIV-related neuropathology with findings including reductions in grey matter volume, white matter abnormalities and altered resting state functional connectivity variably affecting the cognitive control network, ventral attention and default mode networks (Kamat et al., 2014; Melrose, Tinaz, Castelo, Courtney, & Stern, 2008; Ortega, Brier, & Ances, 2015; Spies, Ahmed-Leitao, Fennema-Notestine, Cherner, & Seedat, 2016; Thomas, Brier, Snyder, Vaida, & Ances, 2013). Similarly in HIV-positive children and adolescents, findings have included: reductions in global or regional grey matter volume (mainly in the frontal, temporal and insular regions, and cerebellum) with Yu et al. finding further reductions in the right prefrontal, parietal and motor areas after a year of follow-up relative to controls (Lewis-de los Angeles et al., 2017; Nwosu et al., 2018; Yu et al.,

2019); reduced gyrification (Nwosu et al., 2018); deformed subcortical structures (Lewis-de los Angeles et al., 2016); white matter abnormalities (variably affecting the corpus callosum, corticospinal tract, inferior fronto-occipital fasciculus, superior and inferior longitudinal fasciculi, and right forceps minor) which may become more extensive with time despite ART and virological suppression (Hoare et al., 2012; Jankiewicz et al., 2017). The involvement of areas playing a role in EF suggest that it might be particularly vulnerable in HIV infection.

Psychosocial risk factors may also contribute to the increased risk of poorer EF. Psychologically, adolescents may have only recently found out their HIV status and be adjusting to the diagnosis of a lifelong, stigmatised disease which may impact their intimate relationships (Mavhu et al., 2013). They may have to cope with internalised stigma affecting their self-esteem negatively, and negative evaluation or treatment by peers with the potential psychological trauma of isolation or bullying due to their status (L. D. Cluver, Gardner, & Operario, 2008; Mburu et al., 2014). They may also live in households affected by high levels of stress due to parental loss, poverty and food insecurity, violence, and substance abuse, all of which may be associated with poorer mental health and EF (Hermetet-Lindsay et al., 2017; Hochhauser, Gaur, Marone, & Lewis, 2008; Mavhu et al., 2013; Mellins & Malee, 2013; Nabunya & Ssewamala, 2014; Ramaiya et al., 2016).

A systematic review and meta-analysis of cognitive impairment in perinatally acquired HIV found that EF and processing speed are the main cognitive domains in which HIV-positive cases performed more poorly than HIV-unaffected controls (Phillips et al., 2016). Processing speed is not considered part of EF, but a slow processing speed

may affect performance on time-dependent EF task measures. Behaviourally acquired HIV may also be associated with certain EF deficits in adolescents (Nichols et al., 2013). This is explored further in Study 1 (Chapter 2) and Study 3 (Chapter 4) in this thesis.

1.5. HIV and adolescence

Most young people with HIV live in low- and middle-income countries (LMICs); 84% live in sub-Saharan Africa (UNAIDS, 2018a). South Africa has the largest HIV epidemic globally with 7.2 million people and 19% of 15-49-year-old people living with HIV (UNAIDS, 2018a). It is a generalised epidemic in this region; however, adolescent females are one of the high-risk groups. 15-24-year-old adolescent females account for 67% of new infections in this age group (UNICEF, 2018). Access to life-saving ART has increased, meaning that many people are now surviving and living with HIV as a chronic, manageable disease; however, it is still a leading cause of death amongst young people in Africa and globally. HIV-positive adolescents consist of a mixed cohort of those who have grown up with vertically transmitted HIV i.e. acquired perinatally from their mothers, and those who acquired it behaviourally. In a Southern African context, behaviourally acquired infection during adolescence is usually transmitted through unprotected sex (UNAIDS, 2016). Age-disparate sexual relationships between young women and older men are an important driver of the epidemic (Evan et al., 2016; Maartens, Celum, & Lewin, 2014; Schaefer et al., 2017). It is often transactional sex i.e. motivated by the assumption that sexual involvement with an older, usually wealthier partner, will result in his giving her favours, gifts,

money or other material provision (Kilburn et al., 2018; Stoebenau, Heise, Wamoyi, & Bobrova, 2016).

I focus on HIV-positive adolescents in this thesis because they tend to have poorer outcomes than HIV-positive adults. HIV-positive adolescents are less likely to be accessing ART and more likely to be non-adherent when on ART (MacPherson et al., 2015; Zanoni, Archary, Buchan, Katz, & Haberer, 2016). They are therefore less likely to achieve disease control (as indicated by virological suppression or an undetectable serum viral load). Disease control is important for the health of HIV-infected individuals and to prevent HIV transmission to their sexual partners or children (MacPherson et al., 2015; UNAIDS, 2018b; Zanoni et al., 2016). Adolescents often struggle with the transition from paediatric to adult services and are harder to retain in care which can lead to poorer outcomes (Bernays, Jarrett, Kranzer, & Ferrand, 2014; MacPherson et al., 2015).

There are various subpopulations of HIV-affected adolescents included in this thesis. The first two subpopulations are HIV-positive; the second two are HIV-negative, but still affected by HIV and at risk of acquiring HIV.

HIV-positive:

1. **Perinatally HIV-infected** (**PHIV**) adolescents: adolescents who acquired HIV during the period shortly before, during or after their birth from an HIV-infected mother or from being breastfed by an infected caregiver (‘vertical’ transmission). In this thesis, adolescents diagnosed with HIV before the age of 10 years are

assumed, if mode of transmission is not reported, to have been infected perinatally. This population is examined in Studies 1 and 4 (Chapters 2 and 5).

2. **Behaviourally HIV-infected** (**BHIV**) adolescents: adolescents who acquired HIV behaviourally, usually through sexual or substance use behaviour ('horizontal' transmission). In this thesis, adolescents who were diagnosed with HIV from the age of 10 years onwards are assumed to have been infected behaviourally, if not reported. This definition is not without complications: this is because some adolescents with perinatally acquired HIV may have only been diagnosed during adolescence, because up to a third of HIV-positive people are 'slow progressors' and have a much slower progression of immune deterioration and development of symptoms (McHugh et al., 2016). This population is examined in Studies 1 and 3 (Chapters 2 and 4).

HIV-negative:

3. **Perinatally HIV-exposed uninfected** (**PHEU**) adolescents: adolescents who were exposed to HIV, and possibly ART, perinatally through their mothers being HIV-infected during pregnancy and/or lactation but who did not become infected perinatally. They are still at risk of acquiring HIV behaviourally (Mellins et al., 2011). This population is examined as a control group in Study 1 (Chapter 2).
4. HIV-affected **perinatally HIV-unexposed uninfected** (**PHU**) adolescents: adolescents who were not perinatally HIV exposed or infected but who currently live in an HIV-affected household where a caregiver and/or sibling is infected with HIV. They are still at risk of acquiring HIV behaviourally. This population is examined as a control group in Study 1 (Chapter 2).

1.6. Research gap

Although EF is predictive of important outcomes and emerging as the cognitive domain in which there may be deficits in HIV-positive adolescents on ART, there are few studies focused specifically on EF in HIV-affected adolescents, especially from LMICs. The associations between different EF components and both perinatally and behaviourally acquired HIV have not been clearly characterised. In order to characterise EF profiles, valid and sensitive measures to assess EF at scale in HIV-endemic settings are needed. Factors associated with and potentially predictive of EF deficits in these populations need to be delineated as these may point to potential mechanisms and targets for intervention. Potential consequences of EF deficits also need to be explored. This will help provide the rationale for intervening. Finally, locally relevant and scalable cognitive rehabilitation interventions need to be developed and tested in HIV-endemic settings such as South Africa.

1.7. Research hypotheses

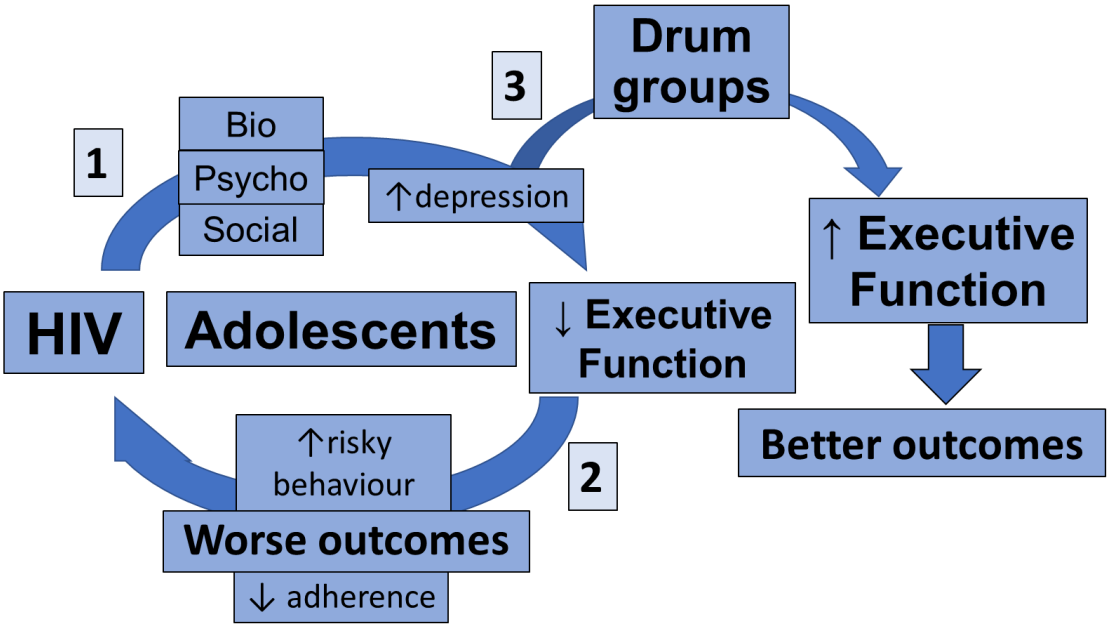


Figure 4. Summary of the three major research hypotheses

I have three major research hypotheses which are summarised diagrammatically in Figure 4 and listed below.

1. The relationship between HIV and EF in adolescents with HIV

1. EF deficits are more common in HIV-positive adolescents.
    1.1. If HIV infection occurs early in the life course, the EF deficits are greater; therefore, adolescents with vertically transmitted HIV acquired perinatally have larger and more global deficits than adolescents with later behaviourally acquired HIV.
    1.2. EF deficits are related partly to the influence of HIV, a neurotropic virus, on the brain and partly to associated risk factors that are commonly found in HIV-affected households.

1.2.1. Markers of more advanced disease or uncontrolled disease are associated with poorer EF in HIV-positive adolescents.

1.2.2. EF deficits in HIV-positive adolescents are more marked when compared to HIV-unaffected controls than when compared to HIV-affected controls.

1.2.3. Perinatally HIV-exposed uninfected adolescents have mild EF deficits compared to healthy HIV-unaffected adolescents.

1.3. Perinatally acquired HIV is associated with a distinct pattern of EF deficits with effect sizes varying by EF component.

1.4. Behaviourally acquired HIV is associated with a distinct pattern of EF deficits with effect sizes varying by EF component.

2. The relationship between EF and risk-taking behaviour in adolescents

2.1. EF deficits are associated with increased risky sexual behaviour and substance use.

2.2. EF deficits are associated with lower adherence to ART in HIV-positive adolescents.

3. The development and testing of an intervention aiming to improve EF in HIV-positive adolescents

3.1. A short-term group drumming programme is a feasible and acceptable intervention in HIV-positive adolescents in rural South Africa.

3.2. Participation in a short-term group drumming intervention improves EF in HIV-positive adolescents in rural South Africa.

3.3. Participation in a short-term group drumming intervention improves depression and anxiety symptoms in HIV-positive adolescents in rural South Africa.

1.8. Overview of chapters

Chapter 2 (Study 1) describes a systematic review and meta-analysis of EF in HIV-affected children and adolescents (hypotheses 1, 1.1, 1.2, 1.3, 1.4, 2.1, 2.2). The review objectives were to determine: whether HIV infection and HIV exposure are associated with EF deficits, and if so, in which EF components and to what degree; factors associated with EF (potential predictors or outcomes) in these subpopulations; and the EF effects of interventions that have been tested so far in these subpopulations.

Chapters 3 and 4 are based on secondary cross-sectional data analysis from a cognitive study within a large cohort of 17-24-year-old adolescent females in rural South Africa. Chapter 3 (Study 2) describes the validation of Oxford Cognitive Screen - Executive Function (OCS-EF), a tool for assessing EF in LMICs, by confirming the factorial validity of the tool in this population and context. Chapter 4 (Study 3) describes the association between EF and various risky sexual and substance use behaviours amongst middle and late adolescent females with and without HIV in rural South Africa (hypothesis 2.1) to assess whether poorer EF is associated with more risk-taking behaviour. Chapter 4 (Study 3) also characterises the EF profiles of adolescent females with behaviourally acquired HIV in rural South Africa compared to socio-demographically matched HIV-negative controls using a nested case-control study (hypotheses 1.1 and 1.4).

Chapter 5 summarises the literature on musical training and EF in children and adolescents, and the effects of group drumming interventions in children, adolescents and adults. It provides the theoretical background for Chapter 6.

Chapter 6 (Study 4) describes the AHEAD (Adolescent HIV Executive Function and Drumming) Study, a feasibility trial of a group drumming programme, in which I assess whether EF is associated with adherence to treatment (hypothesis 2.2). It also outlines the development and initial testing of a musical training intervention amongst 12-19-year-old HIV-positive adolescents in rural South Africa to determine its feasibility and acceptability (hypothesis 3.2), and to explore its effects on EF (hypotheses 3.1) and associated secondary socio-emotional and behavioural outcomes.

Chapter 7 is a general discussion chapter which links the findings from the previous chapters. It covers emerging issues, the thesis strengths and limitations, contributions and potential future directions before concluding the thesis.

Chapter 2: Study 1, a systematic review with meta-analyses of executive function in HIV-affected children and adolescents

Chapter outline:

2.1. Background
2.2. Methods
    2.2.1. Eligibility criteria
    2.2.2. Search strategy
    2.2.3. Study appraisal
    2.2.4. Data extraction
    2.2.5. Meta-analysis
    2.2.6. Qualitative synthesis of results
2.3. Results
    2.3.1. Study selection and included studies
    2.3.2. Perinatally acquired HIV compared to healthy perinatally HIV-unexposed uninfected controls
    2.3.3. Perinatally acquired HIV compared to perinatally HIV-exposed uninfected
    2.3.4. Perinatally acquired HIV compared to mixed perinatally HIV-exposed uninfected or HIV-unexposed uninfected controls living in HIV-affected households
    2.3.5. Perinatally HIV-exposed uninfected compared to healthy perinatally HIV-unexposed uninfected controls
    2.3.6. Perinatally acquired HIV subgroup comparisons
    2.3.7. Behaviourally acquired HIV compared to HIV-negative controls
    2.3.8. Factors associated with executive function
    2.3.9. Interventions affecting executive function
2.4. Discussion

2.4.1. Main findings and implications

2.4.2. Research gaps and how I plan to address them

2.4.3. Conclusions

2.1. Background

In order to address the first two thesis hypotheses, I performed a systematic review and meta-analysis of executive function in HIV-affected children and adolescents. Although my thesis is focused on adolescents, I decided to include children 2-9-years-old in this review for two reasons. Firstly, a preliminary screen of the literature suggested that most of the cognitive studies in this population included a broad age range spanning childhood and adolescence. Secondly, I felt that it would be important to understand any pre-existing deficits that perinatally HIV-infected (PHIV) and/or perinatally HIV-exposed uninfected (PHEU) adolescents might carry into adolescence from childhood. The thesis hypotheses addressed in this systematic review were:

1. The relationship between HIV and EF in adolescents with HIV

1. EF deficits are more common in HIV-positive adolescents.

    1.1. The earlier that HIV infection occurs in the life course, the greater the EF deficits; therefore, adolescents with vertically transmitted HIV acquired perinatally have larger and more global deficits than adolescents with later behaviourally acquired HIV.

    1.2. EF deficits are related partly to the influence of HIV, a neurotropic virus, on the brain and partly to associated risk factors that are commonly found in HIV-affected households. I thus expected that:

1.2.1. EF deficits would be larger in those with more advanced or uncontrolled HIV. Conversely, they would be smaller in those with early, well-controlled or slowly progressing disease (so-called ‘slow progressors’).

1.2.2. EF deficits would be larger in perinatally acquired HIV compared to healthy perinatally HIV-unexposed uninfected (PHU) controls not living in HIV-affected households than when compared to perinatally HIV-exposed uninfected (PHEU) or PHU controls living in HIV-affected households.

1.2.3. PHEU and/or PHU adolescents living in HIV-affected households have mild EF deficits compared to PHU not living in HIV-affected households due to the risks associated with perinatal HIV exposure, antiretroviral exposure, and/or living in an HIV-affected household.

1.3. Perinatally acquired HIV is associated with a distinct pattern of EF deficits with effect sizes varying by EF component.

1.4. Behaviourally acquired HIV is associated with a distinct pattern of EF deficits with effect sizes varying by EF component.

2. The relationship between EF and risk-taking behaviour in adolescents

2.1. EF deficits are associated with increased risky sexual and substance use behaviour.

2.2. EF deficits are associated with lower adherence to ART in HIV-positive adolescents.

The review objectives were to determine:

- whether there are EF deficits and if so to what extent for the various EF components in the different subpopulations of HIV-affected children and adolescents,
- the factors associated with EF which may be potential predictors, markers and/or outcomes,
- the EF effects of any interventions tested so far.

2.2. Methods

2.2.1. Eligibility criteria

Study inclusion and exclusion criteria are listed in Table 1. Three subpopulations of HIV-affected children and adolescents were included as target populations to address all the sub-hypotheses of Hypothesis 1. In studies including children less than 10-years-old only, perinatally acquired HIV (PHIV) was presumed (if not stated). Adult studies including adolescents 18-24-years-old were included if the study population fell primarily within this age range or age-disaggregated data was presented. Studies which included HIV-affected controls (either PHEU or perinatally HIV-unexposed, uninfected (PHU) living in HIV-affected households), healthy PHU controls or population norms for comparison were included.

Table 1. Study inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Population	Three subpopulations of HIV-affected children and adolescents (2-24-years-old): 1. Perinatal HIV infection (PHIV): children infected by their HIV-positive mothers during pregnancy and/or lactation; 2. Perinatally HIV exposed uninfected (PHEU): children whose mothers were HIV-positive during pregnancy and/or lactation, but child was not infected; 3. Behaviourally acquired HIV (BHIV): HIV acquired by the child or adolescent later than the perinatal period by horizontal means, usually sexual or substance use behaviour. HIV-positive participants were included in the narrative synthesis regardless of ART status.	Transfusion-acquired HIV, animals
Outcomes	Primary: 1. Core EF components (working memory, set-shifting, or inhibition) measured with objective cognitive task/s; 2. Complex EF (planning) measured with objective cognitive task/s; 3. Global EF in daily life measured with subjective behavioural report measures (e.g. self-report, parent-report). Secondary: 1. Measures of association between EF and other associated factors (including potential predictors or outcomes); 2. Change in EF from pre- to post-intervention (with or without comparison to change in a control arm).	

Study design	1. Observational (cross-sectional or longitudinal), with or without controls 2. Experimental or quasi-experimental (pre-post) research studies	Case studies, case series, retrospective chart reviews. Systematic reviews, meta-analyses.
Criteria	Inclusion	Exclusion
Source	Primary sources Grey literature (e.g. conference papers, theses)	Secondary sources (e.g. reviews, editorials, textbooks, guidelines)

Key: ART = antiretroviral therapy; EF = executive function

2.2.2. Search strategy

After piloting the search terms, I conducted the full search in 13 databases and 8 conference websites (Table 2) using three groups of search terms (Table I, Appendix 1: Study 1 methods) and relevant search limits (Table 2) according to the method I registered with PROSPERO (registration number CRD42017067813).

Table 2. Search strategy: sources and limits

Databases	**Conferences**	**Search limits**
MEDLINE, MEDLINE In Process & Other Non-Indexed Citations, CINAHL, PubMed, PsycINFO, Cochrane Database of Systematic Reviews, Web of Science, SCOPUS, WorldCat, EMBASE, EBSCO Child Development & Adolescent Studies, Global Index Medicus and OpenGrey.	International AIDS Conference (AIDS); International AIDS Society (IAS) Conference on HIV Science; Conference on Retroviruses and Opportunistic Infections (CROI); International Conference on AIDS and STIs in Africa (ICASA); International Workshop on HIV Paediatrics; British HIV Association (BHIVA); European AIDS Conference;	1. human subjects 2. published between January 1981 and February 2017 (updated: July 2019) 3. any language (non-English full texts translated into English

	Australasian HIV & AIDS Conference.	using Google Translate)

After de-duplication, two independent reviewers screened abstracts and selected full texts for inclusion. We settled any disagreements by discussing our reasons for inclusion or exclusion. I performed reference harvesting to find additional full texts for inclusion and updated the search on 9 July 2019.

2.2.3. Study appraisal

A co-reviewer and I conducted independent quality assessments using the 27-item Downs and Black checklist with modified scoring (Downs & Black, 1998; Hooper, Jutai, Strong, & Russell-Minda, 2008). Criteria cover reporting, external validity, bias, confounding, and power. Relevant criteria, predetermined by study type, were used (see Table II and III, Appendix 1: Study 1 methods) and a proportion quality score generated with a higher score indicating superior quality (85-100% excellent, 65-84% good, 50-64% fair, <50% poor) (Hooper et al., 2008). Minor discrepancies (differences of ≤ 2 points) were resolved by averaging. Major discrepancies (> 2 points) were settled by joint re-scoring. Quality assessment did not affect inclusion, but it affected weighting of studies included in meta-analyses.

2.2.4. Data extraction

I extracted key data (Table IV, Appendix 1: Study 1 methods) into two charting tables in a Microsoft Access database and calculated effect sizes (with Hedge's correction) using MetaXL (Hedges & Olkin, 1985). My three co-reviewers checked the tables for inaccuracies.

2.2.5. Meta-analysis

Aggregate participant data meta-analysis was done using raw or unadjusted means and standard deviations. If some of the included studies in a particular meta-analysis also reported adjusted results, the meta-analysis was repeated using adjusted findings to see if adjustment changed the meta-analytic results. Where necessary, I reflected means to achieve consistent directionality (e.g. so that higher scores represented better results across all studies). If studies reported 95% confidence intervals, standard errors or separate subgroup results, these were converted or combined using methods described in the Cochrane Handbook (*Cochrane Handbook for Systematic Reviews of Interventions*, 2011) (Table V, Appendix 1: Study 1 methods). If there were multiple reports on the same EF subtype from the same longitudinal cohort, only the baseline data on the full sample was included for meta-analysis. I performed separate meta-analyses by EF subtype and subpopulations if at least two studies compared the same EF across the two subpopulations. The EF subtypes I meta-analysed were: verbal working memory; visuospatial working memory; inhibition; set-shifting; planning; global EF (caregiver-report); global EF (self-report). The subpopulation comparisons were:

- PHIV on antiretroviral therapy (ART) (at least 70% sample on ART) versus healthy PHU controls;
- PHIV slow progressors not on ART (unique subset with slow HIV progression therefore analysed separately) (Lechenadec et al., 2007; Muenchhoff, Prendergast, & Goulder, 2014; Ofori-Mante et al., 2007) versus healthy PHU controls;

- PHIV on ART versus PHEU;
- PHIV versus mixed PHEU/PHU;
- PHEU versus PHU;
- PHIV CDC C[3] (advanced disease) versus PHIV non-C (early disease);
- behaviourally acquired HIV (BHIV) versus HIV-negative controls.

I used quality effects models which account for study quality when weighting studies during meta-analyses in MetaXL (Doi & Thalib, 2008). The quality effects estimator results in a lower mean squared error[4] while maintaining the correct coverage probability of the confidence interval even if there is high between-study heterogeneity (Doi, Barendregt, Khan, Thalib, & Williams, 2015a, 2015b). It is robust to bias in quality assessment with the mean squared error matching that of the random effects estimator when quality assessment scores are entered randomly (Doi et al., 2015a, 2015b). Between-study heterogeneity was assessed using Cochran's Q and the I^2 statistic. Publication bias was assessed using Doi plot asymmetry and the Luis Furuya-Kanamori (LFK) index because they have been shown to have higher discriminative ability and sensitivity than using a funnel plot with Egger's regression to detect publication bias (Furuya-Kanamori, Barendregt, & Doi, 2018). Effect sizes

[3] Centres for Disease Control and Prevention (CDC) categorises HIV into three stages based on clinical symptoms with A being the earliest (asymptomatic, persistent generalised lymphadenopathy, or acute HIV infection), B being in the middle (mild or moderate clinical symptoms or disease), and C being the most advanced (severe or AIDS-defining conditions including HIV encephalopathy)
[4] Mean squared error: the mean of the individual squared error terms with a lower value indicating less error and better model fit

were interpreted using Cohen's rule (small d = 0.2-0.49; medium d = 0.5-0.79; large d ≥ 0.8) (J. Cohen, 1988).

2.2.6. Qualitative synthesis of results

Studies that could not be meta-analysed but presented relevant outcomes were described in the narrative synthesis.

2.3. Results

Firstly, I present an overview of the study selection process and included studies, then I present the meta-analytic findings with integrated narrative syntheses by subpopulations compared. Finally, I present the factors associated with EF followed by a summary of the interventions tested so far.

2.3.1. Study selection and included studies

The search revealed 1784 records, after de-duplication, published 1987-2019 (Figure 5). I found five additional studies using reference lists. 1363 records were excluded at abstract screening; 396 records underwent full text review (reasons for exclusion listed in Figure 5). 61 studies (93 records) were included in the narrative synthesis with 32 studies (34 records) included in meta-analyses. Eight studies (8 records) required data pre-processing prior to meta-analysis: combining subgroups (k = 5); converting 95% confidence intervals to standard deviations (k = 2); converting standard errors to standard deviations (k = 1). Inter-rater agreement for study selection was high (Cohen's kappa = 0.81).

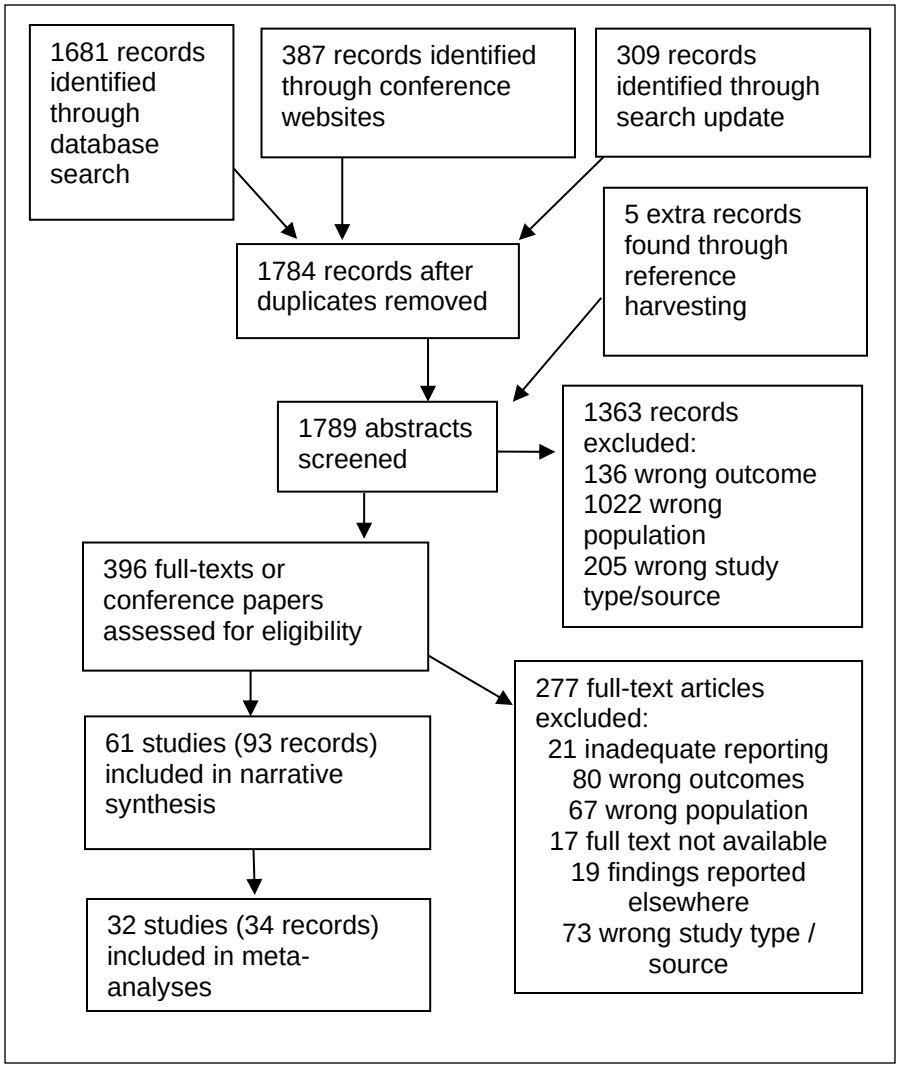


Figure 1. PRISMA flow diagram of study selection process

Observational study types (k = 52) included: 20 cohort studies and 32 cross-sectional studies (see Tables A and B in Appendix 2: Study 1 included studies). Experimental and quasi-experimental study types (k = 9) included: eight randomised controlled trials (RCTs) and one pre-post study (see Table C in Appendix 2: Study 1 included studies).

In total, data from 12373 participants were included in the narrative synthesis (n = 7884 in meta-analyses):

- 5417 (44%) HIV-positive:
    - 5011 (41%) perinatally acquired HIV (PHIV);
    - 334 (3%) behaviourally acquired HIV (BHIV);
    - 72 (< 1%) source of infection not reported.
- 6874 (56%) HIV-negative:
    - 2679 (22%) perinatally HIV-exposed uninfected (PHEU);
    - 3254 (25%) perinatally HIV-exposed uninfected (PHU) not living in HIV-affected households;
    - 1123 (9%) mixed PHEU/PHU living in HIV-affected households.

Most studies (k = 40; 66%) included children and adolescents; 20% (k = 12) were adolescent-only; 15% (k = 9) were child-only. 37 studies (61%) were conducted in LMICs (44% Africa-based). 24 studies (39%) were conducted in high-income countries (21% US-based).

For the quality assessments, 16% of studies underwent joint re-scoring due to inter-rater discrepancies > 2 points. The mean quality assessment score was 60% (range 11-92%). There was generally a high risk of selection bias with most studies employing facility-based recruitment and response rates seldom reported.

2.3.2. Perinatally acquired HIV compared to healthy perinatally HIV-unexposed uninfected controls

2.3.2.1. Verbal working memory

Meta-analysis of fourteen studies (all using digit span backwards, alone or in combination) comparing PHIV on ART to PHU (PHIV n = 1245; PHU n = 886) found a large, significant effect (Figure 6), unchanged with adjusted estimates. There was high between-study heterogeneity (Figure 6) and evidence of publication bias (LFK index = -2.19; major asymmetry). Two non-included studies also found significantly poorer performance in PHIV (Benki-Nugent et al., 2016; Maganlal, 2013).

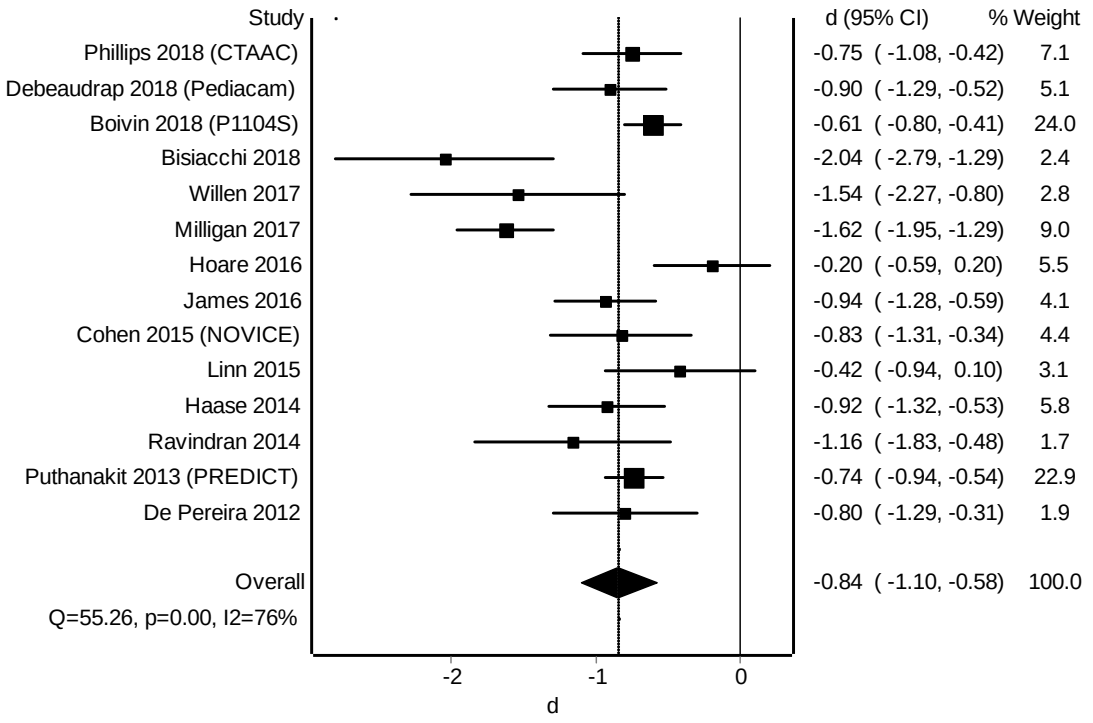


Figure 6. Forest plot of meta-analysis of verbal working memory effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Negative effect sizes represent poorer performance by the HIV-positive group.

Meta-analysis of three African studies (all using digit span backwards, alone or in combination) comparing slow progressors not on ART to PHU (PHIV n = 133; PHU n = 155) found a small, insignificant effect with low between-study heterogeneity (Figure 7) and evidence of publication bias (LFK index = 4.13; major asymmetry).

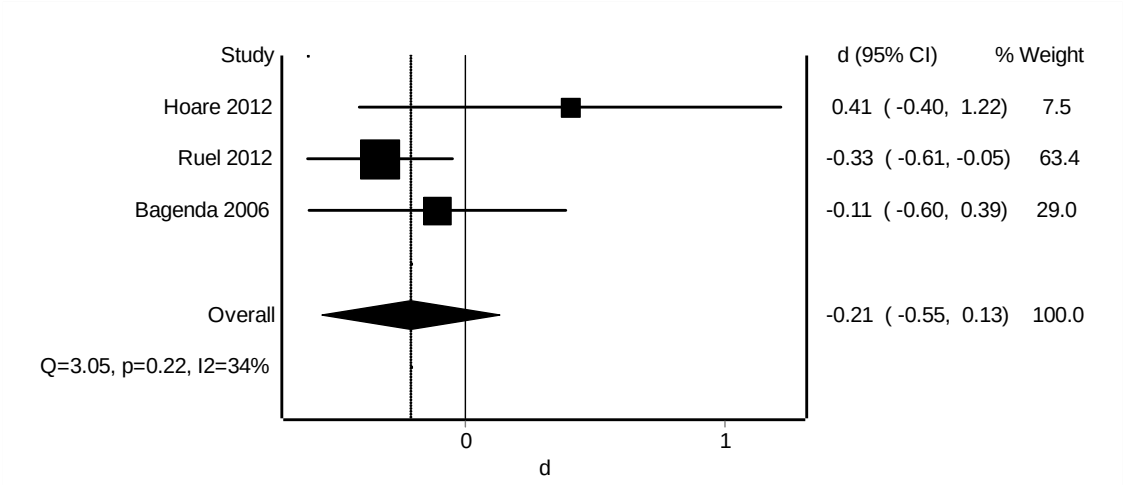


Figure 7. Forest plot of meta-analysis of verbal working memory effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV who are slow progressors not on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Negative effect sizes represent poorer performance by the HIV-positive group.

The Ugandan Rakai cohort (< 70% on ART), found no difference between PHIV and PHU (Brahmbhatt et al., 2017). A Congolese study (advanced disease prior to ART) found a large, significant negative effect with poorer performance by PHIV (Boivin et al., 1995).

2.3.2.2. Visuospatial working memory

Meta-analysis of five studies (three using spatial span alone or in combination) comparing PHIV on ART to PHU (PHIV n = 670; PHU n = 479) found a medium, significant effect (Figure 8), similar with adjusted estimates. There was high between-

study heterogeneity (Figure 8) and evidence of publication bias (LFK index = -1.39; minor asymmetry).

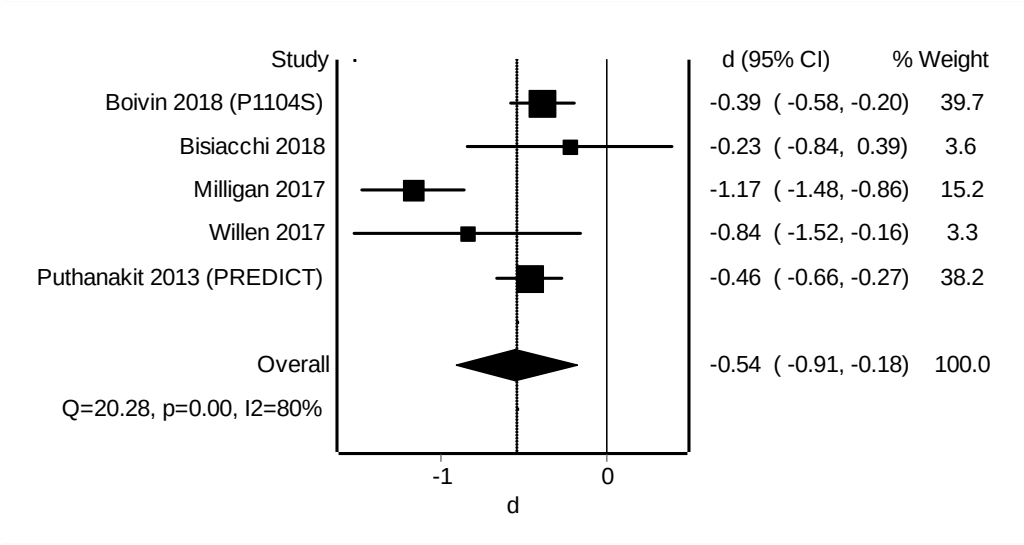


Figure 8. Forest plot of meta-analysis of visuospatial working memory effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Negative effect sizes represent poorer performance by the HIV-positive group.

Two small non-included studies (using hand movements tasks) compared PHIV not on ART to PHU. The first found that PHIV slow progressors did not differ from PHU (Bagenda et al., 2006). The study in more advanced disease found a large, significant negative effect with poorer performance by PHIV (Boivin et al., 1995).

2.3.2.3. Inhibition

There were four studies (three using Stroop[5] tasks) included in this meta-analysis comparing PHIV on ART to PHU (PHIV n = 401; PHU n = 327). The effect was of

[5] The Stroop (or colour-word interference) task is named after John Ridley Stroop who first published on the Stroop effect. It is harder and slows down performance to describe the font colour of a word if the word meaning and the font colour are different or incongruent (e.g. 'red' written in blue font) than if they are congruent (e.g. 'red' written in red font). This is because it requires inhibition or interference control.

medium size but insignificant (Figure 9), similar with adjusted estimates. There was high between-study heterogeneity (Figure 9) and evidence of publication bias (LFK index = -3.16; major asymmetry). A non-included study in adolescents found a small, significant negative effect with poorer performance by PHIV (Maganlal, 2013).

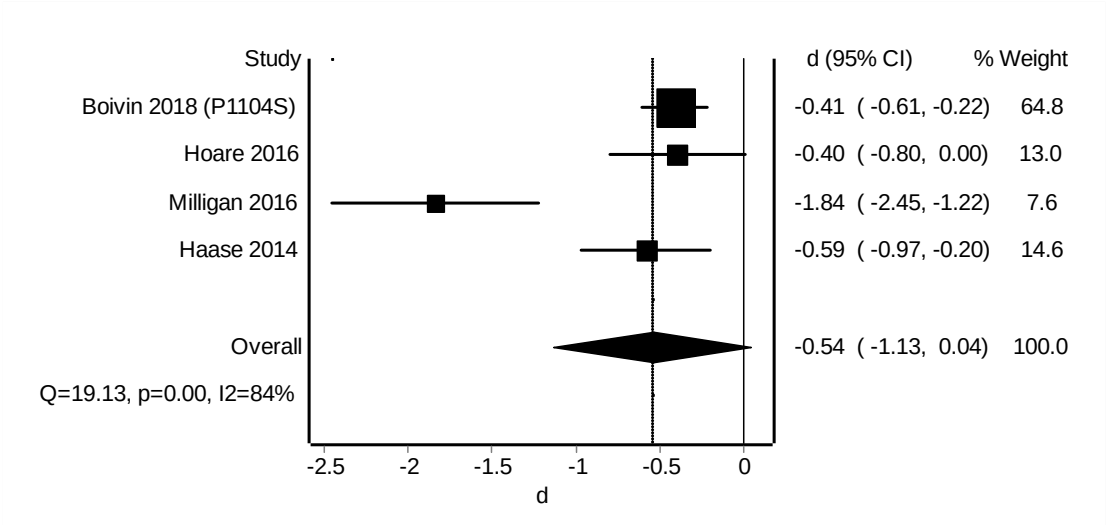


Figure 9. Forest plot of meta-analysis of inhibitory control effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Negative effect sizes represent poorer performance by the HIV-positive group.

Meta-analysis of two studies comparing slow progressors not on ART to PHU (PHIV n = 105; PHU n = 118) revealed no effect with low between-study heterogeneity (Figure 10).

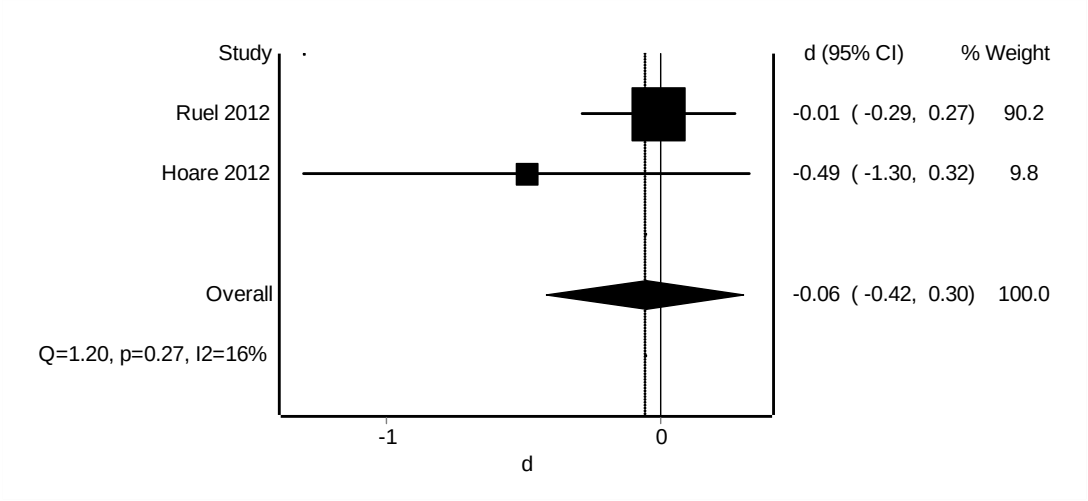


Figure 10. Forest plot of meta-analysis of inhibitory control effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV who are slow progressors not on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.2.4. Set-shifting

Meta-analysis of seven studies (using trails shifting tasks) comparing PHIV on ART to PHU (PHIV n = 672; PHU n = 340) found no effect (Figure 11), similar with adjusted estimates. There was high between-study heterogeneity (Figure 11) and evidence of publication bias (LFK index = -3.50; major asymmetry). A non-included study found a small, significant negative effect with poorer performance by PHIV (Maganlal, 2013). A small study comparing slow progressors to PHU found a large, insignificant negative effect with poorer performance by PHIV (Hoare et al., 2012).

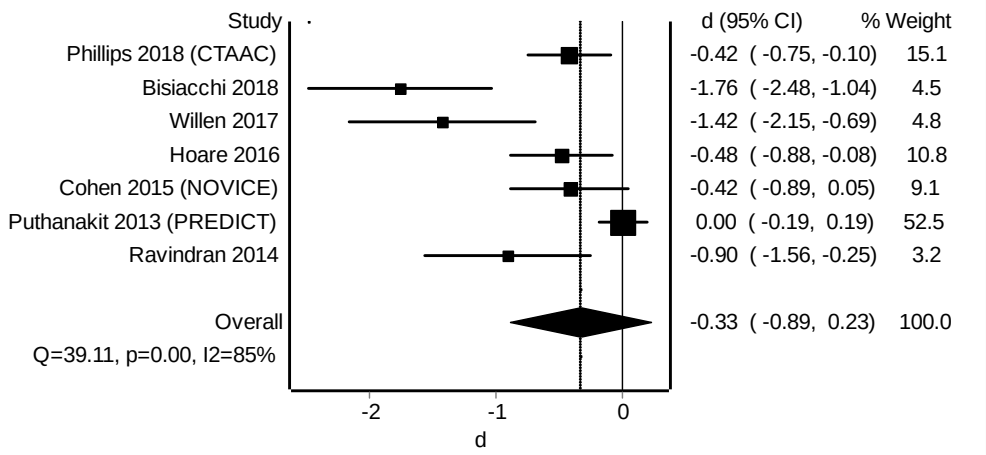


Figure 11. Forest plot of meta-analysis of set-shifting effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.2.5. Planning

Meta-analysis of six studies (using various tasks) comparing PHIV on ART to PHU (PHIV n = 409; PHU n = 376) found a medium, significant effect (Figure 12) becoming insignificant with adjusted estimates (d = -0.29 [95% CI -0.68, 0.10]). There was low between-study heterogeneity (Figure 12) and no evidence of publication bias (LFK index = 0.04; no asymmetry). A non-included study found no difference (Maganlal, 2013). A study comparing slow progressors to PHU found a small, insignificant difference (Ruel et al., 2012).

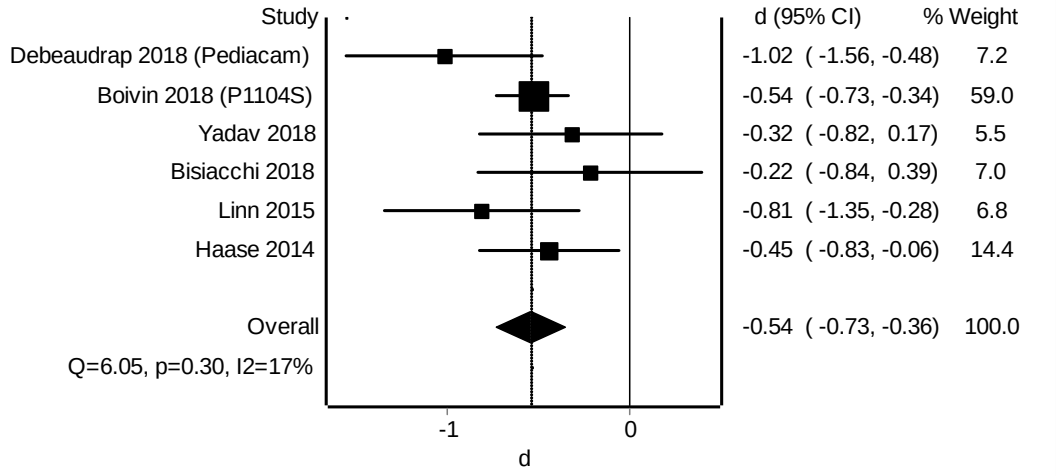


Figure 12. Forest plot of meta-analysis of planning effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.2.6. Global executive function

Meta-analysis of two studies comparing caregiver-reported global EF problems (on BRIEF[6]-PR) in PHIV on ART to PHU (PHIV n = 304; PHU n = 235) found a small, insignificant effect with high between-study heterogeneity (Figure 13). One study assessing self-reported global EF problems (on BRIEF-SR) found a large, significant difference with PHIV having more problems (Ezeamama et al., 2016).

[6] Behaviour Rating Inventory Executive Function (BRIEF) is a questionnaire tool designed to assess executive function in the home and school environments. It consists of two broad indices: Behavioural Regulation and Metacognition which are combined into a Global Executive Composite score. The questionnaire comes in parent-report (PR), teacher-report (TR) and self-report (SR) versions.

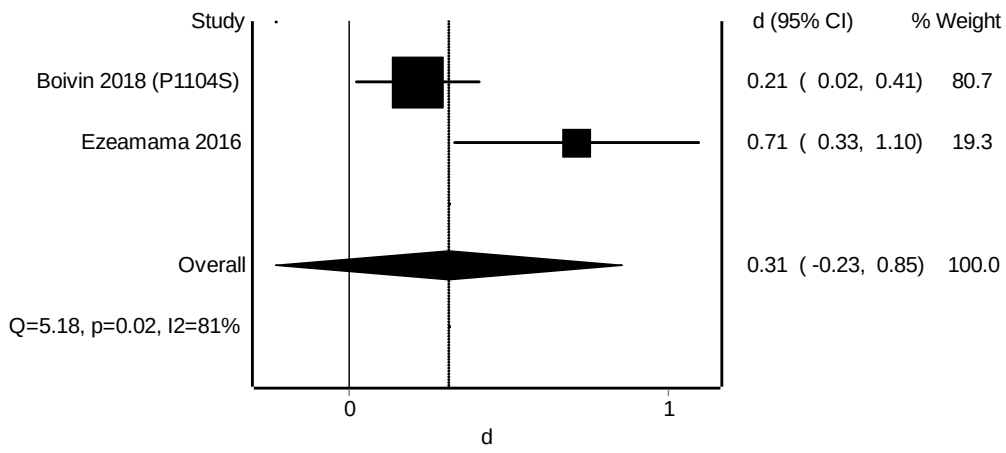


Figure 13. Forest plot of meta-analysis of caregiver-reported global executive function effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to healthy HIV-unexposed uninfected controls. Positive effect sizes represent more reported problems in the HIV-positive group.

2.3.2.7. Comparison with norms and special populations

Three studies comparing PHIV to norms found significantly worse performance in PHIV with large effect sizes or high proportions with impairment; however, a German study did not (Blanchette, Smith, King, Fernandes-Penney, & Read, 2002; Garcia-Navarro et al., 2013; Martin et al., 2006; Weber et al., 2017). A Dutch study comparing PHIV to norms found a medium effect for visuospatial working memory, a small effect for inhibition, and no effect for set-shifting (Koekkoek, de Sonneville, Wolfs, Licht, & Geelen, 2008). The CoRISpeS[7] cohort performed poorly on verbal fluency and set-shifting, but not inhibition (Garcia-Navarro et al., 2013). A Ugandan study comparing

[7] CoRISpeS: Cohort of the Spanish Paediatric HIV Network

PHIV to children with past severe malaria found significantly fewer caregiver-reported EF problems in PHIV (I. Familiar et al., 2015).

2.3.2.8. Longitudinal changes

The P1104S[8] cohort found significant improvement in inhibition in both PHIV and PHU over two years of follow up (Boivin, Chernoff, et al., 2017; M. J. Boivin et al., 2018). Both groups improved in planning; however, the PHIV group still lagged behind after two years (M. J. Boivin et al., 2018). Only PHIV improved on caregiver-reported global EF after one year (Boivin, Chernoff, et al., 2017). The Dutch NOVICE cohort found no significant change in working memory in PHIV or PHU over 4 years; however, the PHIV group deteriorated in set-shifting (Van den Hof et al., 2019). The Asian PREDICT[9] cohort found that PHIV still had inferior EF to PHU at follow-up (S. J. Kerr et al., 2018).

2.3.3. Perinatally acquired HIV compared to perinatally HIV-exposed uninfected

2.3.3.1. Verbal working memory

Meta-analysis of six studies (five using digit span, alone or in combination) comparing PHIV on ART to PHEU (PHIV n = 1116; PHEU n = 701) found a small, significant effect (Figure 14), similar with adjusted estimates. There was high between-study heterogeneity (Figure 14) and no evidence of publication bias (LFK index = 0.15; no asymmetry). Meta-analysis of the four LMIC studies found a significant medium effect

[8] P1104S: A Longitudinal Developmental and Neuropsychological Assessment of the P1060 Clinical Trial Cohorts and Perinatally HIV-Exposed but Uninfected Controls based in South Africa, Zimbabwe, Malawi and Uganda.
[9] PREDICT: Paediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand, a longitudinal cohort study post-randomised controlled trial of early versus deferred antiretroviral therapy

(d = -0.63 [95% CI -0.75, -0.50]) with low between-study heterogeneity (Q = 2.39, I^2 = 0%, p = 0.50); whereas meta-analysis of the two high-income country studies found no effect (d = -0.11 [95% CI -0.26, 0.05]) with no evidence of heterogeneity (Q = 0.30, I^2 = 0.00%, p = 0.584). A small non-included study only found a significant difference between CDC C and PHEU, not non-C and PHEU (Bisiacchi, Suppiej, & Laverda, 2000). A study comparing slow progressors not on ART to PHEU found a small, insignificant difference (Bagenda et al., 2006). A study in more advanced disease pre-ART found a small, insignificant difference (Boivin et al., 1995).

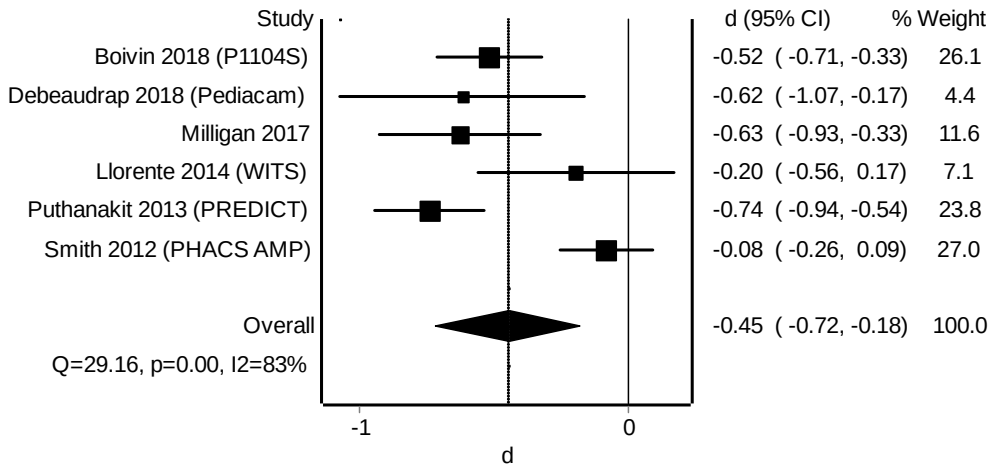


Figure 14. Forest plot of meta-analysis of verbal working memory effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to perinatally HIV-exposed uninfected children and adolescents. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.3.2. Visuospatial working memory

Meta-analysis of four studies comparing PHIV on ART to PHEU (PHIV n = 699; PHEU n = 486) found a small, significant effect (Figure 15), similar with adjusted estimates. There was high between-study heterogeneity (Figure 15) and evidence of publication bias (LFK index = 1.82; minor asymmetry). A study comparing slow progressors not

on ART to PHEU found a medium, significant negative effect with poorer performance by PHIV (Bagenda et al., 2006). A study in advanced disease pre-ART found a large, significant effect of HIV (Boivin et al., 1995).

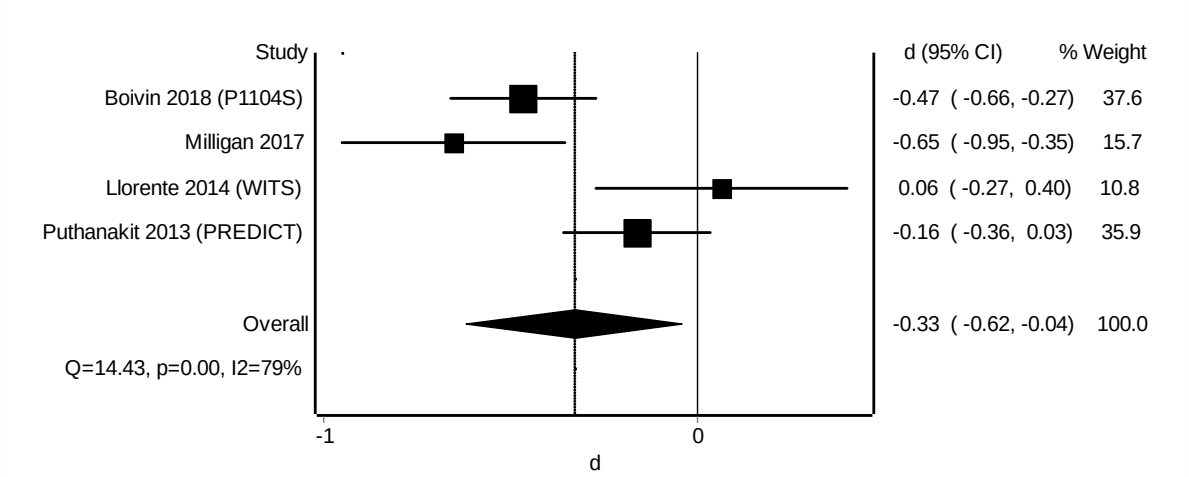


Figure 15. Forest plot of meta-analysis of visuospatial working memory effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to perinatally HIV-exposed uninfected children and adolescents. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.3.3. Inhibition

Meta-analysis of three studies comparing PHIV on ART to PHEU (PHIV n = 448; PHEU n = 297) found a small, significant effect (Figure 16), similar with adjusted estimates. There was minimal between-study heterogeneity (Figure 16) and no evidence of publication bias (LFK index = 0.20; no asymmetry).

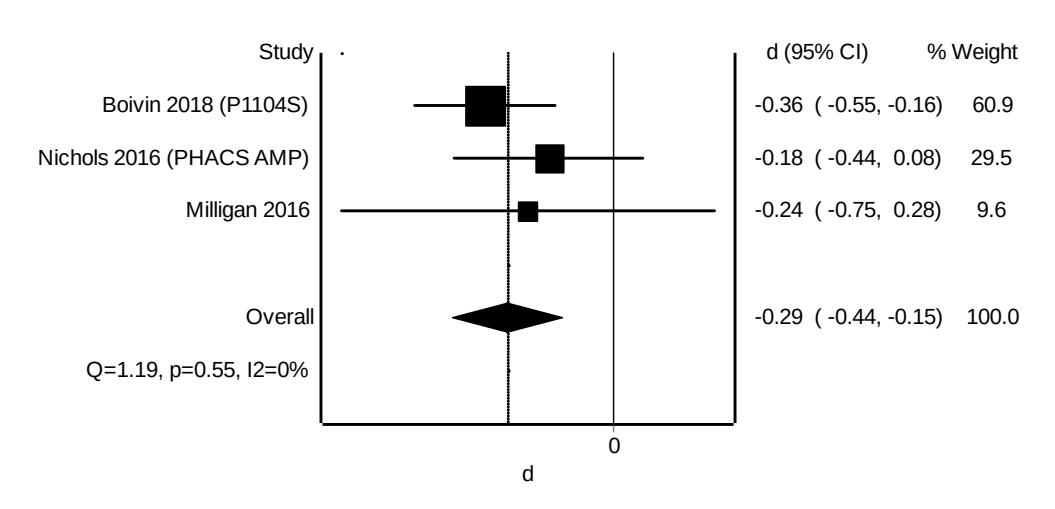


Figure 16. Forest plot of meta-analysis of inhibitory control effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to perinatally HIV-exposed uninfected children and adolescents. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.3.4. Set-shifting

Meta-analysis of three studies (two using trails tasks) comparing PHIV on ART to PHEU (PHIV n = 531; PHEU n = 295) found no effect (Figure 17), unchanged with adjusted estimates. There was minimal between-study heterogeneity (Figure 17) and no evidence of publication bias (LFK index = 0.43; no asymmetry). An early non-included study found poorer performance by PHIV (Bisiacchi et al., 2000).

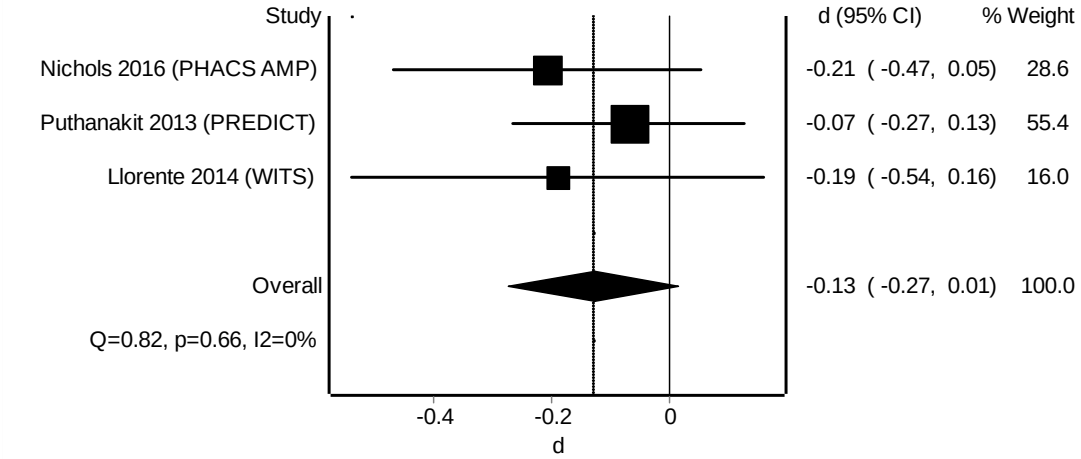


Figure 2. Forest plot of meta-analysis of set-shifting effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to perinatally HIV-exposed uninfected children and adolescents. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.3.5. Planning

Meta-analysis of four studies comparing PHIV on ART to PHEU (PHIV n = 704; PHEU n = 454) found a small, insignificant effect (Figure 18), similar with adjusted estimates. There was high between-study heterogeneity (Figure 18) and no evidence of publication bias (LFK index = 0.90; no asymmetry).

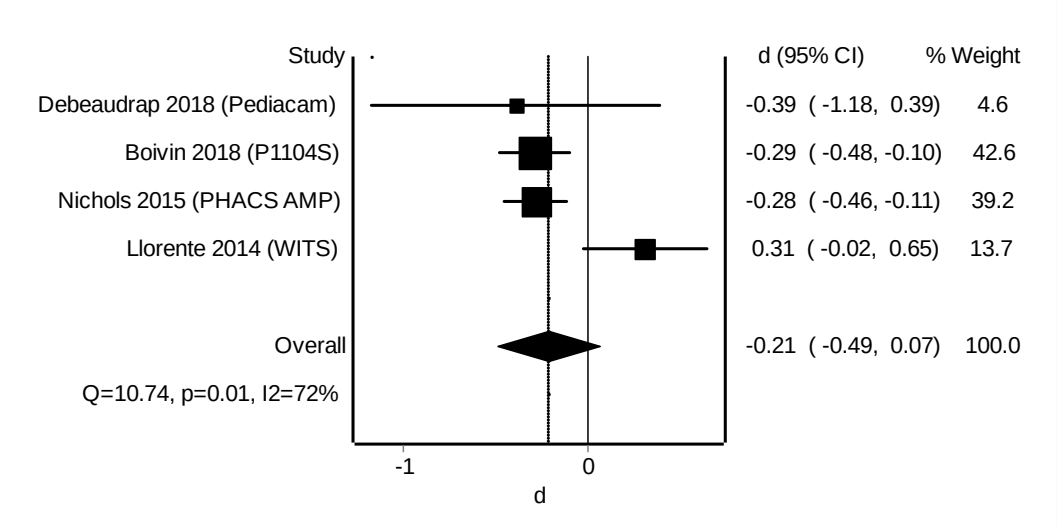


Figure 18. Forest plot of meta-analysis of planning effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to perinatally HIV-exposed uninfected children and adolescents. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.3.6. Global executive function

Meta-analysis of two studies comparing caregiver-reported global EF in PHIV on ART to PHEU (PHIV n = 304; PHEU n = 238) found a small, insignificant effect of HIV with moderate between-study heterogeneity (Figure 19). A non-included study had similar results (I. Familiar et al., 2016). A study examining self-reported global EF (on BRIEF-SR) found a large effect with PHIV having more problems (Ezeamama et al., 2016).

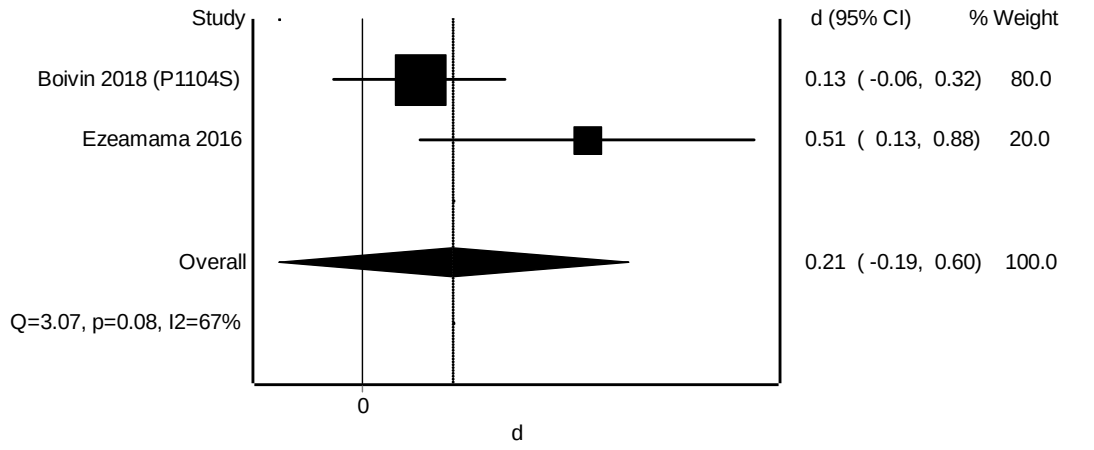


Figure 19. Forest plot of meta-analysis of caregiver-reported global executive function effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to perinatally HIV-exposed uninfected children and adolescents. Positive effect sizes represent more reported problems in the HIV-positive group.

2.3.3.7. Longitudinal changes

In the CASAH[10] cohort, PHIV and PHEU improved similarly in working memory and set-shifting over time from middle to late adolescence, with PHIV having lower working memory at some visits and lower set-shifting at one visit (R. Robbins et al., 2018; R. N. Robbins et al., 2019). In the P1104S cohort, PHIV and PHEU improved in inhibition

[10] CASAH: Child and Adolescent Self-Awareness and Health

and caregiver-reported EF over time (Boivin, Chernoff, et al., 2017). In the PHACS AMP[11] cohort, PHIV (CDC C and non-C) and PHEU improved similarly on set-shifting and inhibition (Malee et al., 2017). The WITS[12] cohort found no differences between PHIV and PHEU at 8-years-old or 10-years-old (Llorente et al., 2014).

2.3.4. Perinatally acquired HIV compared to mixed perinatally HIV-exposed uninfected or HIV-unexposed uninfected controls living in HIV-affected households

2.3.4.1. Verbal working memory

Meta-analysis of six studies (two using digit span; two using paced auditory serial addition tests; two using other tasks) comparing PHIV on ART to PHEU/PHU (PHIV n = 945; PHEU/PHU n = 1185) found a small, significant effect with moderate between-study heterogeneity (Figure 20) and evidence of publication bias (LFK index = -3.98; major asymmetry).

[11] PHACS AMP: Paediatric HIV/AIDS Cohort Study Adolescent Master Protocol
[12] WITS: Women and Infants Transmission Study

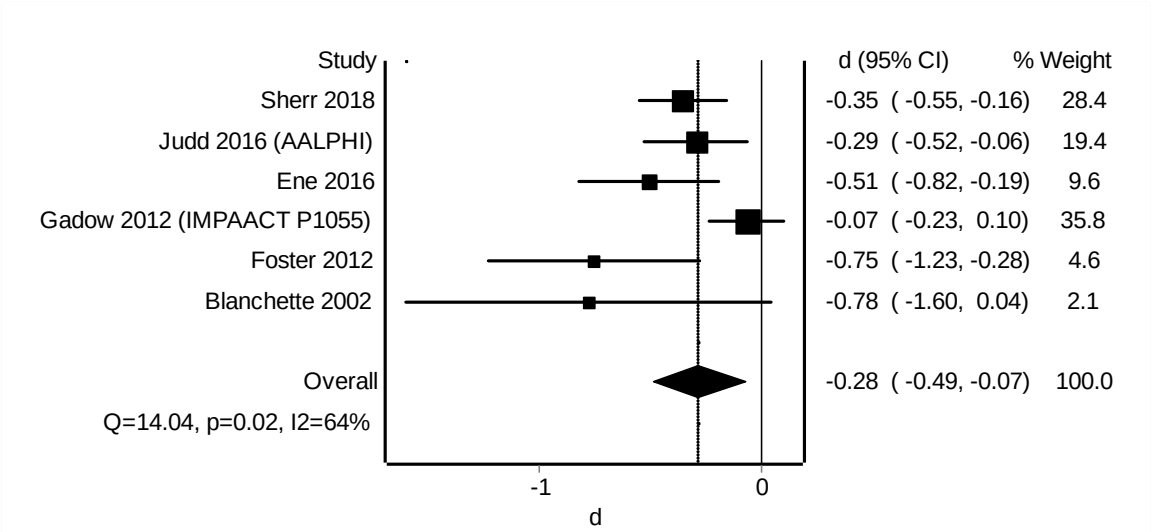


Figure 20. Forest plot of meta-analysis of verbal working memory effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to a mixed control group of perinatally HIV-exposed uninfected and perinatally HIV-unexposed uninfected children and adolescents living in HIV-affected households. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.4.2. Inhibition

Meta-analysis of four studies comparing PHIV on ART to PHEU/PHU (PHIV n = 371; PHEU/PHU n = 163) found no effect (Figure 21) with minimal between-study heterogeneity (Figure 21) and evidence of publication bias (LFK index = -3.04; major asymmetry).

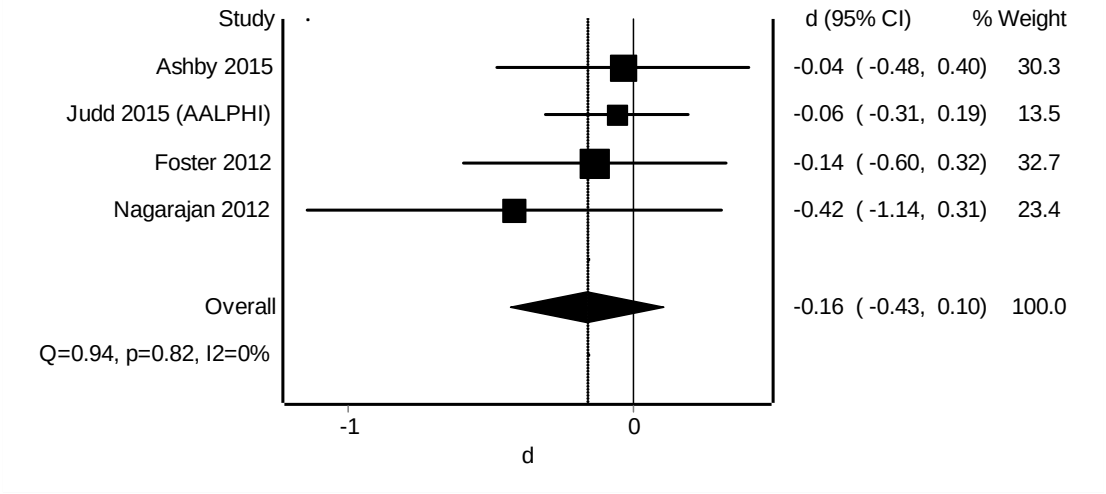


Figure 21. Forest plot of meta-analysis of inhibitory control effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to a mixed control group of perinatally HIV-exposed uninfected and perinatally HIV-unexposed uninfected children and adolescents living in HIV-affected households. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.4.3. Set-shifting

Meta-analysis of three studies comparing PHIV on ART to PHEU/PHU (PHIV n = 492; PHEU/PHU n = 158) found a small, significant effect with low between-study heterogeneity (Figure 22) and no evidence of publication bias (LFK index = -0.04; no asymmetry).

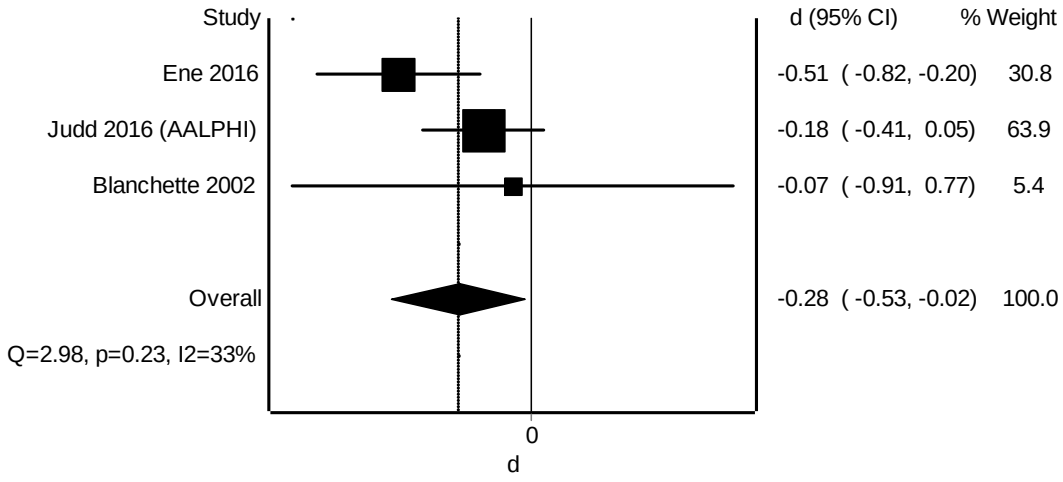


Figure 3. Forest plot of meta-analysis of set-shifting effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to a mixed control group of perinatally HIV-exposed uninfected and perinatally HIV-unexposed uninfected children and adolescents living in HIV-affected households. Negative effect sizes represent poorer performance by the HIV-positive group.

2.3.4.4. Global executive function

Meta-analysis of two studies comparing self-reported global EF problems (on BRIEF-SR or Frontal System Behaviour Scale) in PHIV on ART to PHEU/PHU (PHIV n = 232; PHEU/PHU n = 86) found a small, significant effect with minimal between-study heterogeneity (Figure 23). A study assessing caregiver-reported global EF problems (on BRIEF-PR) found a small, insignificant effect (Foster et al., 2012).

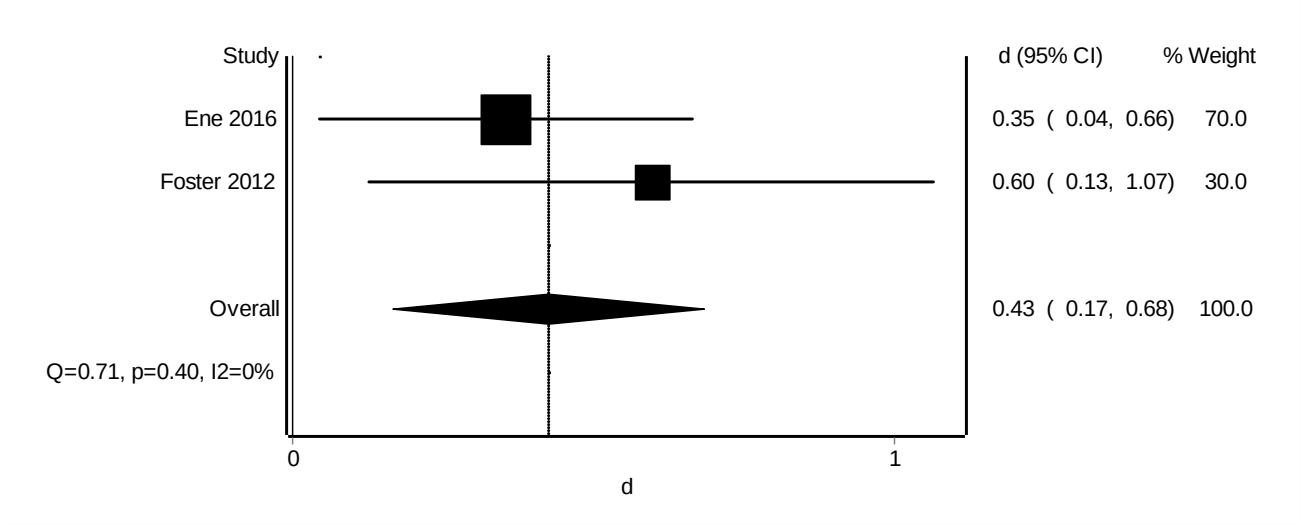


Figure 23. Forest plot of meta-analysis of global self-reported executive function effect size estimates (based on unadjusted data) in children and adolescents with perinatally acquired HIV on antiretroviral therapy compared to a mixed control group of perinatally HIV-exposed uninfected and perinatally HIV-unexposed uninfected children and adolescents. Positive effect sizes represent more reported problems in the HIV-positive group.

2.3.4.5. Longitudinal changes

In an African cohort, PHIV and PHEU/PHU improved similarly with PHIV still having deficits at follow-up (Sherr, Hensels, Tomlinson, Skeen, & Macedo, 2018). A US cohort found no significant changes (Foster et al., 2012). In the UK AALPHI[13] cohort, EF remained similar in PHIV (both CDC C and non-C) and PHEU/PHU at follow-up (Arenas-Pinto et al., 2019).

[13] AALPHI: Adolescents and Adults Living with Perinatal HIV

2.3.5. Perinatally HIV-exposed uninfected compared to healthy perinatally HIV-unexposed uninfected controls

2.3.5.1. Verbal working memory

Meta-analysis of six studies (PHEU n = 648; PHU n = 624) found no effect with high between-study heterogeneity (Figure 24) and evidence of publication bias (LFK index = -3.36; major asymmetry). A South African cohort found no difference (Rochat et al., 2016).

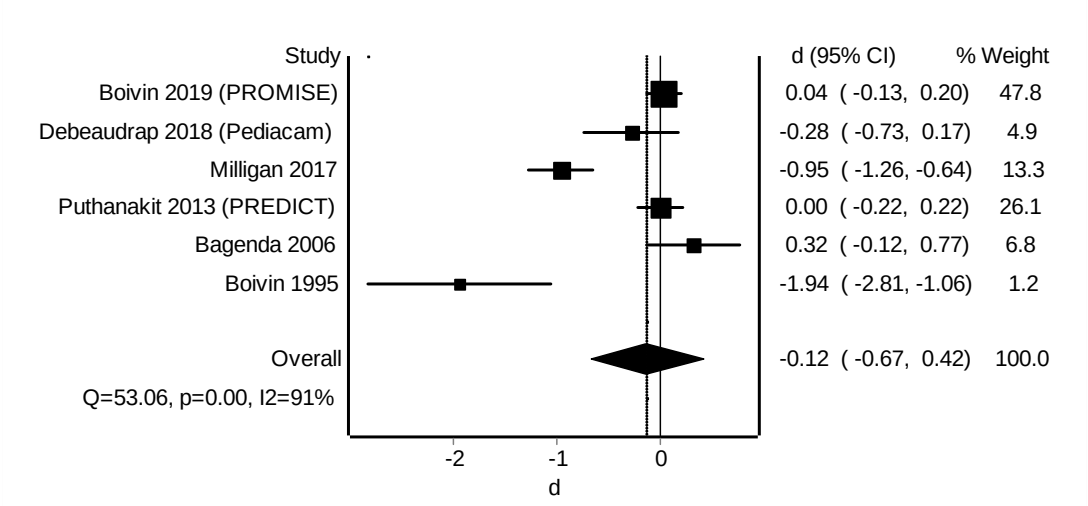


Figure 24. Forest plot of meta-analysis of verbal working memory effect size estimates (based on unadjusted data) in children and adolescents who are perinatally HIV-exposed uninfected compared to those who are perinatally HIV-unexposed uninfected. Negative effect sizes represent poorer performance by the HIV-exposed group.

2.3.5.2. Visuospatial working memory

Meta-analysis of six studies (PHEU n = 658; PHU n = 888) found no effect with high between-study heterogeneity (Figure 25) and evidence of publication bias (LFK index = -2.19; major asymmetry).

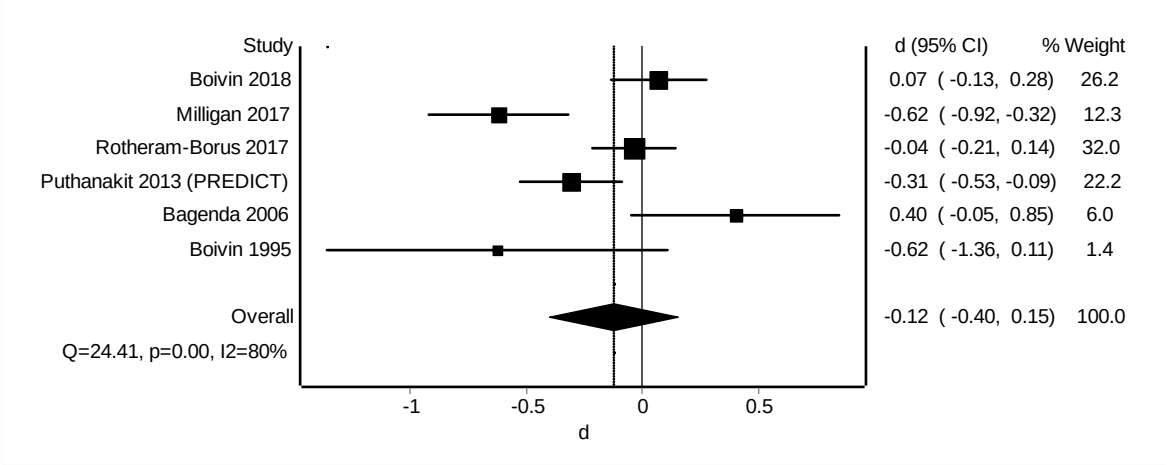


Figure 25. Forest plot of meta-analysis of visuospatial working memory effect size estimates (based on unadjusted data) in children and adolescents who are perinatally HIV-exposed uninfected compared to those who are perinatally HIV-unexposed uninfected. Negative effect sizes represent poorer performance by the HIV-exposed group.

2.3.5.3. Inhibition

Meta-analysis of two studies (PHEU n = 212; PHU n = 211) found a small, insignificant effect, similar with adjusted estimates, and high between-study heterogeneity (Figure 26). A South African cohort found no difference (Rochat et al., 2016).

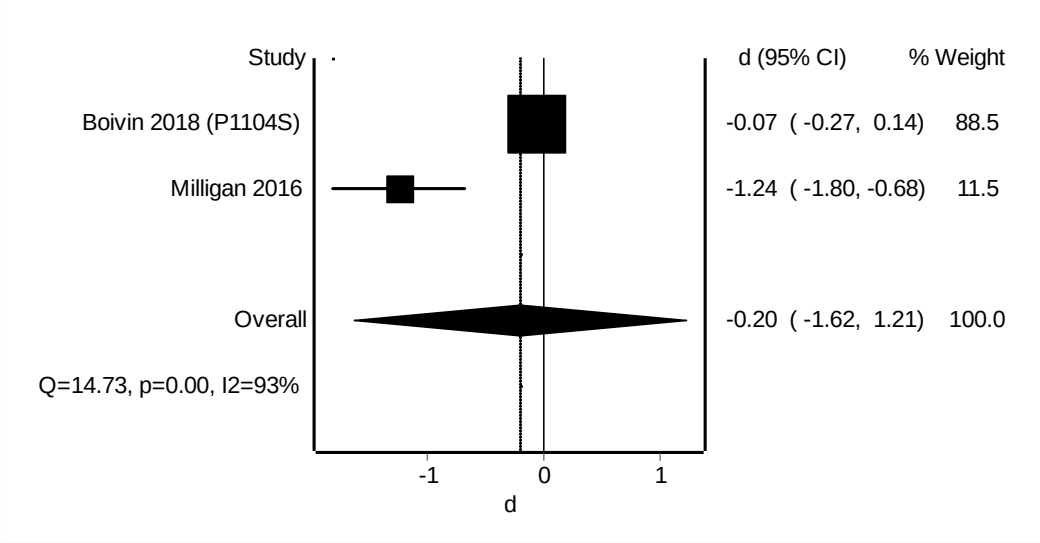


Figure 26. Forest plot of meta-analysis of inhibitory control effect size estimates (based on unadjusted data) in children and adolescents who are perinatally HIV-exposed uninfected compared to those who are perinatally HIV-unexposed uninfected. Negative effect sizes represent poorer performance by the HIV-exposed group.

2.3.5.4. Set-shifting

Meta-analysis of two studies assessing set-shifting was not possible (insufficient reporting). PREDICT found superior set-shifting in PHEU, whereas the Africa-based cohort found no significant difference (Puthanakit et al., 2013; Rochat et al., 2016).

2.3.5.5. Planning

Meta-analysis of two studies (PHEU n = 191; PHU n = 212) found no effect with moderate between-study heterogeneity (Figure 27). A non-included African cohort also found no difference (Rochat et al., 2016).

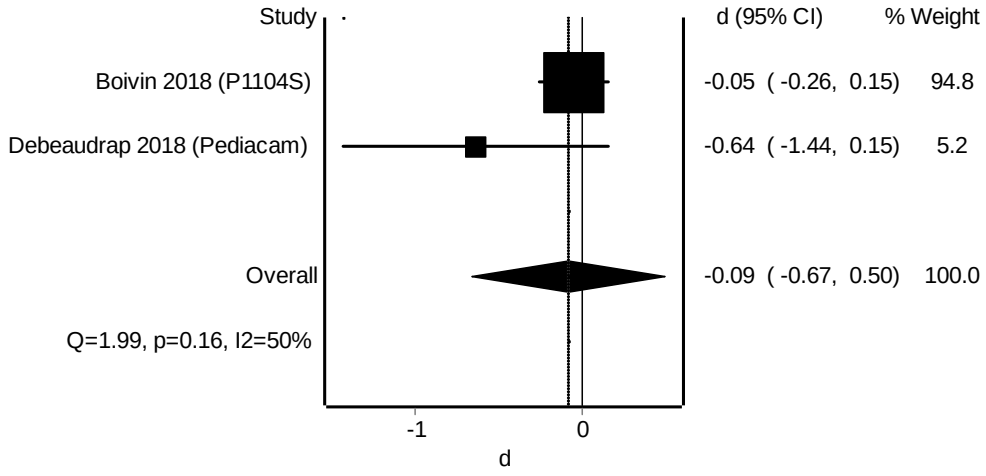


Figure 27. Forest plot of meta-analysis of planning effect size estimates (based on unadjusted data) in children and adolescents who are perinatally HIV-exposed uninfected compared to those who are perinatally HIV-unexposed uninfected. Negative effect sizes represent poorer performance by the HIV-exposed group.

2.3.5.6. Global executive function

Meta-analysis of two African studies assessing caregiver-reported global EF (PHEU n = 238; PHU n = 235) found no effect with minimal between-study heterogeneity (Figure 28). PREDICT found a small, insignificant difference in caregiver-reported attention problems (on Child Behaviour Checklist) (S. J. Kerr et al., 2014). A study assessing self-reported global EF found a small, significant effect with PHEU having more problems (Ezeamama et al., 2016).

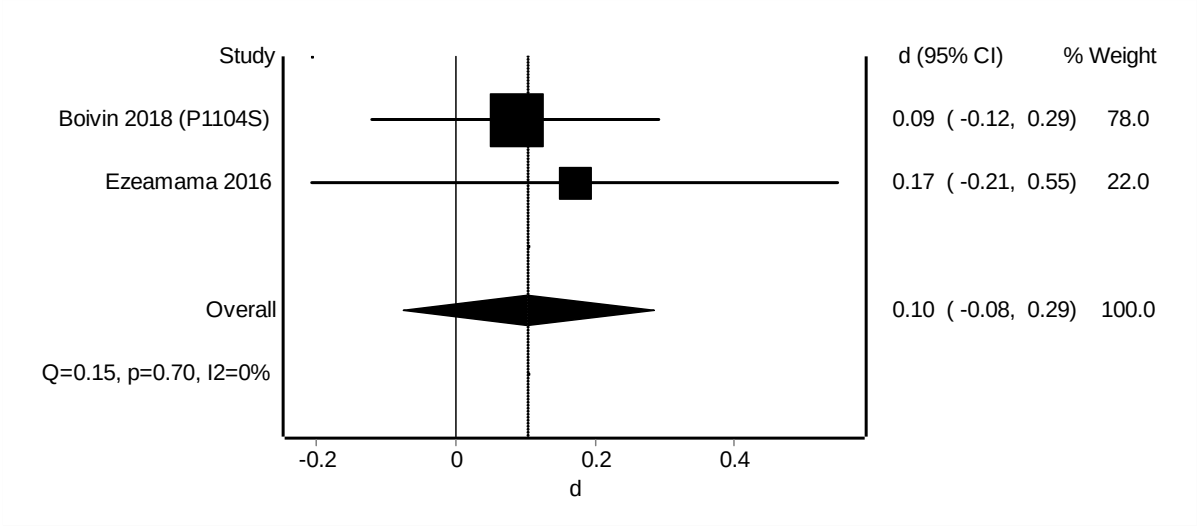


Figure 28. Forest plot of meta-analysis of caregiver-reported global executive function effect size estimates (based on unadjusted data) in children and adolescents who are perinatally HIV-exposed uninfected compared to those who are perinatally HIV-unexposed uninfected. Positive effect sizes represent more reported problems in the HIV-exposed group.

2.3.5.7. Longitudinal changes

The P1104S cohort saw significant improvements in inhibition in PHEU and PHU over a year, with PHEU also improving on caregiver-reported global EF (Boivin, Chernoff, et al., 2017). A South African cohort found similar EF in both groups at 3-years and 5-years-old (M. J. Rotheram-Borus et al., 2018; M. J. Rotheram-Borus, Tomlinson, Scheffler, Harris, & Nelson, 2017). The PREDICT cohort found no difference in EF between PHEU and PHU at follow-up (S. J. Kerr et al., 2018).

2.3.6. Perinatally acquired HIV subgroup comparisons

2.3.6.1. Verbal working memory

Meta-analysis of four studies comparing PHIV CDC C to non-C (PHIV C n = 203; PHIV non-C n = 523) found a small, significant effect (Figure 29), similar with adjusted estimates. There was minimal between-study heterogeneity (Figure 29) and evidence of publication bias (LFK index = -1.67; minor asymmetry). A Jamaican study

comparing PHIV on ART with and without a history of HIV encephalopathy found a large, negative effect (S. Y. Walker, Pierre, Christie, & Chang, 2013).

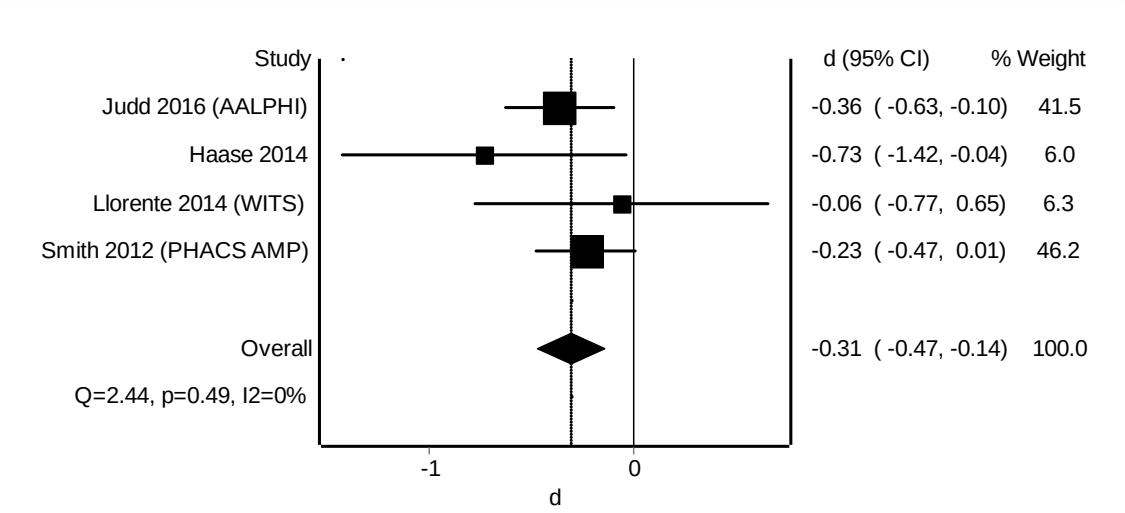


Figure 29. Forest plot of meta-analysis of verbal working memory effect size estimates (based on unadjusted data) in children and adolescents with perinatal HIV infection with a history of CDC Class C (more advanced) disease compared to those with non-C disease. Negative effect sizes represent poorer performance by the CDC Class C group.

2.3.6.2. Visuospatial working memory

The WITS study (using NEPSY[14] visual attention) comparing PHIV CDC C to non-C found no effect after adjustment (Llorente et al., 2014). A Jamaican study comparing PHIV on ART with and without a history of HIV encephalopathy (using spatial span) found a large, negative effect (S. Y. Walker et al., 2013).

[14] NEPSY: Developmental Neuropsychological Assessment

2.3.6.3. Inhibition

Meta-analysis of two studies comparing PHIV CDC C to non-C (PHIV CDC C n = 73; non-C n = 140) found a small negative effect, unchanged with adjusted estimates, and minimal between-study heterogeneity (Figure 30).

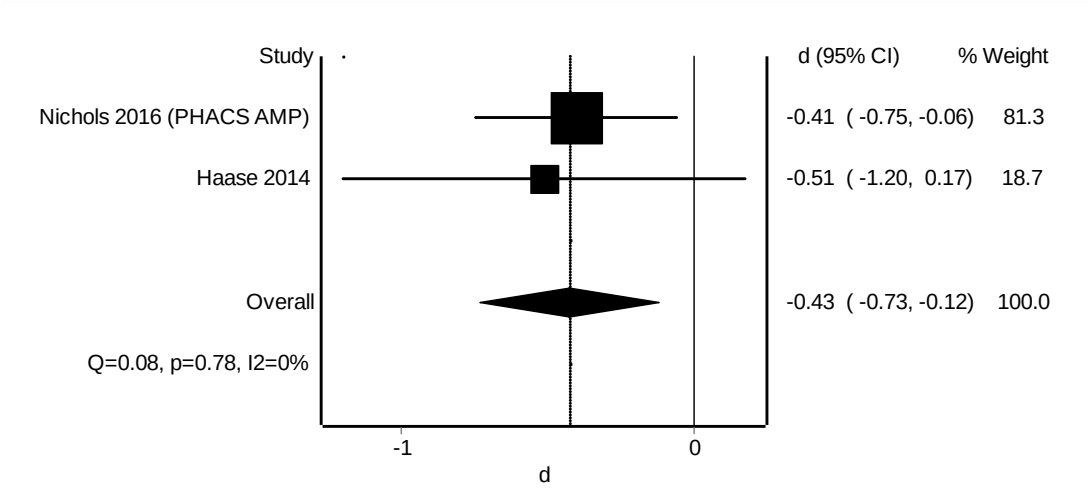


Figure 30. Forest plot of meta-analysis of inhibitory control effect size estimates (based on unadjusted data) in children and adolescents with perinatal HIV infection with a history of CDC Class C (more advanced) disease compared to those with non-C disease. Negative effect sizes represent poorer performance by the CDC Class C group.

2.3.6.4. Set-shifting

Meta-analysis of three studies comparing PHIV CDC C to non-C (PHIV CDC C n = 135; non-C n = 376) found a small, significant effect (similar with adjusted estimates) with minimal between-study heterogeneity (Figure 31).

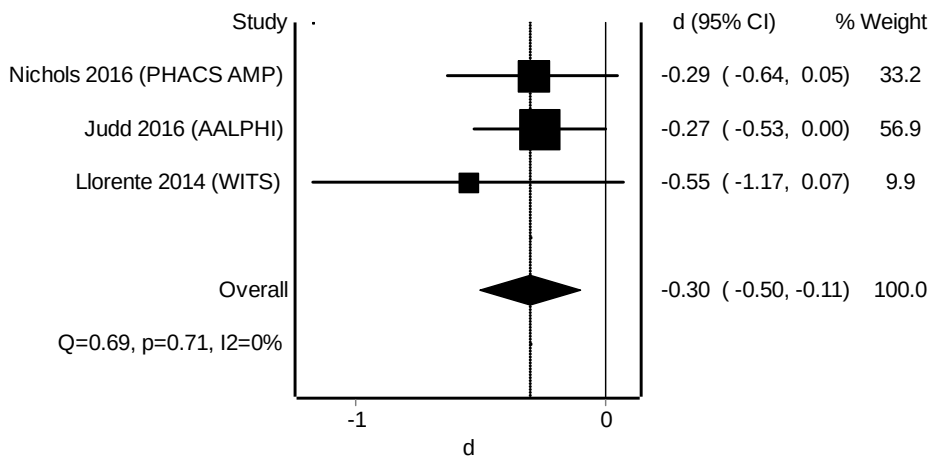


Figure 31. Forest plot of meta-analysis of set-shifting effect size estimates (based on unadjusted data) in children and adolescents with perinatal HIV infection with a history of CDC Class C (more advanced) disease compared to those with non-C disease. Negative effect sizes represent poorer performance by the CDC Class C group.

2.3.6.5. Planning

Meta-analysis of two studies (using tower tasks) comparing PHIV CDC C to non-C (PHIV CDC n = 41; non-C n = 49) found no effect and minimal between-study heterogeneity (Figure 32). In PHACS AMP, there was a large negative effect with those having a history of encephalopathy showing poorer performance (Nichols et al., 2015).

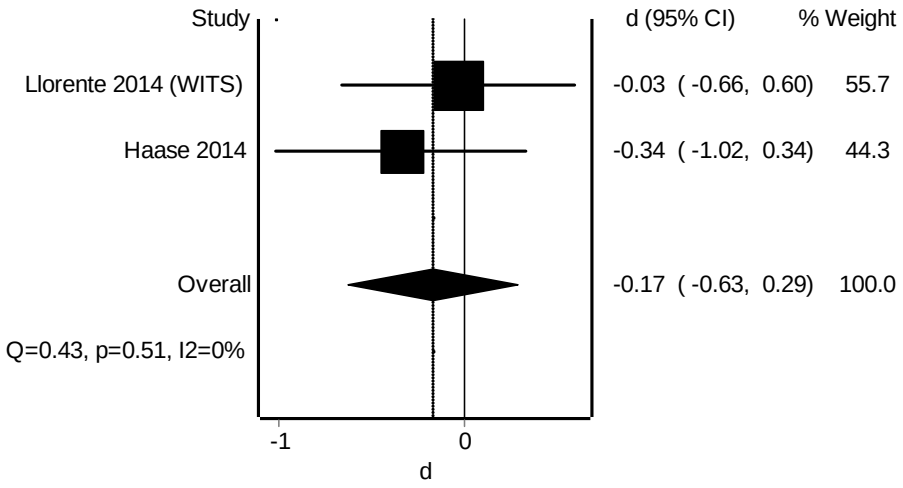


Figure 32. Forest plot of meta-analysis of set-shifting effect size estimates (based on unadjusted data) in children and adolescents with perinatal HIV infection with a history of CDC Class C (more advanced) disease compared to those with non-C disease. Negative effect sizes represent poorer performance by the CDC Class C group.

2.3.6.6. Global executive function

In PHACS AMP, there was no effect on global EF on caregiver-report (BRIEF-PR) or self-report (BRIEF-SR) (Nichols et al., 2015). In a large African cohort, late ART initiation compared to early initiation had a small, insignificant effect on caregiver-reported global EF (M. J. Boivin et al., 2018).

2.3.6.7. Longitudinal changes

In PHACS AMP, PHIV CDC C and non-C improved similarly in EF (Malee et al., 2017). In PREDICT, there were no significant changes in EF in the early or deferred ART arms at initial follow-up; later longitudinal analysis revealed three distinct cognitive trajectory phenotypes: high, medium, and low-scoring with only the high group improving over time (Patel et al., 2018; Puthanakit et al., 2013).

2.3.7. Behaviourally acquired HIV compared to HIV-negative controls

2.3.7.1. Verbal working memory

A US study found a small, insignificant effect (d = -0.34 [95% CI -0.94, 0.25]) (Baker et al., 2014). Another US study, ATN 071[15], comparing early BHIV to norms found no difference (Nichols et al., 2013).

2.3.7.2. Inhibition and set-shifting

In the ATN 071 cohort, BHIV had similar proportions with impaired inhibition (on Stroop) to norms; however, they had a higher proportion with impaired set-shifting (on trails shifting) (Nichols et al., 2013). Meta-analysis of two small studies assessing set-shifting (BHIV n = 55; HIV-negative n = 47) found no effect with moderate between-study heterogeneity (Figure 33). A US study found no difference between BHIV and norms on the Wisconsin card sorting test (Salama et al., 2013).

[15] ATN: The Adolescent Medicine Trials Network for HIV/AIDS Interventions

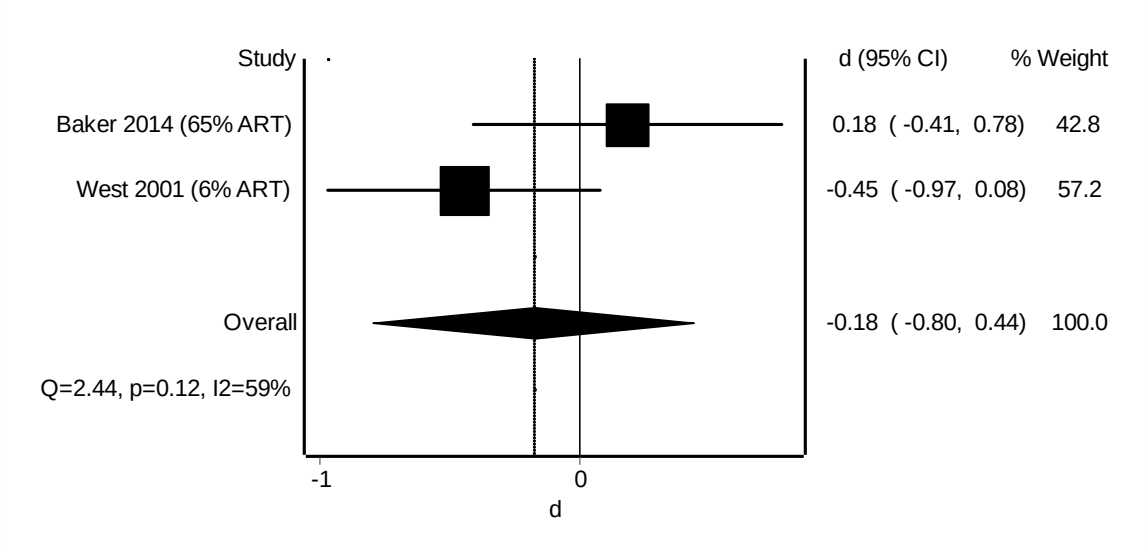


Figure 33. Forest plot of meta-analysis of set-shifting effect size estimates (based on unadjusted data) in adolescents with behaviourally acquired HIV infection compared to HIV-negative controls. Negative effect sizes represent poorer performance by HIV-positive group.

2.3.7.3. Longitudinal changes

ATN 071 found improved performance in the core EF components in BHIV over three years, unrelated to timing of ART initiation (Nichols, Bethel, et al., 2016).

2.3.8. Factors associated with executive function

Several potential predictors have been assessed for their association with EF in PHIV and PHEU (Table 3). For many factors, findings varied across studies or EF subtypes. Past advanced disease and/or encephalopathy were generally associated with poorer working memory and EF (Judd et al., 2015; Malee et al., 2017; R. Smith et al., 2012; S. Y. Walker et al., 2013). There were mixed findings for current disease markers with a high viral load being variably associated with lower EF (Bangirana et al., 2016; Kapetanovic et al., 2010; Malee et al., 2017; Martin et al., 2006; Nagarajan et al., 2012; Nichols et al., 2015; Ruel et al., 2012). Factors positively associated with EF

included: growth parameters, education level, sleep duration, biological parent as caregiver, maternal intelligence, good parenting, socio-economic status, cash transfers, and higher immunological markers at ART initiation (Boivin, Nakasujja, et al., 2017; Brahmbhatt et al., 2017; Foster et al., 2012; Koekkoek et al., 2008; Sherr, Macedo, Tomlinson, Skeen, & Cluver, 2017; R. Smith et al., 2012). Factors negatively associated with EF included: past advanced disease, low socio-economic status, educational risk (e.g. grade repetition or special education), caregiver depression (associated with increased caregiver-reported EF problems), latent Toxoplasma infection, attention-deficit/hyperactivity disorder (ADHD) (Burkey et al., 2015; Ene et al., 2016; I. Familiar et al., 2018; I. Familiar et al., 2016; Judd et al., 2015; Malee et al., 2017; Nichols et al., 2015; Patel et al., 2018; R. N. Robbins et al., 2019; R. Smith et al., 2012; S. Y. Walker et al., 2013). The relationship between EF and ART factors was variable with some studies finding later ART initiation associated with poorer EF (Benki-Nugent et al., 2016; J. Hoare et al., 2019; Van den Hof et al., 2019). Potential neuroimaging, vascular and immunological markers associated with EF in PHIV and BHIV were identified (Table 4). EF was negatively associated with the following brain markers: an increased choline:creatine ratio in white matter (suggesting ongoing glial proliferation) (Van Dalen et al., 2016); and CSF neurofilament heavy-chain (a marker of neuronal damage) (Blokhuis et al., 2019). EF was positively associated with the following brain markers: higher grey matter volumes globally and in frontal regions of interest (Lewis-de los Angeles et al., 2017); higher fractional anisotropy and axial diffusion in certain key white matter tracts (J. Hoare et al., 2019; Uban et al., 2015). EF was negatively associated with the following peripheral blood markers: higher pro-

inflammatory cytokine activation (Foster et al., 2012), high sensitivity C-reactive protein (a marker of low-grade inflammation) (J. Hoare et al., 2019); higher soluble CD 14 (a marker of macrophage activation) (Kim-Chang et al., 2019). EF was positively associated with the following peripheral blood markers: higher low-density lipoprotein cholesterol (J. Hoare et al., 2019); higher soluble vascular adhesion molecule (a marker of vascular inflammation and endothelial activation) (Kim-Chang et al., 2019). Positive functional associations with EF in PHIV and/or PHEU (Table 5) included: academic achievement, adherence (associated with behavioural regulation) (Garvie et al., 2017; Sirois et al., 2016). In adolescents with BHIV, EF was positively associated with education level, negatively associated with psychological distress, had mixed associations with current disease markers (Baker et al., 2014; Nichols et al., 2013; Nichols, Bethel, et al., 2016; Salama et al., 2013), and was not associated with risky behaviour in one study (Baker et al., 2014) (Table 6).

Table 3. Potential predictors associated with executive function in children and adolescents with perinatally acquired HIV and/or perinatal HIV exposure without infection

	Association and direction of effect on EF or EF subtype		
Level	**Significant & in same direction in ≥ 1 study**	**Mixed findings**	**No association**
Individual	Highest level of education (years of schooling): +WM, +PL [1] Sleep duration: +WM [2]	Older age: +EF, -WM [1,3,4] Female sex: +WM [5], +TS [5], IC, PL, EF [1,3,4] Weight: +WM [1], PL [1], +PR EF [6] Height: +PR EF [6], WM, PL [1] ADHD diagnosis: -PR EF, WM, IC, PL [7]	
Perinatal			Low birth weight, duration of exclusive breastfeeding: EF [3]

Level	Significant & in same direction in ≥ 1 study	Mixed findings	No association
Caregiver	Biological parent as caregiver: +WM [8]	Maternal IQ: +WM [8], EF [3] Caregiver depression: -PR EF [9, 10], EF Higher maternal age: +EF [3]	Parental stress, perceived wealth, maternal education [3]
Family or household	Cash receipt, good parenting: +WM [11]	Crèche attendance, mother as income provider, home stimulation: +EF [3] Higher socio-economic status: +WM [8], +TS[12], EF[3]	
Treatment-related	Increase in age in those on ART: -WM, -PL [1] Higher CD4% at ART initiation: +WM, +EF [13]	Currently on ART: +TS [14], -WM [1] Longer ART duration: ±WM [1,4,13,15], ±IC [5,13], +TS [5], PL [1], EF [4] NNRTI-based regimen: -WM [15], EF [16] Delayed ART: -WM [17], PL, TS [17-19] Older age at ART initiation: -TS [20], -WM [21], EF, PL, SR EF, PR EF [1,18,22, 23]	
HIV-related		Past advanced disease (e.g. Stage 4 HIV or encephalopathy or more hospital admissions): -WM [7,19,24], -TS [19], -EF[25, 26], -SR & PR EF [22] Current CD4 count: +IC [26,27], +WM [4,15,27], EF [28], PL[27] Current viral load: -WM [4,23,27], TS[19], -IC [26,27], -PL [27], -PR EF [22,29], EF [21,28,30] HIV-1 viral subtype A versus D: -WM, IC, PL, EF [30,31] Timing of disease severity: -EF, -SR EF [22,26] Latent Toxoplasma infection: -EF [32]	Nadir CD4 count: TS [19]

Key: + = positive; - = negative; ± = positive or negative association; WM = working memory; PL = planning; EF = executive function; PR = parent-reported; TS = task switching (set-shifting); IC = inhibitory control (inhibition); NNRTI = non-nucleoside reverse transcriptase inhibitor; SR = self-reported; ART = antiretroviral therapy; 1 (Brahmbhatt et al., 2017); 2 (Foster et al., 2012); 3 (Rochat et al., 2016); 4 (Martin et al., 2006); 5 (Maganlal, 2013); 6 (Boivin, Nakasujja, et al., 2017); 7 (Burkey et al., 2015); 8 (R. Smith et al., 2012); 9 (I. Familiar

et al., 2016); 10 (I. Familiar et al., 2018); 11 (Sherr et al., 2017); 12 (Patel et al., 2018); 13 (Koekkoek et al., 2008); 14 (Willen, Cuadra, Arheart, Post, & Govind, 2017); 15 (Nachman et al., 2012); 16 (Bangirana, Boivin, Ruel, & Achan, 2015); 17 (Benki-Nugent et al., 2016); 18 (Puthanakit et al., 2013); 19 (R. N. Robbins et al., 2019); 20 (Van den Hof et al., 2019); 21 (J. Hoare et al., 2019); 22 (Nichols et al., 2015); 23 (Kapetanovic et al., 2010); 24 (S. Y. Walker et al., 2013); 25 (Judd et al., 2016); 26 (Malee et al., 2017); 27 (Ruel et al., 2012); 28 (Nagarajan et al., 2012); 29 (Ruisenor-Escudero et al., 2015); 30 (Bangirana et al., 2016); 31 (Boivin, Ruel, et al., 2010); 32 (Ene et al., 2016)

Table 4. Potential markers associated with executive function in HIV-affected children and adolescents with perinatally acquired HIV and behaviourally acquired HIV

	Association and directionality (if any)	
Level	**Significant in ≥1 study**	**No association**
Neuro-imaging	PHIV: Higher Cho:Cre ratio in the brain: -WM, -EF [1] Bilateral precentral gyrus, LH rostral middle frontal gyrus, and total GM volumes: +WM [2] Higher right IFO, EC, CP, SFO fractional anisotropy and axial diffusion on DTI: +WM [3,4], +TS [4] Abnormalities on CT-Brain: -WM [5]	
Immuno-logical or vascular	PHIV: Pro-inflammatory cytokine (TNF-α, IFN-γ) activation: -WM [6]; hs-CRP: -TS, -EF, -WM [7]; LDL-C: +TS, +WM [7]; higher CSF NFH: -WM [8] BHIV: Higher sCD14: -EF [9] Higher sVCAM-1: +WM, +EF [9]	PHIV: 9 markers of vascular dysfunction: WM [10]

Key: PHIV = perinatally acquired HIV infection; Cho = choline; Cre = creatine; WM = working memory; EF = executive function; LH = left hand side; GM = grey matter; IFO = inferior fronto-occipital fasciculus; EC = external capsule; CP = cerebral peduncle; SFO = superior fronto-occipital fasciculus; DTI = diffusion tensor imaging; CT = computed tomography; TNF = tumour necrosis factor; IFN = interferon; hs-CRP = high sensitivity C-reactive protein; TS = task switching; LDL-C = low-density lipoprotein cholesterol; CSF = cerebrospinal fluid; NFH = neurofilament heavy-chain; BHIV = behaviourally acquired HIV; sCD14 = soluble CD 14, a marker of macrophage activation; sVCAM = soluble vascular adhesion molecule, a marker of vascular inflammation and endothelial activation; PHEU = perinatally HIV-exposed uninfected; 1 (Van Dalen et al., 2016); 2 (Lewis-de los Angeles et al., 2017); 3 (Uban et al., 2015); 4 (J. Hoare et al., 2019); 5 (Martin et al., 2006); 6 (Foster et al., 2012); 7 (J. Hoare et al., 2019); 8 (Blokhuis et al., 2019); 9 (Kim-Chang et al., 2019); 10 (Kapetanovic et al., 2010)

Table 5. Potential functional outcomes associated with executive function in children and adolescents with perinatally acquired HIV and/or perinatally HIV-exposed without infection

	Association and directionality (if any)		
Type of EF measure	**Significant in ≥1 study**	**Mixed findings**	**No association**
Cognitive tasks	+Academic achievement [1]	+Adaptive behaviour [1]	Adherence [2]
Behavioural report	+Education risk: WM problems [3,4], TS problems[4]	Adherence: + self-reported behavioural regulation; global self-report or caregiver-report EF [5]	Medication responsibility [5]

Key: EF = executive function; WM = working memory; TS = task switching (set-shifting); 1 (Sirois et al., 2016); 2 (Garcia-Navarro et al., 2013); 3 (Nichols, Chernoff, et al., 2016); 4 (R. N. Robbins et al., 2019); 5 (Garvie et al., 2017)

Table 6. Potential predictors and outcomes associated with executive function in adolescents with behaviourally acquired HIV

	Association and direction (if any) of effect on EF or EF subtype		
Level	**Significant in ≥1 study**	**Mixed findings**	**No association**
Individual	Psychological distress: -EF [1], -TS [2] Highest level of education: +TS [2]		Age, sex: TS [2]
HIV-related		Current CD4 count: +EF [1,3], WM [3], TS [2] Current viral load: -EF [1,3,4], WM [3], TS [2]	Time since diagnosis: TS [2] Advanced disease: EF, WM [3]
Behavioural			Risky sexual & substance use behaviour [3]

Key: EF = executive function; TS = task switching (set-shifting); WM = working memory; 1 (Nichols, Bethel, et al., 2016); 2 (Salama et al., 2013); 3 (Baker et al., 2014); 4 (Nichols et al., 2013)

2.3.9. Interventions affecting executive function

There were eight intervention studies; two were pharmacological (Table C, Appendix 2). PREDICT assessed the EF effects of delaying ART initiation in PHIV until immunological markers were low. It found no difference between delayed and early arms (Puthanakit et al., 2013). PENTA 11 assessed the effects of a planned treatment

interruption in PHIV versus continuous treatment and found no difference one or two years later (Ananworanich et al., 2016).

A study in pre-schoolers with PHIV or PHEU tested a year-long mediational intervention for sensitising caregivers (MISC) compared to UCOBAC (Uganda Community Based Association for Women and Children Welfare) nutrition and hygiene curriculum. The UCOBAC group had fewer caregiver-reported EF problems after one year (PHIV: d = -0.36 [95% CI -0.73, 0.00]; PHEU: d = -0.45 [95% CI -0.71, -0.18]) which was maintained in the PHEU group after two years but not in the PHEU group (Bass et al., 2017; Boivin, Nakasujja, et al., 2017). A Kenyan study in 4-8-year-olds, mostly PHEU, found no difference in verbal working memory improvements after 18 months of beef or soya biscuits, compared to wheat biscuits (Loo et al., 2017).

Three studies (two RCTS; one uncontrolled) tested 1-2 months of computerised cognitive rehabilitation therapy (CCRT) 2-3 times per week in school-aged children and adolescents. None found effects on inhibition or verbal working memory. All found improvements in maze learning (spatial working memory, planning) (full RCT: d = 1.37 [95% CI 0.95, 1.79]) and KABC-II planning index (full RCT: d = 0.41 [95% CI 0.03, 0.80]) (Boivin, Busman, et al., 2010; Boivin, Nakasujja, Sikorskii, Opoka, & Giordani, 2016; Giordani et al., 2015). In the full RCT, there was no significant difference at endline between full (uptitration of difficulty level) and limited (no uptitration) CCRT (Boivin et al., 2016).

A pilot RCT in HIV-positive adolescents assessed the effects of nine sessions of mindfulness-based stress reduction (MBSR) over two months compared to ‘Healthy Topics’ health education programme. The groups performed similarly on Stroop

inhibition at immediate and 3-month follow-up, except for superior accuracy of the MBSR group on a negative emotion Stroop immediately post-programme (d = 2.86 [95% CI 2.20, 3.53]) (Webb, Perry-Parrish, Ellen, & Sibinga, 2017).

2.4. Discussion

2.4.1. Main findings and implications

Table 7. Summary of pooled effect size based on meta-analysis by subpopulations compared and type of executive function

Target group	Comparator group			
	PHU (not HIV-affected)	PHEU	Mixed PHEU/PHU (HIV-affected)	PHIV
PHIV	Verbal WM: -0.84 (-1.10, -0.58)* Visuospatial WM: -0.54 (-0.91, -0.18)* IC: -0.54 (-1.13, 0.04) TS: -0.33 (-0.89, 0.23) PL: -0.54 (-0.73, -0.36)* PR EF: 0.31 (-0.23, 0.85)	Verbal WM: -0.45 (-0.72, -0.18)* Visuospatial WM: -0.33 (-0.62, -0.04)* IC: -0.29 (-0.44, -0.15)* TS: -0.13 (-0.27, 0.01) PL: -0.21 (-0.49, 0.07) PR EF: 0.21 (-0.19, 0.60)	Verbal WM: -0.28 (-0.49, -0.07)* IC: -0.16 (-0.43, 0.10) TS: -0.28 (-0.53, -0.02)* SR EF: 0.43 (0.17, 0.68)*	CDC C vs non-C: Verbal WM: -0.34 (-0.60, -0.09)* IC: -0.43 (-0.73, -0.12)* TS: -0.30 (-0.50, -0.11)* PL: -0.17 (-0.63, 0.29)
PHIV slow progressors	Verbal WM: -0.21 (-0.55, 0.13) IC: -0.06 (-0.42, 0.30)			
PHEU	Verbal WM: -0.12 (-0.67, 0.42) Visuospatial WM: -0.12 (-0.40, 0.15) IC: -0.20 (-1.62, 1.21) PL: -0.09 (-0.67, 0.50) PR EF: 0.10 (-0.08, 0.29)			
BHIV	TS: -0.18 (-0.80, 0.44)			

Key: Effect sizes = Cohen's d with 95% confidence interval; PHU = perinatally HIV-unexposed uninfected; PHEU = perinatally HIV-exposed uninfected; PHIV = perinatally HIV-infected; WM = working memory; * = $p < 0.05$; IC = inhibitory control (inhibition); TS = task shifting (set-shifting); PL = planning; PR = parent-reported; EF = executive function; SR = self-reported; BHIV = behaviourally acquired HIV; vs = versus

These meta-analytic findings supported thesis hypothesis 1 that EF deficits are more common in HIV-positive adolescents. The findings also supported sub-hypothesis 1.3 that there is a distinct pattern of EF involvement in the context of perinatal HIV infection and exposure in children and adolescents (Table 7). In general, verbal and visuospatial working memory had the largest effect sizes, with smaller effects for planning, inhibition and self-reported global EF, and the smallest effects for set-shifting and caregiver-reported global EF. The effect sizes were larger when comparing PHIV on ART to healthy HIV-unaffected controls. They diminished when controls lived in HIV-affected households, with or without perinatal HIV exposure. This finding supports sub-hypothesis 1.2.2 and suggests that effects are partly related to perinatal HIV exposure and associated psychosocial risks from living in an HIV-affected household. This is supported by the findings that psychosocial resilience factors (e.g. higher SES, cash receipt, good parenting, biological parent as caregiver, longer schooling) were usually associated with better EF (Brahmbhatt et al., 2017; Patel et al., 2018; Rochat et al., 2016; Sherr et al., 2017; R. Smith et al., 2012).

Meta-analyses comparing PHEU with PHU not living in HIV-affected households did not find any effect of perinatal HIV exposure; however, there was high between-study heterogeneity with negative effects on working memory and inhibition in some contexts (Boivin et al., 1995; Milligan, 2016; Milligan & Cockcroft, 2017). There was limited evidence for set-shifting, planning or global EF in daily life. These findings only partially support sub-hypothesis 1.2.3 and suggest that context may play an important role in determining whether living in an HIV-affected household conveys additional risk in terms of EF.

For perinatal HIV infection, pooled effect sizes were medium to large for working memory compared to healthy controls reducing to small when compared to controls with perinatal HIV exposure and/or living in HIV-affected households. The effects may differ by context with HIV possibly being associated with larger EF deficits in LMICs. This may be due to different HIV subtypes which predominate in the different contexts (Tyor, Fritz-French, & Nath, 2013), and/or due to cumulative risks in LMICs with limited buffering (L. Cluver & Orkin, 2009; Engle & Black, 2008; Mellins & Malee, 2013). Effects were medium for planning and inhibition compared to healthy PHU controls diminishing when compared to HIV-affected controls. Effects were small and mostly insignificant for set-shifting. For behavioural report measures of global EF, effects were medium for self-report and small and insignificant for caregiver-report.

The association between perinatal HIV infection and EF seems to be related partly to the specific immunological and virological course of the disease, affected by infection timing, treatment, other host and viral factors and their interactions (Muenchhoff et al., 2014). For example, viral subtype (A versus D) has been shown to moderate cognitive effect sizes in PHIV slow progressors not yet on ART (Boivin, Ruel, et al., 2010) but not in children and adolescents on ART (Bangirana et al., 2016). Meta-analyses comparing PHIV with a history of advanced CDC C disease to PHIV without such a history revealed worse verbal working memory, inhibition and set-shifting (small effects) in those with a history of advanced disease. Meta-analyses revealed no association between HIV and working memory or inhibition in slow progressors. These findings provide support for sub-hypothesis 1.2.1.

Although the evidence is still limited and requires replication, the current biomarker data suggests that both ongoing systemic low-grade inflammation (Foster et al., 2012; J. Hoare et al., 2019; Kim-Chang et al., 2019) and neuroinflammation may be potential mechanisms involved in neuronal injury in HIV-positive children and adolescents. Both grey matter, particularly frontal (Lewis-de los Angeles et al., 2017), and white matter abnormalities have been associated with poorer EF (J. Hoare et al., 2019; Uban et al., 2015; Van Dalen et al., 2016). Biological risk factors that are common in HIV infection (e.g. stunting, latent Toxoplasma infection) may also contribute to risk for poorer EF (Boivin, Nakasujja, et al., 2017; Brahmbhatt et al., 2017; Ene et al., 2016).

The evidence was more limited for adolescents with BHIV. Meta-analysis found no effect on set-shifting which provides partial evidence to support sub-hypothesis 1.1 that EF deficits are larger and more global in perinatal HIV compared to behaviourally acquired HIV; however, more evidence is needed to elucidate the pattern of deficits, if any, across all EF subtypes in adolescents with behaviourally acquired HIV (sub-hypothesis 1.4).

In terms of developmental trajectories, most longitudinal data suggested improvement in PHIV on ART with similar changes to control groups. The extent to which improvement could be attributed to developmental factors, task familiarity, and other factors (e.g. ART duration) was difficult to assess. In the adolescent BHIV cohort, ART timing did not affect improvement (Nichols, Bethel, et al., 2016). Two studies in PHIV with delayed ART initiation or planned treatment interruption found no EF effects.

Some of the factors associated with EF may act as potential targets for psychosocial interventions (e.g. increased schooling years, good parenting, cash transfers, caregiver depression, and adolescent psychological distress). A few interventions have been tested at different developmental stages. CCRT in school-aged children and early adolescents has shown some near transfer but no far transfer to other EF components or behaviour (Boivin, Busman, et al., 2010; Boivin et al., 2016; Giordani et al., 2015). Mindfulness-based stress reduction in adolescents resulted in short-term improvements in inhibition in negative emotive contexts, but these were not maintained (Webb et al., 2017).

Challenges and limitations

There were several challenges and limitations in conducting this review. The heterogeneity of control groups used as comparators for PHIV complicates this literature. I performed separate analyses by control group type, but it meant there were fewer studies in each meta-analysis. It also meant there were multiple comparisons performed in this systematic review resulting in a higher risk of type 1 errors (Bender et al., 2008). The multiplicity issue may have been compounded by examining multiple EF subtypes separately. There was often evidence of publication bias. There may have been selective reporting of positive findings by included studies. The number of studies for meta-analysis was better for working memory, but in most meta-analyses it was low resulting in imprecise estimates.

In relation to measurement, there are several challenges faced when measuring EF particularly cross-culturally which may affect the comparability of studies from different parts of the world. Working memory has been assessed more frequently because it is

likely the easiest EF subtype to measure consistently using measures that have been validated or normed in multiple contexts globally. Inhibition, set-shifting and planning may be harder to assess in a valid way cross-culturally, making them harder to compare across contexts. The use of different outcome measures and EF tasks, some more sensitive than others, to measure inhibition, set-shifting and planning may have affected the effect sizes obtained. Some tasks have been used in LMICs with poor test adaptation or without local validation to ensure the task is valid and reliably measures EF in the context. When studying EF, there is also the more general "task impurity" problem. EF tasks, although predominantly reflective of one EF subtype, often place demands on other EF components and non-EF cognitive processes. Sometimes there is disagreement regarding the main EF assessed by a particular task. The behavioural report measures of EF are subjective, and reporting may be affected by the rater's mental health. For example, depressed caregivers are more likely to rate their children as having more EF problems (I. Familiar et al., 2016).

Although most studies with control groups attempted to achieve a balance of key confounders, differences between groups were not always considered in analysis; and some only presented unadjusted results. I repeated each meta-analysis using adjusted data when available and findings were mostly similar; however, it is possible that if more adjusted results were available, effect sizes would have diminished. The quality assessment score, which affected meta-analytic weighting, did take these factors into account. The low number of studies available for each meta-analysis also precluded meta-regression (*Cochrane Handbook for Systematic Reviews of*

Interventions, 2011) which could help to quantify the extent to which various moderators affect pooled effect sizes.

There were also limitations with regards to the sampling strategy and eligibility criteria of included studies. Since most studies spanned childhood and adolescence, I was unable to discern differential patterns of deficits that may be associated with HIV exposure or infection at distinct periods during the trajectory of EF development and maturation. Most studies used facility-based recruitment meaning these samples are not representative of the most vulnerable HIV-affected children and adolescents who may be undiagnosed, unlinked to care or lost to follow-up. Some studies excluded more advanced HIV also decreasing their representativeness.

2.4.2. Research gaps and how I plan to address them

More adolescent-only studies or adolescent-disaggregated data are needed if we are to understand EF deficits in this unique developmental period and what interventions might be effective to improve EF and associated outcomes during adolescence. I address this gap in Studies 3 and 4 (Chapters 4 and 6). More research is needed on EF in adolescents with BHIV particularly in Africa where HIV amongst adolescents is most prevalent. I address this gap in Study 3 (Chapter 4).

More research is needed on “cool” EF other than working memory, and “hot” EF in emotional (affective) contexts which may be more closely related to certain important outcomes in adolescence (e.g. risk-taking, emotional problems) (Botdorf et al., 2017; Poon, 2017). I address this gap by validating an EF battery including both cool (working and non-working memory tasks) and hot tasks in Study 2 (Chapter 3), and then using the battery in Studies 3 and 4 (Chapters 4 and 6).

One study examined the relationship between EF and risky sexual and substance use behaviour in BHIV and found no association (which does not support hypothesis 2.1) (Baker et al., 2014); however, more evidence is needed in all three HIV-affected subpopulations. I plan to address this gap in Studies 3 and 4 (Chapters 4 and 6). Only two studies addressed hypothesis 2.2 regarding a potential relationship between adherence to treatment and EF in PHIV and generally found no association (which does not support hypothesis 2.2); however, more evidence is needed (Garcia-Navarro et al., 2013; Garvie et al., 2017). I plan to address this gap in Study 4 (Chapter 6).

Many studies used either behavioural report or cognitive task measures. Behavioural report and cognitive tasks should be used together in future studies to allow triangulation and assessment of the extent of everyday functional impairment.

Some of the cohort studies have started to address potential mechanisms through neuroimaging and biomarker sub-studies. These suggest that, similar to adult HAND, systemic and CNS inflammation may also play a role in children and adolescents (Blokhuis et al., 2019; Foster et al., 2012; J. Hoare et al., 2019); however, more research in paediatric HAND is needed still.

Intervention research is limited currently. Pharmacological treatments showing promise in adults (e.g. CCR5-antagonist Maraviroc) (Ndhlovu et al., 2014) should be considered for testing in paediatric HIV. The EF effects of different antiretroviral drugs with varying CNS-penetration effectiveness should be evaluated more thoroughly in paediatric populations (Smurzynski et al., 2011). Complex psychosocial interventions targeting multiple EF determinants should also be tested. I begin to address this gap

by developing and testing a group musical training intervention in Study 4 (Chapter 6).

2.4.3. Conclusions

This systematic review with meta-analyses summarised the EF profiles of HIV-exposed and HIV-infected children and adolescents globally. It confirmed that PHIV is associated with EF deficits despite the widespread use of antiretroviral therapy; however, the evidence is limited for adolescents with BHIV. I found that PHIV is associated with larger working memory deficits with smaller deficits in inhibition, planning, and possibly set-shifting. I explored factors associated with EF in these populations, finding some associations with disease-related factors and others with psychosocial and behavioural factors. Finally, I found that interventions tested so far in different age groups have shown limited effects. I highlighted important research gaps that need to be filled to enhance our understanding and management of HIV-affected children and adolescents with EF deficits and mentioned where I have started to address these gaps in the thesis, when relevant.

Chapter 3: Study 2, the validation of OCS-EF, a tool for assessing executive function, amongst late adolescent females in the HPTN 068 cohort

Chapter outline:

3.1. Background

- 3.1.1. Context
- 3.1.2. Rationale
- 3.1.3. Objectives

3.2. Methods

- 3.2.1. Study design
- 3.2.2. Materials and administration
- 3.2.3. Task descriptions
- 3.2.4. Data analysis

3.3. Results

- 3.3.1. Sample characteristics
- 3.3.2. Data integrity
- 3.3.3. Task durations
- 3.3.4. Task performance
- 3.3.5. Confirmatory factor analysis

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- 3.4.1. Summary and interpretation of main findings
- 3.4.2. Limitations
- 3.4.3. Recommendations for future improvement
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- 3.4.5. Conclusion

3.1. Background

Firstly, I describe the context for this study and the following two studies in the thesis. I then go on to explain the rationale and finally the objectives for this study.

3.1.1. Context

Three of the studies in this thesis (Studies 2-4) were based at the MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt). It is one of the extramural research units of the South African Medical Research Council (MRC) and is part of the University of the Witwatersrand (Wits) School of Public Health. It is also known as the Agincourt Health and Socio-Demographic Surveillance System (HDSS) because it has functioned as an HDSS collecting annual census data on resident status and vital events within its boundaries since 1992. It provides a platform for research on rural southern African populations, their health, social transitions and their effects at different stages in the life course (Kahn et al., 2012). Observational and intervention studies nested within this longitudinal platform benefit by making use of the existing census and study data, the research infrastructure and the established relationship with the community and local health facilities through the public engagement office and the community advisory board (a subset of whom are randomly selected to help with each study). Community consent for the ongoing research was obtained from both civic and traditional leadership authorities. Verbal and written consent are obtained continually at the household and individual level. Every study receives approval from the Wits Human Research Ethics Committee (Medical) and the Mpumalanga Provincial Department of Health Ethics Committee

("MRC/Wits-Agincourt Unit: Rural Public Health and Health Transitions Research Unit," 2019).

The HDSS spans 420 km^2. It is situated in rural north-east South Africa in the Bushbuckridge Local Municipality, Ehlanzeni District, Mpumalanga Province next to the Mozambican border (Figure 34). Infrastructure development there has continued slowly post-apartheid. There is still no piped water to the vast majority of dwellings; most people collect water from communal taps. There are only basic sanitation facilities; most households use pit latrines. Most roads are made of dirt although some of the roads connecting villages are now tarred or currently being tarred. There is no formal public transport system; however, there are two minibus taxi networks which follow fixed routes within and between the village main roads. There is a primary school in every village and most villages have a secondary school; however, the quality of education is still poor and there are few local opportunities for tertiary education or employment after school completion (Kahn et al., 2012). Many households rely on South Africa's social grant system, particularly the old age pension and child support grant, for income. There are eight primary health care facilities (clinics or community health centres) within the study site and three district hospitals within a 60km radius (Kahn et al., 2012). There are also more than 300 traditional healers in the Bushbuckridge Municipality (Audet, Ngobeni, Graves, & Wagner, 2017).

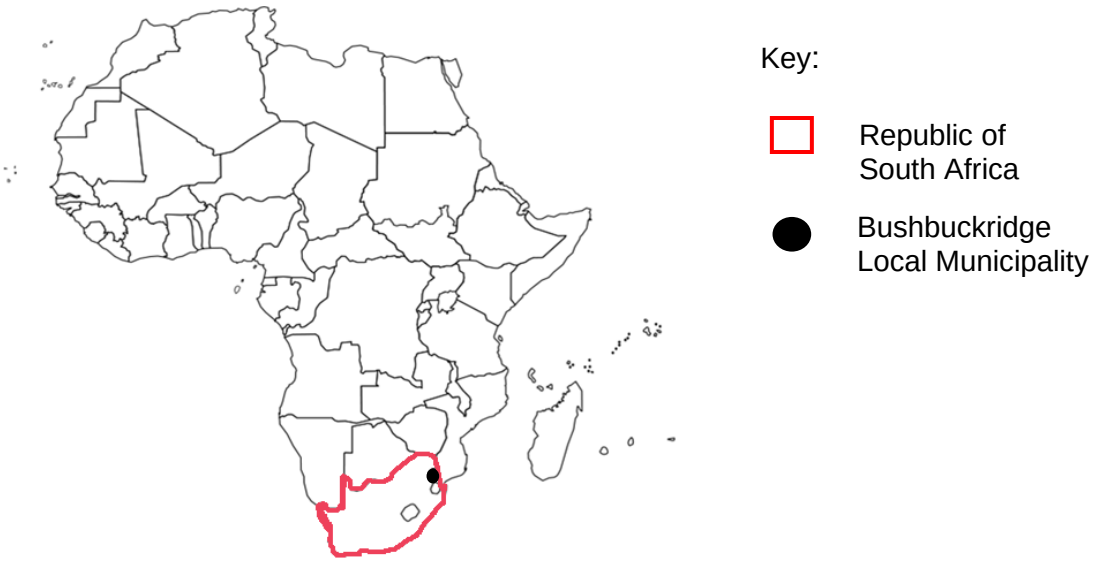


Figure 34. Map of Africa (adapted from worldatlas.com ("Country Map of Africa Outline," 2019)) with the Republic of South Africa outlined and the Bushbuckridge Local Municipality highlighted

There are currently 28 administrative villages spanning three tribal authorities within the study site (Figure 35). In 2017, there were 116,549 people living there in 22,721 households ("MRC/Wits-Agincourt Unit: Rural Public Health and Health Transitions Research Unit," 2019). The population is largely black African with most people speaking the Shangaan dialect of Tsonga as their home language. Approximately 30% of people living in the Bushbuckridge Local Municipality are former Mozambican refugees whose households have been disadvantaged persistently socio-economically (Kabudula et al., 2016). Although wealth (measured by asset ownership) at a population level has increased with time, the improvement has been slower for poorer households (Kabudula et al., 2016). There are high levels of youth unemployment with approximately 88% of female and 62% of male out-of-school 18-24-year-olds in the area being unemployed (A. Wilkinson et al., 2017). The HIV prevalence is high with females being disproportionately affected; 23.9% of females

and 10.6% of males ≥ 15-years-old in the Agincourt sub-district were HIV-positive in 2011 (Mee et al., 2016). The HIV prevalence rises dramatically from middle (15-19-years-old) adolescence (females: 5.5%; males: 0.4%) to late (20-24-years-old) adolescence (females: 27.0%; males: 6.1%) (Gomez-Olive et al., 2013).

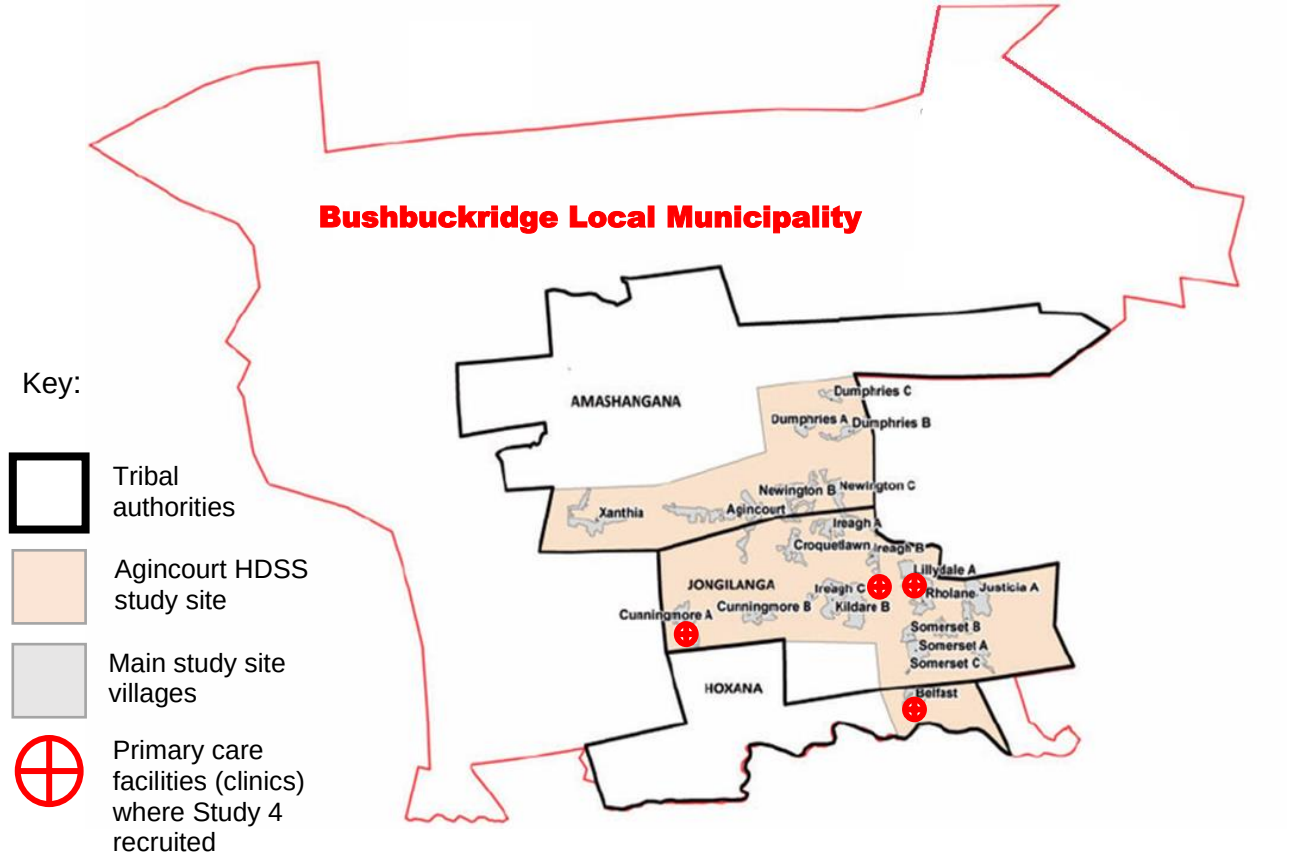


Figure 4. Map of Bushbuckridge Local Municipality (adapted from Paul Mee's figure in the International Journal of Epidemiology (Joubert et al., 2014)) with the three tribal authorities and main study site villages within the Agincourt Health and Socio-Demographic Surveillance System (HDSS) study site illustrated

3.1.2. Rationale

In Study 1, various research gaps emerged, some of which I address in the following chapters; however, I could not start to address the problem of EF deficits until I could measure EF reliably. I therefore needed to find a valid, reliable tool to assess EF, including the various subtypes (verbal and visuospatial working memory, inhibition, set-shifting, planning), in adolescents in rural South Africa. In order to limit costs, I also needed to find a tool for which the developers would not charge me for use. A cheaper cognitive assessment tool is also more likely to be sustainable in a rural LMIC setting. In a rural South African context, there are no neuropsychologists, often no clinical psychologists and sometimes only one educational psychologist covering an entire district; therefore, I also needed a tool that could easily and feasibly be administered by trained lay people or fieldworkers in a standardised manner at scale. I also needed a tool that was not heavily verbal, culture- or language-bound so that it would not be biased against non-English-speaking participants. The University of Oxford Department of Experimental Psychology had recently partnered with the team at the MRC/Wits Agincourt Research Unit to develop a new predominantly non-verbal EF assessment tool called Oxford Cognitive Screen – Executive Function (OCS-EF) which they were administering to a large sample of young women in Agincourt as part of a larger study called HIV Prevention Trials Network (HPTN) 068. The tool was designed to be suitable for adolescents in rural LMIC settings and based on the existing tablet-based OCS-Plus platform (Demeyere et al., 2019; Humphreys et al., 2017). As Study 2 of my thesis, I therefore performed a validation study using this

HPTN 068 sample to confirm the factorial (construct) validity of the tool in a rural South African context.

The evidence from high-income countries suggests that the EF subtypes differentiate during development from a unitary ability into three distinct but related abilities (working memory, set-shifting, inhibition) by late adolescence (Naomi P. Friedman et al., 2008; C. Hughes et al., 2010; Latzman & Markon, 2010; K. Lee, Bull, & Ho, 2013; Miyake et al., 2000; Shing et al., 2010; Wiebe, Espy, & Charak, 2008). Data on the factor structure of EF in adolescents from LMICs are much more limited. A study looking at EF and 'general intelligence' in school-aged children and adolescents in three LMICs in Africa and Asia found a single-factor model explained the data better than a two-factor (EF versus intelligence) model, with no difference in structure between younger and older age groups (Holding et al., 2018); however, more differentiated models were not tested. The South African Siyakhula cohort in primary school-aged children and early adolescents tested a four-factor cognitive model which included two EF-related factors (planning/inhibition/switching and working memory) and found an acceptable fit (Rochat et al., 2017); however, simpler models were not tested. To my knowledge, there are no large studies looking at the factor structure of EF in late adolescents or young adults in LMIC settings.

3.1.3. Objectives

I aimed to:

1. determine the feasibility of large-scale cognitive assessment by lay fieldworkers in a rural African setting;

2. describe task-by-task performance in a normative sample of HIV-negative late adolescents using the OCS-EF as an EF assessment tool in a rural African setting;
3. determine the construct (factorial) validity of OCS-EF in this population and context by confirming whether the factor structure of EF amongst a normative sample of late adolescents in a rural African setting fits one of the two theoretical models of EF (three-factor or hot-cool) developed in high-income country settings.

3.1.4. Hypotheses

1. Large-scale cognitive testing using OCS-EF in rural South Africa is feasible.

2. OCS-EF is a valid tool for measuring EF amongst late adolescents in rural South Africa.3.2. Methods

3.2.1. Study design

Study 2 was a validation study assessing the factorial validity of the OCS-EF cognitive assessment tool. The validation study made use of secondary data from a nested cross-sectional cognitive substudy from the second post-intervention visit of the HPTN 068 study. HPTN 068 is an ongoing longitudinal cohort study post-randomised controlled trial run by the MRC/Wits Agincourt Research Unit in the Bushbuckridge Municipality, Mpumalanga, South Africa. The full details of the original trial and main trial results are reported elsewhere (Pettifor, MacPhail, Hughes, et al., 2016; Pettifor, MacPhail, Selin, et al., 2016). There was no intervention effect found; thus, the trial arms are pooled in this study. Ethical approval was obtained for the study from the

University of Witwatersrand Human Research Ethics Committee (Medical) and the University of North Carolina Institutional Review Board. Caregiver consent and participant consent or assent in the case of minors under 18-years-old was obtained. The inclusion criteria at baseline were: females aged 13-20-years-old enrolled in grades 8-11 at participating public secondary schools, not self-reported married or pregnant, able to complete a tablet-based questionnaire alone, having documentation to open a bank or post office account, having a parent/guardian with similar documentation living in the same residence, currently living in the MRC/Wits Agincourt HDSS villages, and intending to live within the study area until study completion. HIV-positive women were not excluded from the original study to avoid possible stigmatisation; however, they were excluded from this validation study so that data represented only the normative healthy population.

3.2.2. Materials and administration

Socio-demographic data, including an asset index as a marker of socioeconomic status, were obtained with participant Audio Computer-Assisted Self-Interview (ACASI) and caregiver Computer-Assisted Personal Interview (CAPI). Questions were translated into the local language, Tsonga, by staff at the MRC/Wits Agincourt Research Unit. HIV screening with appropriate pre- and post-test counselling was performed at each study visit using two different rapid HIV tests with confirmatory HIV testing being done in the HIV Prevention Trials Laboratory Centre if there was at least one positive result, as described fully elsewhere (Pettifor, MacPhail, Hughes, et al., 2016).

The Oxford Cognitive Screen – Executive Function (OCS-EF) is a tablet-based cognitive assessment tool (© The University of Oxford) mainly targeting EF, both 'cool' and 'hot', which aims to be culturally unbiased, brief (approximately 30 minutes) and easy to administer by a trained lay health worker or fieldworker. It runs as a stand-alone application in Windows or Android with full written on-screen instructions for each task to ensure standardised administration. There is a fixed order of task administration to minimise measurement error due to potential participant by order interaction effects.

The version used in this study was administered on Windows Surface Pro tablets using dedicated styluses with touch input disabled to avoid accidental input. The software was developed by Dr Mihaela Duta at the University of Oxford using Matrix Laboratory (MATLAB) and Psychophysics Toolbox. Six of the seven tasks are non-verbal, making it less language-dependent and more applicable in cross-cultural settings. Stimuli are adapted to be suitable for low-literacy contexts (e.g. shapes instead of numbers and letters on the trails task).

Four of the tasks (trails, figure drawing, rule-finding, selection) are a subset of the Oxford Cognitive Screen Plus (OCS-Plus (Demeyere et al., 2019; Humphreys et al., 2017)). Trails is a geometric version of the trail-making task aiming to assess psychomotor speed, sequencing, planning, monitoring, and task switching (cognitive flexibility). The figure drawing task assesses visuospatial constructional ability (copy condition) and visuospatial working memory and planning (recall condition). The rule-finding task aims to assess visuospatial problem-solving or pattern recognition and

task switching. The selection or cancellation task assesses selective attention (visible condition), and visuospatial working memory and planning (invisible condition).

Three tasks were added to assess verbal working memory (digit recall) and inhibitory control in emotive contexts (emotional go/no-go, Iowa Gambling Task), so-called 'hot' EF. Digit recall is a classic and widely used task that assesses verbal short-term memory or storage (forwards) and verbal working memory (backwards). The emotional go/no-go task is based on the task implementation as described by Hare (Hare et al., 2008). The Iowa Gambling Task was modified from the original task as described by Bechara (Bechara, Damasio, Damasio, & Anderson, 1994). This implementation is based on the Children's Gambling Task as described by Kerr and Zelazo (A. Kerr & Zelazo, 2004). In this thesis, I refer to it as the Iowa Gambling Task. It assesses risk-taking and decision-making in the context of uncertain reward.

For this study, some of the OCS-EF stimuli were adapted for the linguistic and cultural context. The fruit and vegetables in the selection task are commonly found in Agincourt and are familiar to participants in the Bushbuckridge Municipality. Facial stimuli for the emotional go/no-go task were grayscale photographs of three African-American women from the NimStim set of facial expressions (Tottenham et al., 2009). All task instructions were translated from English into Tsonga by the MRC/Wits Agincourt Research Unit and appeared on-screen in Tsonga. Instructions were read in Tsonga but the digits in the digit recall task were verbalised in English due to widespread familiarity with counting in English taught in local schools. Testing was performed in testing rooms at the MRC/Wits Agincourt Research Unit field office or at participants' houses by local trained female fieldworkers fluent in English and Tsonga.

After each task was completed, the tool prompted the examiner to select a test condition from the following predefined list of test conditions: no issue, no speech, visual problems, motor problems, auditory problems, fatigue, refused, technical problems, ran out of time, interruptions, examiner error, other. For analytical purposes, test condition issues were grouped into three broad categories: participant, examiner, environmental/technical. Selection of any condition other than 'no issue' resulted in invalidation of the task and that participant's task data were excluded from the analysis. Task timing (duration and/or reaction time) was recorded automatically. Accuracy was scored automatically during task administration except for tasks that required interpretation of the participant's drawing (figure drawing) or speech (digit recall).

3.2.3. Task descriptions

More detailed task descriptions are provided in Appendix 3: OCS-EF task descriptions.

3.2.3.1. Trails

Participants were presented with an arrangement of squares and circles on the screen and asked to use the stylus to connect them in certain orders. This task consisted of two baseline conditions (connecting circles in ascending order of size; connecting squares in descending order of size) and a switching condition (alternating from largest square to smallest circle to next largest square etc.). See Figure 36. Each condition was preceded by two practice rounds to ensure task comprehension. I derived proportion accuracy scores (total number of correct connections divided by total possible correct connections) scores for the combined baseline conditions and

the switching condition. I derived a switch accuracy cost score by dividing the switch proportion accuracy by the combined baseline proportion accuracy, capped at a maximum of 1 (Humphreys et al., 2017; Rosenberg et al., 2018). I derived a switch duration cost score by dividing the switch duration (capped at 120 seconds) by the combined baseline duration (capped at 120 seconds) (Arbuthnott & Frank, 2000; Sanchez-Cubillo et al., 2009).

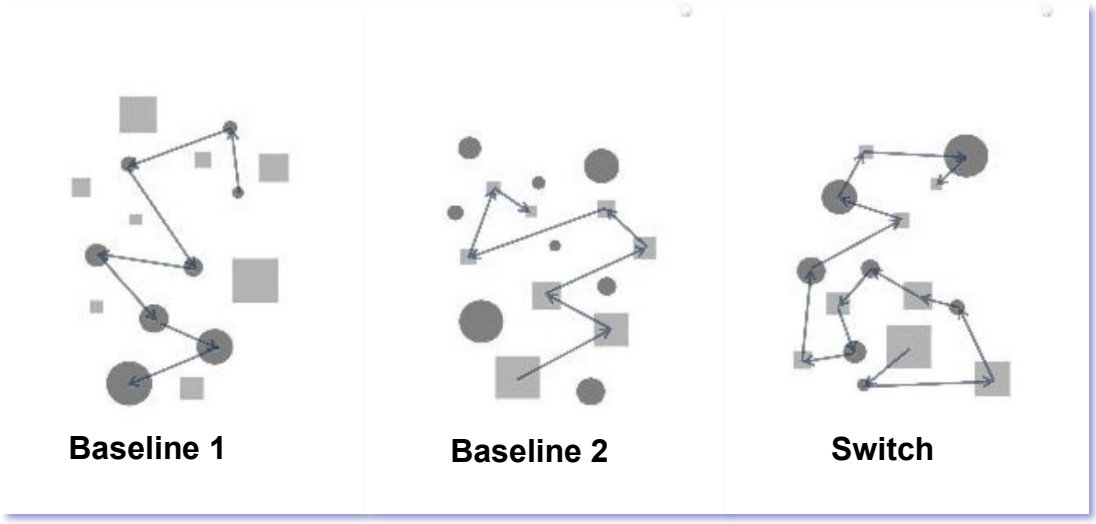


Figure 5. Shape distributions for the baseline and switching conditions for the trails task with illustration of correctly completed trails.

3.2.3.2. Iowa Gambling Task

This task consisted of two decks of cards, an advantageous, low-risk deck (low rewards and low penalties with net gain) and a disadvantageous, high-risk deck (high reward and high loss with net loss). Participants selected a card from each deck for 50 trials and saw their updated total score on screen after each selection. I derived a net score (proportion of advantageous choices minus proportion of disadvantageous choices in the last 30 trials) and a slope score (beta coefficient of the gradient of the slope of the learning curve (Burdick, Roy, & Raver, 2013), based on total points after

each of the 50 trials calculated using a random-effects hierarchical linear model with the conventional variance estimator based on asymptotic theory).

3.2.3.3. Emotional go/no-go task

Participants were presented with a series of visual stimuli: faces belonging to three different women displaying one of three different emotional expressions (happy, neutral or fearful). There was a practice block (six trials) and four test blocks (36 trials each). The neutral faces were the targets in every block. In blocks one and four, distractors were fearful faces (fearful blocks). In blocks two and three, the distractors were happy faces (happy blocks). The correct hit rate (proportion of correct responses to 'go' trials) and the commission error rate (proportion of incorrect responses to 'no-go' trials) were used to derive a sensitivity score (d-prime). D-prime (d') was calculated using the formula: d' = z(accuracy on go trials) – z(commission error rate). Z means applying the z-transformation using the inverse normal cumulative distribution (NORMSINV function in Microsoft Excel). Ceiling scores were converted prior to the d' calculation to avoid data loss when applying the z transformation. 1 (100%) for go-trial accuracy was replaced with 1-1/(2N) with N being the total number of go trials in the task (N = 96). 0 (0%) for commission errors was replaced with 1/(2N) with N being the total number of no-go trials in the task (N = 48) (Macmillan & Kaplan, 1985). After adjusting ceiling scores as described above for d' calculation, the response bias criterion C was calculated using this formula: C = -[(z(accuracy on go trials) + z(commission error rate))/2] (Macmillan & Creelman, 1990). The within-individual mean go-trial reaction time was calculated excluding early reaction times < 200 milliseconds (deemed to be anticipatory) and missed go-trials.

3.2.3.4. Rule-finding task

Participants were presented with three columns with alternating shapes (squares-triangles-squares), eight shapes per column (see Figure 37). A red dot moved from one shape to another following one of five predefined rules. Participants were asked to predict (and tap) where the dot would move next based on previous moves (the preceding position was highlighted). The change from one rule to another was not signalled. The first move in each new rule was not scored. Participants scored 1 point for each move correctly predicted, with a maximum total move proportion accuracy score of 46/46.

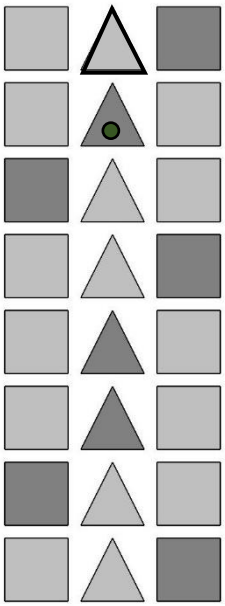


Figure 37. The grid of shapes and mobile red dot in the rule-finding task with the previous position highlighted.

3.2.3.5. Figure drawing task

This task presented participants with a composite drawing consisting of twenty geometrical elements and asked the participants to use the stylus to draw it on the screen. There were two conditions. In the copy condition, participants were asked to

copy the figure (see Figure 38). In the immediate recall condition, participants were asked to draw the same figure from memory after seeing it again briefly. I scored the accuracy manually offline after testing using dedicated figure scoring software. Each of the twenty figure components were scored for presence, accuracy and position to derive an accuracy score with a maximum of 60/60 for both the copy and recall conditions.

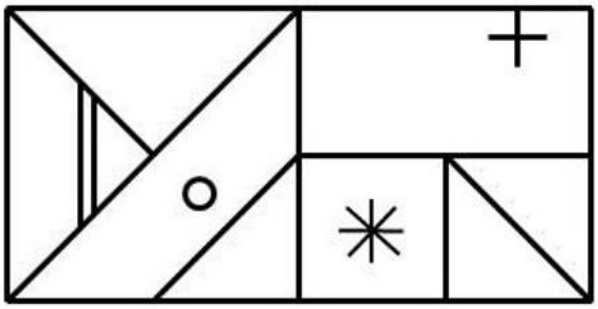


Figure 38. Complex figure used in the figure drawing task

3.2.3.6. Selection task

Participants were presented with a distribution of 60 items: 30 vegetables (10 items of each of three vegetable types) and 30 fruit (10 items of each of three fruit types) (see Figure 39). They had to select (tap) fruits (targets), ignoring the vegetables (distractors). There were two conditions. In the visible condition, there was sustained visual feedback highlighting items already selected. In the invisible condition, the items were highlighted briefly then the feedback disappeared meaning participants had to remember which items they had selected previously to avoid re-selecting items. Accuracy was derived by calculating the proportion of targets selected only once i.e. re-selection of targets was penalised for both the visible and invisible conditions (maximum 30/30 for each condition).

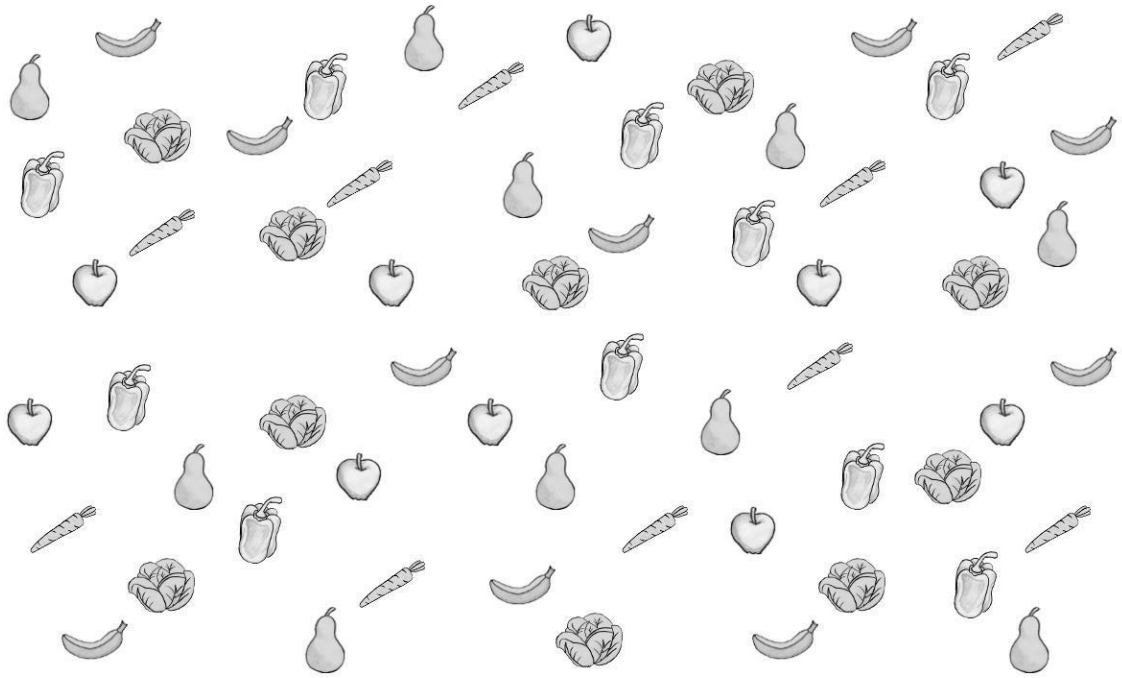


Figure 39. Distribution of fruit and vegetables for the visible condition of the selection task

3.2.3.7. Digit recall task

Participants were asked to recite a series of digit sequences (read out loud slowly by the examiner as they flashed on the screen) of increasing length (from 2 to 9 digits in length) using digits 1 to 9. There were two conditions: forwards (numbers repeated in the same order); backwards (numbers repeated in reverse order). The examiner tapped the digits on the screen as the participant recited them. There was a maximum of three attempts at each level (different sequences of a certain length). Correctly reciting a sequence resulted in progression to the next level. The digit span was scored by the length of the longest sequence the participant recalled correctly in each condition (minimum of 0; maximum of 9).

3.2.4. Data analysis

All data analysis was performed in Stata 14.

3.2.4.1. Objective 1: feasibility

Data integrity was described with reporting of proportions of data loss due to inconsistent data files (e.g. missing folder, duplicate files), missing HIV status, or missing cognitive data. Invalid test conditions on one or more tasks (as described in 3.2.2. Materials and administration) resulted in exclusion of these participants' data.

3.2.4.2. Objective 2: normative task performance in this population

I calculated task-by-task measures of central tendency (e.g. mean), dispersion (e.g. standard deviation) and frequency distributions. Comparison of accuracy between easier baseline and more challenging test conditions was done graphically with two-way kernel density plots for applicable tasks (trails, figure drawing, selection, digit recall) to see if the expected shifts to the left occurred on the more challenging test conditions.

3.2.4.3. Objective 3: factorial validity

I performed a confirmatory factor analysis to assess the factorial validity of the EF measures based on the methods described by Wiebe and Friedman for confirming the factor structure of EF (Naomi P. Friedman et al., 2008; Wiebe et al., 2007). I compared two common theoretical models of EF: Friedman and Miyake's tripartite (three-factor) model (N. P. Friedman, Miyake, Robinson, & Hewitt, 2011; Miyake et al., 2000), and Zelazo and Müller's hot-cool two-factor model (P.D. Zelazo & Müller, 2002). For the three-factor model, the three factors were task switching (indicators: trails switch accuracy cost, rule-finding proportion accuracy), inhibitory control (indicators: go/no-go d-prime, Iowa Gambling Task net score) and working memory (indicators: digit span backwards, invisible selection penalised accuracy, figure recall

accuracy). For the two-factor model, the two factors were hot (indicators: go/no-go d-prime, Iowa Gambling Task net score) and cool (indicators: trails switch accuracy cost, rule-finding proportion accuracy, digit span backwards, invisible selection penalised accuracy, figure recall accuracy).

3.2.4.4. Preliminary data cleaning and preparation

Participants with HIV (n = 100) or unknown HIV status (n = 26) were excluded because HIV may be associated with neurocognitive impairment. Participants with invalidated task scores (unfavourable test conditions) or missing data were excluded by listwise deletion. Total duration scores were calculated by adding the planning and drawing durations for the figure drawing and selection tasks. Accuracy scores were converted to proportion accuracy scores ranging from 0 to 1 for all except the digit recall spans.

3.2.4.5. Construct definition and indicator selection

A single indicator from each of the seven EF tasks was chosen for inclusion in the confirmatory factor analysis based on it theoretically being the score most likely to reflect EF or due to its comparability with other measures used in the literature (see Appendix 4: Justification for choice of measures for each task). I chose at least two indicators for each latent variable (factor) so that confirmatory factor analysis models could be identified (Kline, 2016). I assumed that the latent variables have a standardised unit of measurement and fixed their variances to 1 (Jöreskog & Sörbom, 1993; Schumacker & Lomax, 2004).

- Trails: switch accuracy cost.
- Iowa Gambling Task: net score.
- Emotional go/no-go: D-prime.

- Rule-finding: proportion accuracy score.
- Selection: invisible proportion accuracy score.
- Figure drawing: figure recall proportion accuracy score.
- Digit recall: backwards span.

Other task scores derived to assess norms in the context but not included in the confirmatory factor analysis:

- Trails: switch proportion accuracy score; baseline combined proportion accuracy; switch duration cost score.
- Iowa Gambling Task: regression coefficient (beta) of the slope of the individual's learning curve.
- Emotional go/no-go: response bias criterion C; mean go reaction time.
- Selection: visible accuracy score.
- Figure drawing: figure copy accuracy score; figure copy total duration; figure recall total duration.
- Digit recall: forwards span.

3.2.4.6. Assumptions and estimation method

I screened for extreme collinearity amongst the variables by running several multiple regressions, each using a different variable as the dependent variable and the rest as predictor variables, to calculate the squared multiple correlation coefficients (R^2_{smc}). There was no extreme collinearity ($R^2_{smc} > 0.90$) present. I also assessed the pairwise Pearson's correlations between the EF measures. Due to departures from normality in the indicator variables found on box plots, the Satorra-Bentler estimator in Stata 14

was used with maximum likelihood estimation to achieve more robust estimates of standard errors (Hu, Bentler, & Kano, 1992; Satorra & Bentler, 1994).

3.2.4.7. Assessment of model fit

The goodness-of-fit of each model was assessed locally by examining the size of the parameter estimates, the standardised residual variances, and the squared multiple correlation coefficients, a measure of the reliability of each indicator. Standardised regression coefficients were interpreted as Pearson's correlations with correlation size being interpreted according to Cohen's rule: large r > |0.5|; medium r > |0.3|; small r > |0.1| (J. Cohen, 1988; Kline, 2016). Standardised residual variances were interpreted like standardised z scores (more than 1.96 being suggestive of model misspecification) (Schumacker & Lomax, 2004). Model fit was assessed globally by examining the following indices of fit: Satorra-Bentler scaled χ^2 test (Satorra & Bentler, 2010), the Steiger-Lind Root mean squared error of approximation (RMSEA) (Steiger & Lind, 1980), the Satorra-Bentler comparative fit index (CFI) (Bentler, 1990), and the standardised root mean squared residual (SRMR). The comparative model fit was assessed using a χ^2 difference test for comparing nested models (Satorra & Bentler, 2001). Hu and Bentler's cut-off values were used to determine good model fit: RMSEA < 0.06; CFI > 0.95; SRMR < 0.06 (Hu & Bentler, 1999).

3.3. Results

3.3.1. Sample characteristics

The summary statistics of the sociodemographic characteristics of the HIV-negative cognitive subsample are presented in Table 8.

Table 8. Sociodemographic characteristics of HPTN 068 cognitive subsample

Characteristic	HIV-negative (n = 932)
Age	
Mean (SD)	19.71 (1.34)
Median (IQR)	20 (19-20)
Range	17-25
Highest level of education (%)	
Some high school	27.71
Completed high school	33.30
More than high school	38.99
Socio-economic status (%)	
Low (lowest asset quartile)	27.07
Middle (middle 2 asset quartiles)	49.51
High (highest asset quartile)	23.42

3.3.2. Data integrity

See Figure 40 below for diagram of participant flow through HPTN 068 including cognitive sub-studies.

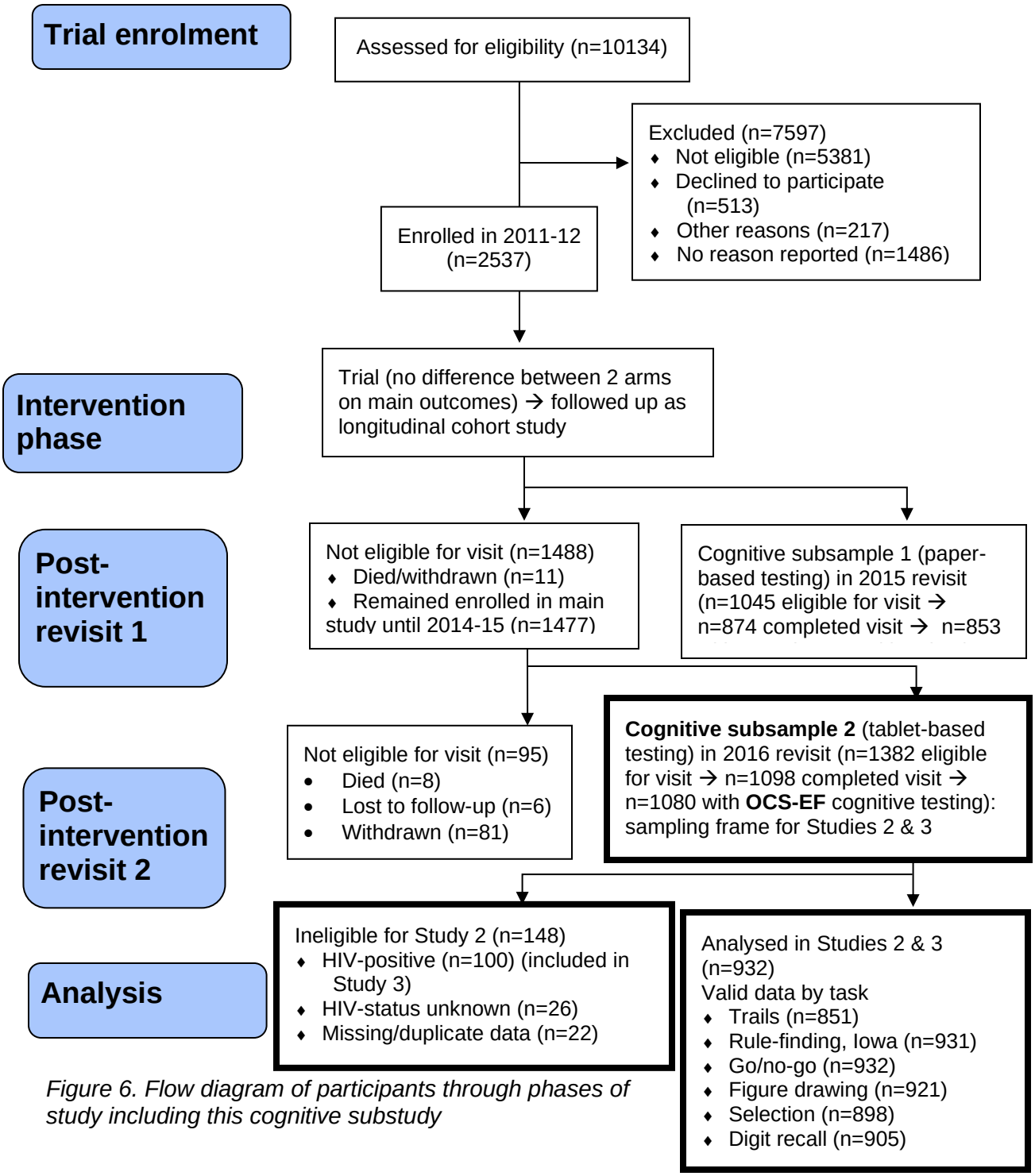


Figure 6. Flow diagram of participants through phases of study including this cognitive substudy

1080 participants were administered the cognitive tests. 100 of these were HIV-positive and therefore not eligible for inclusion in this analysis. Of the eligible pool of 980 HIV-negative participants, data from 932 (95%) participants were analysed; 48 (5%) were excluded for the following reasons: 3% (n = 26) HIV-status unknown; 2% (n = 22) inconsistent cognitive data e.g. missing or duplicate files. For the confirmatory factor analysis, participants with invalid data on any of the tasks due to unsatisfactory testing conditions (n = 144) as well as two participants with missing task data were excluded leaving 786 (80%) participants with complete, valid data on all tasks. See Figure 41 for reasons for invalid testing conditions for each task. Four of the tasks had ≥ 98% valid data with satisfactory test conditions. Three tasks had 2-9% invalidated data due to unsatisfactory test conditions. The most commonly reported technical problem was freezing of the Windows Surface Pro tablets during very hot weather conditions that sometimes resulted in examiners double clicking and accidentally skipping task sections in the trails and selection tasks. Some participants had to be tested at their homes, either inside or outside in the yard, where interruptions were more frequent.

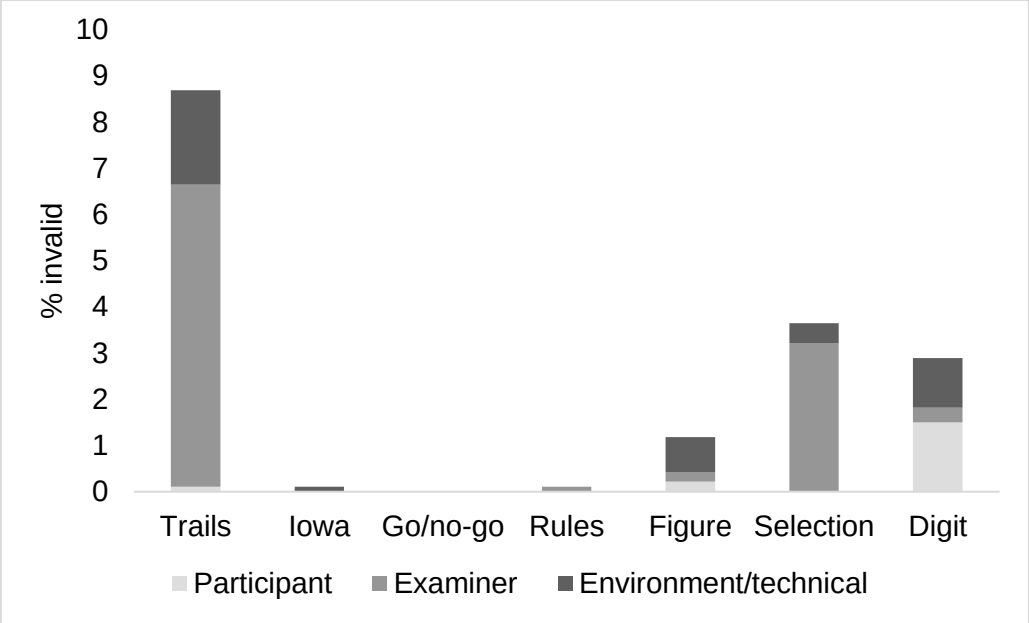


Figure 41. Reasons for invalid test conditions across tasks

3.3.3. Task durations

Task durations of the actual test were recorded for 5 of the 7 tasks. Summary statistics for the sample are presented in Table 9. These 5 tasks took approximately 11 minutes to complete on average; however, this excludes the practice round for trails, the instruction screen between each block on the go/no-go task, and the instruction screens before each task condition during which the examiner explains the task to the participant.

Table 9. Table of summary statistics of recorded test durations by task

Task	Condition	Mean (SD) duration (seconds)	Median (IQR) duration (seconds)	Range (seconds)	Shape of distribution
Trails	Baseline 1	15.85 (9.91)	14.07 (11.09, 17.76)	2.89, 184.98	Positive skew
	Baseline 2	15.78 (8.50)	14.097 (11.13, 18.23)	2.73, 129.69	Positive skew
	Switch	35.18 (23.00)	32.15 (22.89, 42.94)	6.76, 423.10	Positive skew
Selection	Visible	42.96 (18.03)	38.605 (32.76, 48.51)	12.90, 218.69	Positive skew
	Invisible	34.16 (11.52)	32.460 (26.73, 39.77)	5.62, 115.65	Positive skew
Figure drawing	Copy	75.32 (27.80)	70.12 (57.81, 87.16)	13.78, 294.54	Positive skew
	Recall	56.59 (24.57)	52.16 (40.74, 68.01)	4.59, 183.09	Positive skew
Rule-finding	-	121.38 (48.46)	114.42 (92.60, 144.10)	22.17, 442.30	Positive skew
Go/no-go	Total	Fixed: 300 seconds (2 seconds x 150 trials)			-

3.3.4. Task performance

The summary statistics of the various task measures are presented in Table 10. The pairwise correlation matrix is presented in Appendix 5: Study 2 pairwise correlation matrix between cognitive task outcome measures. There were ceiling effects for accuracy on the trails, selection and figure drawing tasks with negatively skewed sample distributions, worse in the simpler baseline conditions of each task. The Iowa Gambling Task accuracy, particularly the net score, had a bimodal distribution with peaks in the middle and on the far right. Plots of the accuracy distributions for the four tasks with simpler baseline and more challenging test conditions are presented in Appendix 6: Study 2 kernel density plots of shifts from baseline to test condition.

Table 10. Table of task performance summary variables

Task	Measure	n	Mean (SD)	Median (IQR)	Range (Min, Max)	Shape of distribution
Trails	Baseline accuracy	851	0.79 (0.23)	0.86 (0.64, 1.00)	0.00, 1.00	Negative skew
	Switch accuracy	851	0.52 (0.31)	0.50 (0.29, 0.79)	0.00, 1.00	Negative skew
	Switch accuracy cost*	827	0.62 (0.32)	0.64 (0.36, 1.00)	0.00, 1.00	Negative skew
	Switch duration cost	851	1.19 (0.63)	1.09 (0.77, 1.47)	0.11, 4.74	Positive skew
Iowa Gambling Task	Coefficient beta of slope gradient	931	11.78 (30.66)	12.16 (-11.33, 41.50)	-65.26, 67.67	Bimodal with central and high positive peaks
	Net score*	931	0.31 (0.57)	0.13 (-0.07, 1.00)	-1.00, 1.00	Bimodal with central and high positive peaks
Go/no-go	D prime*	930	2.12 (0.96)	2.18 (1.54, 2.78)	-1.11, 4.87	Normal
	Bias criterion C	930	0.10 (0.55)	0 (-0.26, 0.42)	-1.95, 1.62	Normal
	Mean go trial reaction time (milliseconds)	932	511.33 (66.33)	501.29 (467.44, 543.33)	335.99, 847.53	Slight positive skew
Rule-finding	Accuracy*	931	0.48 (0.23)	0.46 (0.30, 0.65)	0.00, 1.00	Slight positive skew
Figure drawing	Copy accuracy	921	0.89 (0.11)	0.92 (0.83, 0.97)	0.00, 1.00	Negative skew
	Recall accuracy*	921	0.80 (0.15)	0.82 (0.70, 0.90)	0.03, 1.00	Negative skew
Selection	Visible penalised accuracy	898	0.94 (0.11)	0.97 (0.93, 1.00)	-0.27, 1.00	Negative skew

	Invisible penalised accuracy*	898	0.72 (0.22)	0.77 (0.60, 0.87)	-0.87, 1.00	Negative skew
Task	**Measure**	**n**	**Mean (SD)**	**Median (IQR)**	**Range (Min, Max)**	**Shape of distribution**
Digit recall	Forwards	905	5.40 (1.49)	5 (5, 6)	0, 9	Normal
	Backwards*	905	3.67 (1.55)	4 (3, 4)	0, 9	Normal

Key: * = variable included as indicator in confirmatory factor analysis

3.3.5. Confirmatory factor analysis

The estimates of the standardised pattern coefficients between the factors and the indicators (measured variables) for the two EF models are shown in Figure 42 for Model 1 (three-factor) and Figure 43 for Model 2 (two-factor). The figures also show the estimates of the variances of the latent factors, co-variances between the latent factors, the intercepts of the indicators, and the residual variances. These estimates of coefficients and covariances are also presented with their measures of dispersion (standard error and 95% confidence intervals), z statistics and associated probability values, and Bentler-Raykov squared multiple correlation coefficients in Table 11 for Model 1 (three-factor) and Table 12 for Model 2 (two-factor).

Table 11. Model 1 (three-factor model) parameter estimates from confirmatory factor analysis

Estimate	Coeff	SE	z	P > |z|	95% CI	SMC
TS → Trails	.25	.06	4.03	< 0.001	.13, .38	.06
TS → Rules	.32	.08	4.18	< 0.001	.17, .47	.10
IC → Iowa	.34	.06	6.00	< 0.001	.23, .45	.12
IC→ Go/no-go	.41	.07	6.17	< 0.001	.28, .54	.17
WM→ Digit	.14	.06	2.54	0.011	.03, .26	.02
WM→ Selection	.19	.07	2.77	0.001	.06, .33	.04
WM→ Figure	.76	.21	3.60	< 0.001	.35, 1.17	.58
Cov (TS, IC)	1.45	.34	4.33	< 0.001	.80, 2.11	-
Cov (TS, WM)	.60	.21	2.83	0.005	.18, 1.02	-
Cov (IC, WM)	-.03	.10	-0.30	0.765	-.22, .16	-

Key: Coeff = Standardised coefficient; SE = standard error; z = z statistic; SMC = squared multiple correlation coefficient; TS = task switching; IC = inhibitory control; WM = working memory; Cov = Covariance.

Table 12. Model 2 (two-factor model) parameter estimates from confirmatory factor analysis

Estimate	Coeff	SE	z	P > |z|	95% CI	SMC
Cool → Trails	.31	.06	5.28	< 0.001	.19, .42	.10
Cool → Rules	.46	.07	6.56	< 0.001	.33, .60	.21
Cool → Digit	.09	.06	1.62	0.106	-.02, .20	.01
Cool → Selection	.13	.06	2.07	0.038	.01, .25	.02
Cool → Figure	.23	.06	3.90	< 0.001	.11, .34	.05
Hot → Iowa	.32	.06	5.25	< 0.001	.20, .44	.10
Hot → Go/no-go	.43	.07	5.81	< 0.001	.29, .58	.18
Cov (cool, hot)	.87	.16	5.51	< 0.001	.56, 1.17	-

Key: Coeff = Standardised coefficient; SE = standard error; z = z statistic; SMC = squared multiple correlation coefficient; Cov = Covariance.

In terms of local fit, none of the standardised residuals were high enough in either model to suggest model misspecification. The correlations between indicators and latent variables varied in size. The correlations were of medium size in both models for rule-finding accuracy, go/no-go d-prime and Iowa net score with the models explaining 10-25% of the variance of each indicator. The correlations were small for digit recall backwards span and invisible selection accuracy score with the models explaining < 10% of the variance of each indicator. Sometimes they varied in size between models. They were large for figure recall accuracy in the three-factor model and small in the two-factor model. They were medium for trails switch cost in the two-factor model and small in the three-factor model. In the three-factor model, the task switching factor was significantly positively correlated with both the inhibitory control and working memory factors; however, the inhibitory control and working memory factors were not correlated. The strong correlation between task shifting and inhibitory control (coefficient >1) suggest the possibility of multicollinearity of these two factors (Jöreskog, 1999). It is therefore unsurprising that in an additional exploratory factor analysis performed, these two factors collapsed into a single factor with a two-factor (switching/inhibition and working memory) solution emerging (see Appendix 7: Study 2 additional exploratory factor analysis using the 7 OCS-EF tasks). Global goodness-of-fit indices are presented in Table 13. The RMSEA, CFI and SRMR indices were all more favourable in model 1 (three-factor). Both models had low residuals (SRMR < 0.06). The two-factor model had a higher RMSEA (> 0.06) suggesting worse fit than the three-factor model (RMSEA < 0.06). Only the three-factor model had a CFI > 0.95 suggesting good model fit. The CFI was higher in the three-factor model than the two-

factor model suggesting it had superior fit. The Satorra-Bentler χ^2 tests revealed that the two-factor model was significantly different to a saturated model; however, the three-factor model was not significantly different to a saturated model suggesting that only the two-factor model should be rejected.

The χ^2 difference test revealed a significant difference between the two models (χ^2 difference = 44.23; *df* = 2; $p < 0.0001$). Fewer highly significant coefficients ($p \leq 0.001$) suggested that the local fit of the second model was less favourable. I therefore retained the initial three-factor model.

Table 13. Goodness of fit indices for the two models

Goodness-of-fit index	**Model 1 (3-factor)**	**Model 2 (2-factor)**
Satorra-Bentler scaled χ^2 test (model vs saturated)	17.43	61.27
Degrees of freedom (*df*)	24	22
P value	0.096	<0.001
Population error RMSEA (Satorra-Bentler)	0.028	0.070
Baseline comparison CFI (Satorra-Bentler)	0.952	0.637
Size of residuals SRMR	0.026	0.050

Key: RMSEA = Root mean squared error of approximation; CFI = Comparative fit index; SRMR = Standardised root mean squared residual

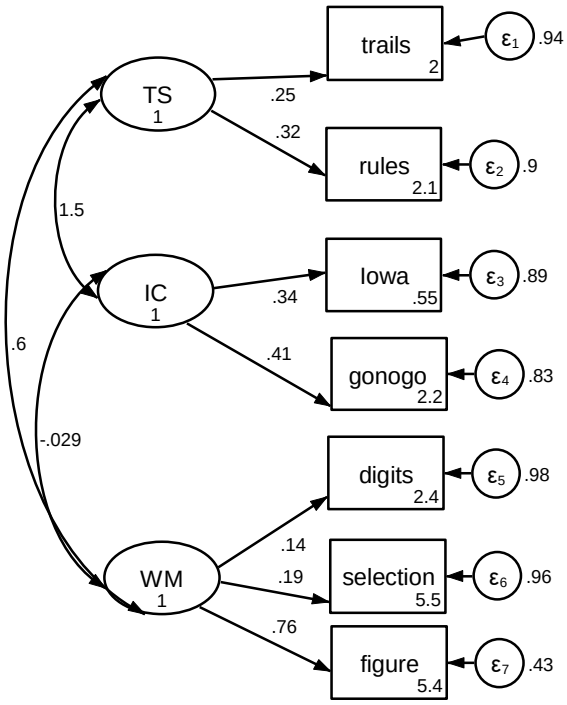


Figure 42. Confirmatory factor analysis model with estimates for tripartite model of executive function. TS = task switching. IC = inhibitory control. WM = working memory. Values on curved arrows are standardised co-variances between latent factors. Values inside the ovals are latent variable variances which are fixed to 1. Values on straight arrows (paths) are standardised beta coefficients. Values in each indicator block are standardised intercepts. Values to the right of error terms (ε) are the residual variances.

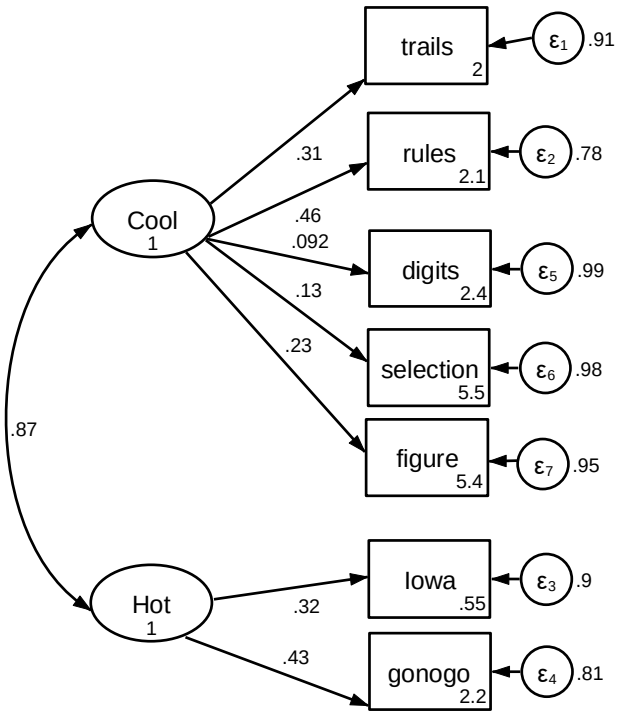


Figure 43. Confirmatory factor analysis model with estimates for two-factor 'hot-cool' model of executive function. Values on curved arrows are standardised co-variances between latent factors. Values inside the ovals are latent variable variances which are fixed to 1. Values on straight arrows (paths) are standardised beta coefficients. Values in each indicator block are standardised intercepts. Values to the right of error terms (ε) are the residual variances.

3.4. Discussion

3.4.1. Summary and interpretation of main findings

This study, to my knowledge, represents the first attempt to confirm the factor structure of EF in a large normative sample of late adolescents in a low-income setting. The large sample size with a high ratio of participants to each parameter requiring estimation (46:1 in model 1; 52:1 in model 2) means that the parameter estimates are likely to be stable. This study adds to the two large studies looking at the factor structure of cognition more broadly in children and younger adolescents in LMIC settings (Holding et al., 2018; Rochat et al., 2017). I found that the factor

structure of EF amongst a large sample of late adolescent females in a rural African LMIC context is similar to the factor structure of EF in adolescents in a high-income context (N. P. Friedman et al., 2011; Latzman & Markon, 2010; K. Lee et al., 2013; Li et al., 2015), with a differentiated tripartite model having better local and global fit to the data than the two-factor model (which I rejected). This three-factor model confirmed that the task switching and inhibitory control factors were significantly and highly correlated. The task switching and working memory factors were also correlated but to a lesser extent, whereas the inhibitory control and working memory factors were uncorrelated. These findings suggest that, like in high-income countries, EF appears to differentiate into distinct but related factors by late adolescence. In contrast to Friedman and Miyake's updated EF model in the US, my model did not suggest that inhibitory control represents a common, underlying factor representing the shared variance across EFs (N. P. Friedman et al., 2011; Naomi P. Friedman et al., 2008) or that all EFs are correlated with one another (Miyake & Friedman, 2012). Perhaps the inhibitory control factor was not correlated with the working memory factor as I expected because I used only hot or affective inhibitory control tasks.

The fact that the three-factor theoretical model of EF had good global and acceptable local fit helps to confirm the factorial validity of this EF assessment tool in a rural LMIC context.

This study used an innovative tablet-based EF assessment tool, OCS-EF, which is almost fully visuospatial and thus useful for cross-cultural use in different low- and middle-income or high-income country settings. It showed that it is feasible to train lay people as assessors to administer cognitive assessments on a large-scale using

OCS-EF in a rural African context. OCS-EF was generally quick to administer, and data integrity was good.

This study has also established normative values for these seven OCS-EF cognitive tasks in late adolescence in South Africa. Only the digit span already had norms listed with Neuropsychology SA (https://www.neuropsychologysa.co.za/). This task has been normed in a South African context (D. Singh et al., 2010; Skuy, Schutte, Fridjhon, & O'Carroll, 2001). I observed the expected shifts to the left in the accuracy distributions from the baseline to the more challenging test conditions for the four tasks with such a structure (trails, figure drawing, selection, and digit recall).The rule-finding, Iowa Gambling and go/no-go tasks explained greater proportions of the shared variance of the EF factors than the selection, digit recall and trails tasks with mixed findings for the figure recall. Some of the tasks may have explained lower proportions of the EF variance because they also measure other aspects of EF or cognition, other than the factors on which they were loaded in this model. The digit recall task was the only verbal task used and may have had more measurement error than other tasks because it is the only task requiring examiner input to capture participant responses. The digit recall backwards loading on the working memory factor may have also been low because the two visuospatial tasks which I used as the other indicators of working memory in the three-factor model (invisible selection and figure recall) relied more upon the higher-order EF of planning than visuospatial working memory. This would explain why the factor loadings were higher for invisible selection and figure recall, both of which require planning, than for the digit recall backwards, a traditional verbal working memory task. The fit for the three-factor model

was likely better than the two-factor model fit because the figure recall factor loading (coefficient) was high in this model; whereas the coefficient decreased substantially when the working memory and task switching factors were collapsed into a single 'cool' factor in the two-factor model. The three-factor model thus explained a higher proportion of the overall variance.

3.4.2. Limitations

There are several limitations to the use of OCS-EF, some of which I deal with in further chapters, but all of which are worth mentioning briefly here. Although the test condition could be flagged on-screen after each task, I cannot guarantee that fieldworkers consistently did this according to the protocol. They received baseline training but there were knowledge gaps identified during a debriefing session post-data collection. It was difficult to ensure standardised laboratory-like conditions for testing of all participants on a large-scale. Most participants were at school during the day so testing sometimes occurred late in the day at participants' homes where interruptions are more common and mental fatigue more likely.

Another limitation is sample composition: the sample included females only and those who met the initial study eligibility criteria; therefore, it is not fully representative of the local population. Cognition was tested at only one time point, so I was unable to assess test-retest reliability or predictive validity. I could not assess concurrent validity because it was not feasible to administer an established EF battery alongside this one in the parent study.

Furthermore, some of the newer tasks (targeting hot EF) were not yet optimised for use with our target population. For example, the inclusion of numeric rewards and

penalties in the Iowa Gambling Task means that it required numeracy skills; however, it could easily be adapted for low-literacy populations.

Finally, the order of task administration meant that the two 'hot' inhibitory control tasks were administered sequentially. Similarly, two working memory tasks were administered sequentially. This may have introduced error due to participant by order interaction which might have resulted in poorer performance on the second task in each case (emotional go/no-go and digit recall) (Miyake et al., 2000). Fatigue was common in digit recall, the last task administered.

3.4.3. Recommendations for future improvement

Ongoing fieldworker training with open two-way communication and feedback is vital for quality assurance purposes. Test conditions should be optimised and standardised as far as possible within the context with its constraints e.g. having a mobile testing van or dedicated testing room. 'Rugged' Android tablets that can withstand the heat and outdoor conditions under which testing may occur would be more suitable for a hot rural environment. Lock-in periods should be programmed into the software to prevent accidental double tapping or skipping of sections. This was done for the OCS-EF version used in Study 4 (Chapter 6). Timed tasks should have in-built duration cut-offs rather than this being performed during analysis. An OCS-EF illiterate version should be developed which includes happy and sad faces for rewards and losses in the Iowa Gambling Task as described in the original Children's Gambling Task (A. Kerr & Zelazo, 2004). The order of task administration could be amended to avoid sequential administration of two tasks assessing the same EF. The digit recall assessor digit recital could be pre-recorded and played off-screen to standardise the

administration further. The Selection task could be replaced with a more widely used visuospatial working memory task e.g. the Corsi blocks spatial span. In Study 4 (Chapter 6), I replaced the Selection task with a dot recall task as a measure of visuospatial working memory. Full automation of scoring with immediate summarised results upon completion of testing could be built in to allow this tool to be implemented more widely.

3.4.4. Gaps for future research

OCS-EF should be evaluated in younger adolescents and samples including males. This is done in Study 4 (Chapter 6). I did not perform a split-sample cross-validation. Therefore, replication in other samples will be necessary to increase our confidence in the stability of the results (Kline, 2016).

3.4.5. Conclusion

This study confirmed the factorial validity of the OCS-EF tablet-based EF assessment tool in a large normative sample of late adolescents in rural South Africa. This gave me the confidence to use the tool to measure EF in both Study 3 (Chapter 4) and the intervention study, Study 4 (Chapter 6), in rural South Africa. This study is likely the largest study to examine the factor structure of EF in a normative sample of late adolescents in a LMIC, and particularly in Africa. Vitally, it has established norms on these tasks for future comparison in people with potential EF deficits e.g. young people living with HIV. OCS-EF will provide clinicians and researchers with a platform for assessing and characterising EF quickly and easily in LMICs. It will enable researchers to explore relationships between EF and important outcomes, as I have done in Study 3 (Chapter 4). It will be useful in clinical settings with limited access to

formal neuropsychological assessment allowing rapid characterisation of EF profiles (e.g. in the context of HIV-associated neurocognitive disorder) which will enable targeted interventions for various types of executive cognitive impairment to be developed, tested, and offered by the health services. It will also allow the assessment of intervention effects through pre- and post-intervention testing, as I have done in Study 4 (Chapter 6).

Chapter 4: Study 3, a cross-sectional study assessing the relationship between executive function, HIV, and risky behaviour in adolescent females in rural South Africa

Chapter outline:

4.1. Background

- 4.1.1. Development of executive function during adolescence
- 4.1.2. Relationships between executive function and risk-taking behaviour
- 4.1.3. Executive function in adolescents with behaviourally acquired HIV
- 4.1.4. Hypotheses

4.2. Methods

- 4.2.1. Study design
- 4.2.2. Data collection
- 4.2.3. Outcome measures
- 4.2.4. Statistical analysis

4.3. Results

- 4.3.1. Sample characteristics
- 4.3.2. Relationship between executive function and risky behavioural outcomes
- 4.3.3. Case-control substudy

4.4. Discussion

- 4.4.1. Key findings
- 4.4.2. Strengths
- 4.4.3. Limitations
- 4.4.4. Conclusions

4.1. Background

4.1.1. Development of executive function during adolescence

EF is important in the top-down control of decision-making and the ability to direct attention towards the fulfilment of long-term goals. EF continues to develop during adolescence and into early adulthood (Casey et al., 2008; Kuhn, 2006; Luna, 2009; Sowell et al., 2002; Steinberg, 2005; Tau & Peterson, 2010). The social brain and social cognition also develop significantly during adolescence and into the early twenties (Kilford, Garrett, & Blakemore, 2016). Adolescence is a period during which peers exert a powerful influence on decision-making. Adolescents are more likely to take risks in the presence of their peers (Albert et al., 2013). They are highly reward-sensitive and have heightened sensation-seeking behaviour (Laurence Steinberg et al., 2017). At the same time, their ability to self-regulate is still maturing. This means that they are prone to take more risks, including high-risk sexual and substance use behaviour (Steinberg, 2008). These risky behaviours may result in adverse outcomes (e.g. acquiring HIV) which may affect their health now, later in adulthood, or the health of their children (G. C. Patton et al., 2018; G. C. Patton et al., 2016).

4.1.2. Relationships between executive function and risk-taking behaviour

EF is necessary to inhibit automatic responses and override purely emotion-driven behaviour in the affective decision-making process. The maturation of the EFs in emotionally significant contexts seems to be more gradual and occur later during adolescence than that of the EFs in emotionally neutral contexts (Prencipe et al., 2011; Philip David Zelazo & Carlson, 2012). It is likely that the decreased ability to exert top-down control in highly emotionally charged contexts will be an important

determinant of real-life decision-making regarding behaviours such as substance use and sexual risk-taking. The protracted development of prefrontal-subcortical neural circuits involved with EF have also been linked to decisions regarding sexual behaviour (Ross, Duperrouzel, Vega, & Gonzalez, 2016; Spinella, 2007). EF development has also been associated with sexual behaviour choices during adolescence. Generally, poorer EF and greater impulsivity are associated with more sexual risk-taking (Arends et al., 2019; Bornovalova, Gwadz, Kahler, Aklin, & Lejuez, 2008; Derefinko et al., 2014; Khurana et al., 2012, 2015; Lejuez et al., 2007; Lejuez et al., 2002; Rosenberg et al., 2018; Ross, Coxe, Schuster, Rojas, & Gonzalez, 2015; Ross et al., 2016). EF deficits may thus alter risk for adverse individual and population health consequences e.g. HIV acquisition or transmission via risky sexual behaviour. 15-24-year-old females in sub-Saharan Africa are one of the most high-risk groups for acquiring HIV (Shisana et al., 2014; 2018a). Understanding factors that might be protective or influence risk is important in identifying those most at risk and designing risk reduction strategies. A previous cognitive substudy in another subset of participants from the HPTN 068 cohort found some associations between poorer EF and risk-taking outcomes (Rosenberg et al., 2018). I aimed to replicate these findings in a larger sample in which I could also control for the main potential confounders. I also aimed to extend the findings by including a more extensive attention and EF battery of tasks that also assesses verbal working memory, selective attention, as well as inhibitory control and decision-making under affective or emotional conditions.

4.1.3. Executive function in adolescents with behaviourally acquired HIV

Adolescents with behaviourally acquired HIV may have had EF deficits before acquiring HIV (e.g. due to attention deficit/hyperactivity disorder) which predisposed them to sexual risk-taking and substance use and thereby HIV acquisition itself (Chen et al., 2018; Hosain, Berenson, Tennen, Bauer, & Wu, 2012). After infection, HIV itself may also lead to impaired EF because of the neurotropic nature of the virus which enters the central nervous system (CNS) and triggers immune activation early after infection (Clifford & Ances, 2013; Phillips et al., 2016; Spudich et al., 2011). Markers of advanced or poorly controlled HIV may thus be associated with poorer EF in HIV-positive adolescents. Poorer EF may be associated with poorer academic and functional outcomes, poorer adherence to treatment with resultant poorer disease control and the development of treatment-resistant HIV strains, and risky sexual behaviour which may result in HIV transmission (Best et al., 2011; Hinkin et al., 2002; Ross et al., 2016; Sirois et al., 2016; Wilson & Vassileva, 2016). A better understanding of the EF profile of adolescents with behaviourally acquired HIV and whether it is associated with markers of advanced or poorly controlled disease is needed. This will lay the foundation for future intervention studies to improve EF in this population and potentially help decrease further HIV transmission. As I demonstrated in Study 2, most studies on EF in HIV-positive adolescents have focused on adolescents with longstanding perinatally acquired HIV with few looking at adolescents with HIV acquired behaviourally during adolescence. ATN[16] 071, a

[16] ATN: The Adolescent Medicine Trials Network for HIV/AIDS Interventions

largely male US-based cohort examining EF in behaviourally acquired HIV, found higher rates of certain EF deficits compared to population norms (Nichols et al., 2013). There have been no large studies looking at EF in adolescent females with behaviourally acquired HIV in HIV-endemic regions of sub-Saharan Africa compared to a socio-demographically matched control group. In this study, I aimed to address this gap and determine if adolescent females with behaviourally acquired HIV in rural South Africa have similar EF deficits to those found in high-income countries and whether EF in this population is related to markers of advanced or poorly controlled HIV.

4.1.4. Hypotheses

The thesis hypotheses tested in this chapter are:

1. EF deficits are associated with an increased risk of risky sexual and substance use behaviour in adolescent females in rural South Africa (thesis hypothesis 2.1);
2. Adolescent females with behaviourally acquired HIV have poorer performance on EF tasks than a socio-demographically matched sample of controls (thesis hypothesis 1);
    a. The earlier that HIV infection occurs in the life course, the greater the EF deficits; therefore, adolescents with vertically transmitted HIV acquired perinatally have larger and more global deficits than adolescents with later behaviourally acquired HIV (thesis hypothesis 1.1).

b. Behaviourally acquired HIV is associated with a distinct pattern of EF deficits with effect sizes varying by EF component (thesis hypothesis 1.4).

c. In those with behaviourally acquired HIV, those with biological markers of more advanced disease (CD4 counts < 350 cells/mm^3) or uncontrolled disease (viral load ≥ 1000 copies/ml) (WHO, 2016) have poorer EF than those with less advanced disease (CD4 count ≥ 350 cells/mm^3) or better controlled disease (viral load < 1000 copies/ml), respectively (thesis hypothesis 1.2.1).

4.2. Methods

4.2.1. Study design

Study 3 consisted of two parts. Part 1 was a cross-sectional correlational study assessing the relationship between EF and risky behavioural outcomes in late adolescents in rural South Africa. Part 2 was a case-control study examining EF in adolescents with behaviourally acquired HIV compared to healthy, socio-demographically matched controls. As with Study 2, the data for this cognitive substudy was obtained from the HPTN 068 cohort study based in rural Mpumalanga, South Africa (see Chapter 3, Section 3.2.1 for details); however, unlike in Study 2, I included the 100 HIV-positive participants. Women who were HIV-positive at baseline (i.e. possible perinatal transmission) were included in some analyses but they were excluded from the analysis looking at HIV as an outcome, and the case-control substudy which focused specifically on behaviourally acquired HIV. I defined adolescents as 10-24-year-olds; however, I included the four 25-26-year-olds who

participated in the cognitive study, except in the case-control substudy where they could not be matched.

4.2.2. Data collection

Data collection methods are described in Chapter 3, Section 3.2.2. Adolescents received group pre-test counselling prior to venous blood sampling for rapid HIV testing, herpes simplex virus type 2 (HSV-2) testing, and additional confirmatory laboratory serum HIV testing (along with serum CD4 cell count and viral load) if one or both HIV rapid tests were reactive. They received individual post-test counselling. Further details regarding biological testing are reported elsewhere (Pettifor, MacPhail, Selin, et al., 2016).

4.2.3. Outcome measures

We measured seven risky behavioural outcomes, two related to substance abuse (binge drinking and illicit substance use) and five related to risky sexual behaviour (unprotected vaginal sex, concurrent relationships, transactional sex, HSV-2 infection, HIV infection), two of which were biological.

Primary behavioural outcomes measured were:

- Substance use:
    - Binge drinking: self-reported drinking of five or more standard alcoholic drinks during drinking episodes. Standard drink was defined as a small glass of wine, a 330 ml can of regular beer, a tot of spirits, or a mixed drink.
    - Drug use: self-reported past (ever) use of recreational or illicit drugs e.g. cannabis or methamphetamine.

- Risky sexual behaviour:
    - Unprotected vaginal sex: present if participant self-reported at least one episode of unprotected vaginal sex (i.e. without using a condom) in the past three months.
    - Concurrent relationships: ongoing relationship with at least two of the up to five most recent sexual partners.
    - Transactional sex: present if participant self-reported engagement in transactional sex with any of the up to five most recent sexual partners. Transactional sex was defined as becoming, staying or feeling like one had to have sex or be sexually involved with a partner in the hope that he would or because he did provide you with money or things like groceries, airtime or clothes.

Primary biological outcomes were:

- HSV-2 infection: testing positive on HSV-2 testing at baseline or subsequent study visits.
- Behavioural HIV infection: testing positive on confirmatory HIV testing during any follow-up study visit in participants who tested negative on two HIV rapid tests at the cohort study baseline.

Primary cognitive outcomes were scores on the seven OCS-EF cognitive tasks (Rowe et al., 2019) as described in Chapter 3, Section 2.3 administered in a fixed order:

1. Trails, a measure of planning and set-shifting (Demeyere et al., 2019; Humphreys et al., 2017).

2. Iowa Gambling Task, a measure of implicit learning, decision-making and inhibitory control in the context of reward (Burdick et al., 2013; Cassotti, Aïte, Osmont, Houdé, & Borst, 2014).
3. Emotional go/no-go, a measure of inhibitory control in emotional conditions (Schulz et al., 2007).
4. Rule-finding task, a measure of set-shifting, visuospatial pattern recognition and problem-solving (Demeyere et al., 2019; Humphreys et al., 2017).
5. Figure drawing task, a measure of constructional ability, visuospatial short-term memory and planning (Demeyere et al., 2019).
6. Selection (cancellation) task, a measure of selective attention, visuospatial short-term memory and planning (Demeyere et al., 2019).
7. Digit recall, a measure of verbal short-term memory and verbal working memory (Baddeley, 2003).

Socio-demographic and control variables:

- Age: in years (continuous variable) calculated using date of birth (self-reported in baseline interview).
- SES: absolute asset index (based on number of baseline household durable goods owned as reported by caregiver in household interview) quartiles derived and used to divide participants into low (lowest quartile), middle (middle two quartiles), and high (highest quartile) SES categories (categorical variable).
- Marital status: married or unmarried as self-reported in adolescent 2016 revisit interview.

- Education level: summarised into three levels (some secondary school, completed secondary school, and post-secondary) based on highest level of education completed as self-reported in adolescent 2016 revisit interview (categorical variable).
- Depression score: total number of depressive symptoms on the Centre for Epidemiologic Studies Depression Scale (CES-D) as self-reported in adolescent 2016 revisit interview (continuous variable).

Biological predictor variables used in the HIV-positive participants only:

- CD4 cell count: measured using the CD4 BECTON–DICKINSON (BD) FACSCALIBUR TRUCOUNT Method (Becton, Dickinson and Company, BD Biosciences, San Jose, California USA).
- Viral load: testing was performed retrospectively by the HPTN Laboratory Centre using RealTime HIV-1 Viral Load assay (Abbott Molecular, Des Plaines, IL).

4.2.4. Statistical analysis

All analysis was performed in Stata 14. All reported p values are two-tailed with no correction applied for multiple comparisons.

The following cognitive scores were derived from each task in the manner described in Chapter 3, Sections 3.2.3 and 3.2.4.5:

1. Trails combined baseline accuracy, switch accuracy, switch accuracy cost, and the switch duration cost.
2. Iowa Gambling Task net score
3. Go/no-go d-prime
4. Rule-finding accuracy
5. Figure drawing copy and recall accuracy
6. Selection visible and invisible accuracy
7. Digit recall forwards and backwards span.

The pattern of missing and invalid data was described for each variable of interest. Participant data were only analysed for a particular task if the test condition was marked on screen as ‘no issue’ as described in Chapter 3, Section 3.2.2. Histograms

of cognitive outcome variables were inspected to assess distributions to determine whether to use parametric or non-parametric tests to compare groups. There was no collinearity or multicollinearity present.

Hypothesis 1: Simple logistic regression models were initially used to examine the associations between the EF variables as predictors of each of the seven risky behavioural outcomes. Multivariable logistic regression was then used to examine the associations between performance on each of the EF outcome variables and each of the seven risky behavioural outcomes controlling for SES, education level and age in the full cognitive sample. In the analysis examining HIV infection as an outcome, we excluded the 22 participants who were HIV-positive at study entry.

Hypothesis 2: A subsample of HIV-negative controls was randomly matched to the adolescent females with HIV acquired during the longitudinal cohort study (i.e. acquired behaviourally during the longitudinal cohort study) based on age and SES using Stata's 'ccmatch' module. This process was repeated (excluding the first set of matched controls) to select a second set of matched controls to produce a final case:control ratio of 1:2. After initial group mean comparisons testing (paired t tests or Wilcoxon signed-rank tests depending on outcome distribution), linear multivariable regression analyses controlling for potential confounders (age, SES, education level) were done to detect differences between the cases and controls on the cognitive outcomes. Assumptions were checked to ensure that the use of linear regression models was appropriate. Q-plots of residual variances were inspected to ensure that the residuals were normally distributed. Homogeneity of residual variances were

assessed using box-and-whisker plots or scatterplots. Residual versus fit plots were also inspected to check for non-linearity, unequal residual variances and outliers.

Hypothesis 3: After initial group mean comparisons testing (paired t tests or Wilcoxon signed-rank tests depending on outcome distribution), multivariable linear regression models were used to assess HIV-related factors (low CD4 count < 350 cells/mm3; high viral load > 1000 copies/ml) potentially impacting the cognitive findings in the behaviourally acquired HIV group (controlling for age, SES, education level). Assumptions were checked as described for Hypothesis 2.

4.3. Results

4.3.1. Sample characteristics

1080 participants received cognitive assessments. 22 (2.0% of the original cognitive study sample) participants were excluded due to missing or duplicate cognitive data files. The full sociodemographic characteristics of the 1058 participants with cognitive data available are listed in Table 14. The mean age was 19.8 years old. 71.6% of the sample had completed secondary school with 39.2% having completed additional post-secondary training. 35 (3.3%) participants were married. 100 (9.5%) participants tested HIV-positive, with 22 (2.1%) testing positive at study entry and 78 (7.4%) acquiring HIV at any point during the cohort study. The number of participants with invalid cognitive test conditions was highest for the trails (n = 90, 8.5%), selection (n = 36, 3.4%) and digit recall (n = 29, 2.7%) tasks and mostly due to examiner error, technical error or interruptions. The other four tasks each had only 0-1% with invalid test conditions. See Chapter 3, Section 3.2 for more details on data integrity.

Table 14. Sociodemographic characteristics of the full cognitive sample (N = 1058)

Characteristic	Cognitive data
Mean age (SD) in years	19.79 (1.38)
Highest level of education, n (%)	
Some secondary school	300 (28.38)
Completed secondary school	343 (32.45)
Post-secondary	414 (39.17)
Missing	1 (0.00)
Socio-economic status, n (%)	
Low	280 (27.16)
Middle	507 (49.18)
High	244 (23.67)
Missing	1 (0.00)
Marital status, n (%)	
Unmarried	1022 (96.69)
Married	35 (3.31)
Missing	1 (0.00)
HIV status	
Negative	932 (88.09)
Positive	100 (9.45)
Missing	26 (2.46)

4.3.2. Relationship between executive function and risky behavioural outcomes

Risky behavioural outcomes varied in frequency within the sample (see Table 15). Unprotected vaginal sex (20.1%), HSV-2 infection (20.1%) and transactional sex (22.0%) were more frequent than HIV-1 infection acquired during the study (7.4%), concurrent relationships (5.0%), past illicit drug use (4.3%) and binge drinking (1.5%).

In overview, there were a few significant associations between cognitive predictors and behavioural outcomes that remained significant after adjustment for potential confounders (age, SES, highest level of education and depression). Better verbal short-term memory/attention (on digit recall forwards) was associated with a significantly decreased risk of HSV-2 infection (Adjusted Odds Ratio (OR) 0.82; 95% CI 0.73, 0.92; p = 0.001) (see Table 18). Better verbal working memory (on digit recall

backwards) was associated with a significantly decreased risk of concurrent relationships (AOR 0.76; 95% CI 0.61, 0.94; p = 0.012) (see Table 17). Better inhibitory control under emotional conditions (on emotional go/no-go d-prime) was associated with a significantly decreased risk of transactional sex (AOR 0.83; 95% CI 0.71, 0.97; p = 0.021) (see Table 17).

There were also a few significant associations that were no longer significant after adjustment for potential confounders (age, SES, highest level of education, depression). Prior to adjustment, better verbal working memory was associated with a significantly decreased risk of acquiring HIV-1 infection (OR 0.85; 95% CI 0.72, 1.00; p = 0.048) (see Table 18). Better planning/sequencing ability (on trails baseline task) was associated with a decreased risk of illicit drug use (OR 0.21; 95% CI 0.06, 0.72; p = 0.012), binge drinking (OR 0.13; 95% CI 0.02, 0.91; p = 0.040), transactional sex (OR 0.49; 95% CI 0.26, 0.92; p = 0.027) and HSV-2 infection (OR 0.47; 95% CI 0.25, 0.92; p = 0.027) (see Table 16, Table 17 and Table 18). Selective attention (on visible selection task) and visuospatial working memory and planning (on invisible selection task) were both associated with a significantly decreased risk of HSV-2 infection (see Table 18). The rule-finding (visuospatial problem-solving and set-shifting) and figure copy (visual-constructional ability) tasks were not associated with any risky behavioural outcomes.

Table 15. Frequency of risk outcomes

Risky behavioural outcome	**N (%)**
Binge drinking	16 (1.51)
Missing	1 (0.09)
Illicit drug use	44 (4.28)
Missing	5 (0.47)
Unprotected vaginal sex	207 (20.06)
Concurrent relationships	52 (5.04)
Transactional sex	233 (22.02)
HSV-2 infection	213 (20.13)
Missing	27 (2.55)
HIV-1 infection during cohort study	78 (7.37)
Past HIV-1 infection	22 (2.08)
HIV status missing	26 (2.46)

Table 16. Results from logistic regression analyses examining executive function as a predictor of risky substance use behavioural outcomes

EF	Binge drinking						Illicit drug use					
	OR (95% CI)	**p**	**n**	**AOR (95% CI)**	**p**	**n**	**OR**	**p**	**n**	**AOR**	**p**	**n**
DF	0.92 (0.65, 1.30)	0.646	1028	1.00 (0.82, 1.24)	0.971	1000	0.95 (0.77, 1.16)	0.598	1024	0.98 (0.79, 1.22)	0.839	999
DB	1.02 (0.73, 1.42)	0.912	1028	0.99 (0.82, 1.21)	0.958	1000	0.87 (0.70, 1.07)	0.184	1024	0.89 (0.70, 1.11)	0.298	999
TB	0.13 (0.02, 0.91)	0.040*	967	1.16 (0.30, 4.52)	0.836	939	0.21 (0.06, 0.72)	0.012*	963	0.27 (0.07, 1.00)	0.050	938
TS	1.39 (0.84, 2.30)	0.195	915	1.44 (0.54, 3.87)	0.469	913	1.12 (0.53, 2.41)	0.762	897	0.63 (0.23, 1.73)	0.371	912
RF	0.97 (0.51, 1.86)	0.932	1030	2.08 (0.62, 6.97)	0.237	1028	0.71 (0.26, 1.95)	0.506	1009	2.02 (0.54, 7.52)	0.293	1027
IGT	1.10 (0.84, 1.43)	0.481	1029	1.08 (0.66, 1.78)	0.760	1027	0.79 (0.53, 1.18)	0.241	1008	0.63 (0.37, 1.07)	0.087	1026
d'	0.79 (0.48, 1.28)	0.334	1054	0.96 (0.72, 1.29)	0.791	1026	0.77 (0.57, 1.04)	0.092	1050	0.81 (0.60, 1.10)	0.183	1025
FC	1.37 (0.01, 158.50)	0.896	1045	2.18 (0.12, 40.80)	0.602	1017	0.48 (0.04, 5.52)	0.561	1041	0.57 (0.04, 7.64)	0.675	1016
FR	0.61 (0.02, 16.84)	0.771	1045	1.46 (0.19, 11.51)	0.717	1017	0.86 (0.11, 6.58)	0.883	1041	1.29 (0.15, 11.35)	0.819	1016
SV	71.90 (0.00, 908.33)	0.838	1021	9.40 (0.09, 973.02)	0.344	993	2.58 (0.05, 139.82)	0.642	1017	4.45 (0.06, 332.04)	0.498	992
SI	0.12 (0.01, 1.18)	0.070	1021	0.42 (0.08, 2.30)	0.320	993	0.68 (0.11, 4.33)	0.680	1017	1.11 (0.14, 8.81)	0.925	992

Key: EF = executive function variable; OR = odds ratio; CI = confidence interval; AOR = adjusted odds ratio (adjusted for age, socio-economic status, highest level of education and depression scores); DF = digit recall forwards; DB = digit recall backwards; TB = trails baseline; TS = trails switch accuracy cost; RF = rule-finding; IGT = Iowa Gambling Task net score; d' = go/no-go d=prime; FC = figure copy; FR = figure recall; SV = selection visible; SI = selection invisible; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 17. Results from logistic regression analyses examining executive function as a predictor of risky sexual behavioural self-reported outcomes

EF	Unprotected vaginal sex						Concurrent relationships						Transactional sex					
task	OR	p	N	AOR	p	n	OR	p	n	AOR	p	n	OR	p	n	AOR	p	n
DF	0.91 (0.82, 1.01)	0.087	1029	0.93 (0.84, 1.04)	0.215	1000	0.85 (0.71, 1.03)	0.094	1029	0.89 (0.72, 1.09)	0.245	1000	0.97 (0.88, 1.07)	0.563	1029	1.00 (0.90, 1.11)	0.974	1000
DB	0.94 (0.85, 1.04)	0.238	1029	0.97 (0.87, 1.08)	0.599	1000	0.74 (0.61, 0.91)	0.004**	1029	0.76 (0.61, 0.94)	0.012*	1000	0.93 (0.84, 1.02)	0.107	1029	0.96 (0.87, 1.07)	0.491	1000
TB	1.12 (0.56, 2.24)	0.742	968	1.32 (0.63, 2.77)	0.457	939	0.40 (0.13, 1.28)	0.122	968	1.04 (1.01, 1.07)	0.282	939	0.49 (0.26, 0.92)	0.027*	968	0.62 (0.31, 1.22)	0.165	939
TS	1.19 (0.72, 1.96)	0.491	941	1.25 (0.75, 2.09)	0.394	913	0.64 (0.26, 1.60)	0.344	941	0.66 (0.26, 1.71)	0.395	913	0.91 (0.57, 1.47)	0.710	941	0.98 (0.60, 1.61)	0.946	913
RF	1.02 (0.54, 1.95)	0.941	1057	1.23 (0.63, 2.39)	0.550	1028	0.52 (0.15, 1.76)	0.293	1057	0.56 (0.16, 1.96)	0.360	1028	0.56 (0.30, 1.05)	0.073	1057	0.62 (0.32, 1.20)	0.156	1028
IGT	1.19 (0.92, 1.56)	0.191	1056	1.13 (0.86, 1.49)	0.372	1027	0.82 (0.51, 1.32)	0.415	1056	0.83 (0.50, 1.37)	0.462	1027	0.91 (0.71, 1.17)	0.473	1056	0.86 (0.66, 1.11)	0.248	1027
d'	1.12 (0.95, 1.31)	0.178	1055	1.15 (0.98, 1.36)	0.086	1026	0.86 (0.65, 1.13)	0.277	1055	0.85 (0.64, 1.14)	0.279	1026	0.83 (0.72, 0.97)	0.018*	1055	0.83 (0.71, 0.97)	0.021*	1026
FC	2.53 (0.58, 11.12)	0.219	1046	3.68 (0.76, 17.71)	0.104	1017	0.86 (0.07, 9.98)	0.902	1046	1.56 (0.10, 25.55)	0.754	1017	0.96 (0.26, 3.52)	0.951	1046	1.46 (0.37, 5.82)	0.588	1017
FR	2.56 (0.87, 7.56)	0.088	1046	3.75 (1.18, 11.89)	0.025*	1017	0.42 (0.07, 2.50)	0.340	1046	0.54 (0.08, 3.55)	0.518	1017	1.19 (0.44, 3.22)	0.416	1046	1.69 (0.58, 4.88)	0.333	1017
SV	0.91 (0.82, 1.01)	0.087	1029	1.85 (0.30, 11.49)	0.511	993	0.85 (0.71, 1.03)	0.094	1029	13.65 (0.09, 1932.08)	0.301	993	0.97 (0.88, 1.07)	0.563	1029	0.53 (0.11, 2.51)	0.422	993
SI	0.94 (0.85, 1.04)	0.238	1029	2.65 (0.87, 8.04)	0.086	993	0.74 (0.61, 0.91)	0.004**	1029	1.89 (0.24, 14.80)	0.546	993	0.93 (0.84, 1.02)	0.107	1029	1.92 (0.68, 5.41)	0.218	993

Key: EF = executive function; OR = odds ratio; CI = confidence interval; AOR = adjusted odds ratio (adjusted for age, socio-economic status, highest level of education and depression); DF = digit recall forwards; DB = digit recall backwards; TB = trails baseline; TS = trails switch accuracy cost; RF = rule-finding; IGT = Iowa Gambling Task net score; d' = go/no-go d=prime; FC = figure copy; FR = figure recall; SV = selection visible; SI = selection invisible; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 18. Results from logistic regression analyses examining executive function as a predictor of risky sexual behavioural biological outcomes

EF	HSV-2 infection						HIV-1 infection					
task	OR	P	n	AOR	p	n	OR	p	n	AOR	p	n
DF	0.77 (0.69, 0.86)	< 0.001***	1002	0.82 (0.73, 0.92)	0.001**	975	0.95 (0.81, 1.11)	0.532	981	1.00 (0.84, 1.18)	0.968	954
DB	0.91 (0.82, 1.01)	0.071	1002	1.00 (0.90, 1.11)	0.984	975	0.85 (0.72, 1.00)	0.048*	981	0.90 (0.77, 1.06)	0.224	954
TB	0.47 (0.25, 0.92)	0.027*	942	0.86 (0.42, 1.79)	0.691	915	0.53 (0.20, 1.43)	0.208	923	1.22 (0.42, 3.59)	0.714	896
TS	1.39 (0.84, 2.30)	0.195	915	1.69 (0.98, 2.91)	0.059	889	1.12 (0.53, 2.41)	0.762	897	1.19 (0.54, 2.58)	0.668	871
RF	0.97 (0.51, 1.86)	0.932	1030	1.34 (0.67, 2.67)	0.405	1003	0.71 (0.26, 1.95)	0.506	1009	1.05 (0.38, 2.91)	0.926	982
IGT	1.10 (0.84, 1.43)	0.481	1029	1.03 (0.78, 1.36)	0.836	1002	0.79 (0.53, 1.18)	0.241	1008	0.78 (0.52, 1.16)	0.215	981
d'	0.90 (0.77, 1.05)	0.186	1029	0.90 (0.76, 1.06)	0.199	1002	0.93 (0.73, 1.18)	0.536	1008	0.91 (0.72, 1.17)	0.466	981
FC	0.64 (0.17, 2.34)	0.498	1020	1.35 (0.32, 5.66)	0.684	993	0.22 (0.04, 1.21)	0.082	999	0.50 (0.08, 3.15)	0.459	972
FR	0.46 (0.17, 1.26)	0.131	1020	0.95 (0.31, 2.85)	0.921	993	0.33 (0.08, 1.40)	0.132	999	0.78 (0.16, 3.90)	0.764	972
SV	0.19 (0.04, 0.82)	0.026*	995	0.28 (0.06, 1.39)	0.119	968	0.19 (0.03, 1.26)	0.085	974	0.18 (0.03, 1.30)	0.089	947
SI	0.40 (0.16, 0.99)	0.047*	995	0.56 (0.20, 1.56)	0.271	968	1.39 (0.29, 6.70)	0.680	974	1.94 (0.37, 10.13)	0.434	947

Key: EF = executive function; OR = odds ratio; CI = confidence interval; AOR = adjusted odds ratio (adjusted for age, socio-economic status, highest level of education and depression); DF = digit recall forwards; DB = digit recall backwards; TB = trails baseline; TS = trails switch accuracy cost; RF = rule-finding; IGT = Iowa Gambling Task; d' = go/no-go d=prime; FC = figure copy; FR = figure recall; SV = selection visible; SI = selection invisible; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

4.3.3. Case-control substudy

For the matched case-control substudy, we matched 77 17-24-year-old participants with behaviourally acquired HIV (acquired in the last few years during the cohort study) with 153 HIV-negative controls to look at associations between behaviourally acquired HIV infection and EF. The HIV-positive participants and controls were similar in terms of the matching variables (age and SES), as well as other sociodemographic variables (see Table 19). The median CD4 cell count of HIV-positive participants was 635 cells/mm3 and the median viral load was 6120 copies/ml (see Table 20). The HIV-positive participants had significantly poorer verbal working memory (digit span backwards) than the controls (Hedge's g = -0.38; 95% CI -0.66, -0.10; p = 0.0076) even after adjustment for covariates (p = 0.010). There were no other significant differences in EF task performance between HIV-positive participants and controls before or after adjustment for covariates (see Table A, Appendix 8: Study 3 results tables). In the HIV-positive participants, a lower CD4 count (< 350 cells/mm3) was associated with significantly better visuospatial problem-solving and set-shifting (on rule-finding) (Hedge's g = 0.77; 95% CI 0.09, 1.44; p = 0.0263) even after adjustment for confounders (see Table B, Appendix 8: Study 3 results tables). Viral load was not associated with performance on any of the EF tasks (see Table C, Appendix 8: Study 3 results tables).

Table 19. Sociodemographic characteristics of HPTN 068 matched cognitive subsample

Characteristic	HIV-positive participants (n = 77)	HIV-negative controls (n = 153)	Mean comparisons & p value	Whole subsample (n = 230)
Mean age (SD) in years	20.29 (1.45)	20.27 (1.43)	t = -0.09 p = 0.93	20.27 (1.44)
Highest level of education, n (%)				
Some secondary	29 (37.66)	37 (24.18)	chi2 = 4.73	66 (28.70)
Completed secondary	20 (25.97)	44 (28.76)	p = 0.094	64 (27.83)
Post-secondary	28 (36.36)	72 (47.06)		100 (43.48)
SES, n (%)				
Low	15 (19.48)	30 (19.61)	chi2 = 0.00	45 (19.57)
Middle	41 (53.25)	81 (52.94)	p = 1.00	122 (53.04)
High	21 (27.27)	42 (27.45)		63 (27.39)
Marital status, n (%)				
Unmarried	74 (96.10)	147 (96.73)	chi2 = 0.56	222 (96.52)
Married	3 (3.90)	6 (3.27)	p = 0.76	8 (3.48)

Key: SES = socio-economic status

Table 20. Disease-related characteristics of HIV-positive participants in case-control substudy

Characteristic	N (%)	Median (IQR)
CD4 cell count (cells/mm3)		
Full sample	68 (88.31)	635 (447-815)
< 350	10 (12.99)	306 (251-329)
≥ 350	58 (75.32)	679 (490-838)
Missing	9 (11.69)	
Viral load (copies/ml)		
Full sample	75 (96.10)	6120 (30-45920)
< 1000	25 (32.47)	30 (30-30)
≥ 1000	49 (63.64)	22880 (7650-73230)
Missing	3 (3.90)	

4.4. Discussion

4.4.1. Key findings

In this sample of late adolescent females from rural South Africa, better EFs in some domains but not all were weakly associated with less risky sexual and substance use behaviour which provides some limited evidence to support thesis

hypothesis 2.1 (Study 3 hypothesis 1) in specific areas of EF but not across all EFs. Better planning ability was associated with a lower risk of recreational or illicit drug use, binge drinking, transactional sex and HSV-2. Better verbal short-term and/or working memory were associated with a lower risk of concurrent relationships, HSV-2 and HIV-1 infections. Better affective inhibitory control was associated with a lower risk of transactional sex. Better selective attention was associated with a lower risk of HSV-2 infection. The association between EF and risky behaviour was, however, relatively weak for specific areas and not global. The associations were generally attenuated and sometimes became insignificant after controlling for relevant confounders, including depression scores.

These findings are similar to those of an earlier cognitive study on a different subset of young women from the HPTN 068 cohort (2015 revisit) in that both studies found an association between EF and risky sexual behaviour; however, there were some differences (Rosenberg et al., 2018). The 2015 revisit used three of the same tasks, but paper-based rather than tablet-based versions. In the 2015 revisit, poorer figure recall and rule-finding were each weakly associated with an elevated risk of a sexual risk outcome (Rosenberg et al., 2018); in contrast, we did not find any consistent associations between performance on these two tasks and sexual risk outcomes. These discrepancies could be due to differences in outcome definitions with this study referring to the last five sexual partners, not just the last three; and including HSV-2 infection occurring at any time point not just recent HSV-2 infection. The discrepancies could also be due to differences in cognitive predictor variables. The previous study used dichotomous scores; this study used continuous scores. Whereas the previous study controlled for baseline scores in the figure drawing task, I analysed the baseline score separately.

In the matched case-control sample focusing on participants with behaviourally acquired HIV compared to socio-demographically matched controls, HIV-positive participants had poorer verbal working memory; the effect size was small. Performance on all other EF tasks was similar to healthy controls which does not support thesis hypothesis 1 in the context of behaviourally acquired HIV. This is in contrast to Study 1 which did provide evidence to support thesis hypothesis 1 in the context of perinatally acquired HIV. This suggests that late adolescents with behaviourally acquired HIV acquired in the last five years during adolescence might have fewer EF deficits than late adolescents with perinatally acquired HIV (Willen et al., 2017), providing evidence to support thesis hypothesis 1.1. It suggests that there may be a pattern of limited EF deficits in adolescents with behaviourally acquired HIV involving verbal working memory only (thesis hypothesis 1.4); however, the pattern found in this study was different to that found in the ATN 071 study in a US-based predominantly male adolescent sample with behaviourally acquired HIV who did not have higher rates of impairment in working memory or inhibitory control but had increased set-shifting impairments. More evidence is thus needed to establish if there is a consistent pattern of EF deficits (thesis hypothesis 1.4).

In contrast to thesis hypothesis 1.2.1 (biological markers of more advanced disease or uncontrolled disease are associated with poorer EF in HIV-positive adolescents), amongst participants with behaviourally acquired HIV in this study, disease markers were mostly unrelated to EF. Serum viral load and CD4 cell count were not associated with EF; except for an unexpected weak association between a higher CD4 cell count and poorer rule-finding accuracy. This may be because these participants were less likely to be on ART. ART initiation in South Africa was

still guided by CD4 count at the time of the study. The power to detect differences between subgroups was limited by the small sample size within the behavioural HIV group overall (n = 77) and even smaller numbers in subgroups. The low CD4 cell count group only contained 10 people, 9 of whom had CD4 cell counts > 200 cells/mm3 i.e. most did not have advanced immune suppression. It may be that an association between other EFs and CD4 cell count would only emerge in the more advanced stages of immune suppression when the CD4 cell count drops below 200 cells/mm3.

4.4.2. Strengths

To my knowledge, this was one of the first large-scale studies to look at the association between EF subtypes (including both affective and non-affective tasks) and risky sexual and substance use behavioural outcomes in young women in sub-Saharan Africa. Strengths of this study include the large sample size and the detailed sociodemographic, behavioural and biological data collected. An array of EF tests was included spanning core EFs (working memory, inhibitory control, set-shifting), higher-order EFs (planning, problem-solving), and EFs in the context of emotion and risk (affective decision-making, emotional inhibition). This allowed me to explore potential associations with EF subtypes which is important because, as I found in this study and Study 1, EFs may be differentially affected in the context of HIV-associated neurocognitive disorder. They may also relate to risky behaviour in different ways (K. A. Walker & Brown, 2018).

4.4.3. Limitations

Limitations included not knowing whether participants were currently on antiretroviral therapy (ART) and whether they were currently pregnant, both of which may affect EF (Al-Khindi, Zakzanis, & van Gorp, 2011; Davies, Lum,

Skouteris, Byrne, & Hayden, 2018). As the cognitive data was cross-sectional, it was not possible to determine directionality of associations and likely causality. Working memory deficits in HIV-positive participants might have been a cause and/or a consequence of HIV infection. Due to the original eligibility criteria for inclusion in the parent study, some of the potentially most vulnerable adolescents (those who were pregnant, married, or not enrolled in school at baseline) were excluded. Finally, due to multiple outcomes being analysed, correction for multiple comparisons would render some of the findings non-significant. Some of the associations might have been chance associations.

4.4.4. Conclusions

Verbal working memory was poorer in late adolescent females with behaviourally acquired HIV than healthy controls; their EFs were otherwise similar. Better EF was weakly associated with a lower risk of certain but not all risky behavioural outcomes in late adolescent females in rural South Africa; those with poorer EF tended to be at greater risk. Potential proximal determinants of risk and risky behaviour are important to understand when developing population interventions to decrease risk of adverse health outcomes e.g. transmission of HIV infection. Young women with EF deficits should be considered when aiming to target high-risk groups in HIV prevention and risk reduction efforts in sub-Saharan Africa. Interventions to improve EF could also be developed and explored as potential interventions to decrease risky behaviour and HIV transmission risk amongst adolescents in high HIV prevalence contexts. In the following chapter, I explore musical training, and specifically group drumming, as an intervention to improve EF directly through training and though improving socio-emotional well-being.

Chapter 5: An overview of the literature on musical training interventions and executive functioning, and the potential effects of group drumming interventions

Chapter outline:

5.1. Musical training interventions and executive function

5.1.1. Background

5.1.2. Experimental and quasi-experimental studies

5.1.3. Observational studies

5.1.4. Summary of musical training and executive function

5.2. Potential effects of group drumming

5.1. Musical training interventions and executive function

5.1.1. Background

In earlier chapters, I demonstrated the need for interventions to improve EF, particularly in adolescents with perinatally acquired HIV (Chapter 2). Musical training is one of the EF enhancing interventions that has been tested in other populations (Chapter 1). In this chapter, I provide the theoretical background on the potential EF effects of musical training more broadly and then the potential socio-emotional benefits of group drumming specifically to justify group drumming as the intervention chosen to test in Chapter 6. In Section 5.1, I provide an overview of the studies on musical training and EF in children, adolescents and adults < 55 years old to examine the association between musical training and EF and to elucidate the potential efficacy of musical training interventions in improving EF. I include both experimental, quasi-experimental and the larger body of observational

studies. In Section 5.2, I provide an overview of the studies on group drumming as an intervention and its potential effects.

Musical training places demands on the executive control system. Playing a musical instrument places demands on phonological working memory (tonal and/or rhythmic and/or verbal) through part memorisation, recital, and error monitoring with updating or correction of the memorised musical sequence during the learning process. It usually involves training in active listening by placing selective attention on specific components of a musical piece while inhibiting simultaneous distracting components and the impulse to copy others' parts (inhibitory control) and switching between parts as foci of attention (set-shifting). In a musical group or ensemble context, there are often even greater executive control demands as the instrumentalist or vocalist needs to sustain his/her own part while simultaneously inhibiting neighbouring musicians' parts sufficiently not to be distracted by them, yet watching for visual cues and listening for auditory cues from the group as a form of error monitoring to update performance in response to feedback e.g. to be sure that they are maintaining the correct tempo (speed) and dynamics (volume) relative to the other group members.

In the next four subsections I will summarise the literature on the relationship between musical training and EF.

5.1.2. Experimental and quasi-experimental studies

5.1.2.1. Clinical populations

There have been two randomised controlled trials (RCTs) of musical training with EF as an outcome amongst clinical child and adolescent populations. The one was a small pilot (n = 6) of six weeks of either musical attention control training, non-

standardised music therapy or no musical intervention amongst 14-18-year-old adolescents with attention/deficit-hyperactivity disorder, oppositional defiant disorder and/or conduct disorder which did not detect an effect on set-shifting or verbal working memory (Abrahams & van Dooren, 2018). The second was an RCT amongst 8-11-year-old dyslexic children (n = 46) which found significant improvements in verbal working memory, the only EF outcome assessed, after 60 sessions of Kodaly and Orff-based group musical training compared to an active (painting) control group (Flaugnacco et al., 2015).

5.1.2.2. Typically developing children and adolescents

There have been a few intervention studies amongst typically developing primary-school children (6-10 years). A four-arm (two music groups; one visual art; one passive) cluster RCT (n = 176) with longitudinal follow-up every 6 months for 2.5 years found the music groups had greater improvements in planning and inhibitory control; the visual art group had greater improvements in visuospatial working memory (Jaschke, Honing, & Scherder, 2018). In contrast, a longitudinal observational study (n = 68) comparing children receiving two years of 'El Sistema' group musical training (6-7 hours/week) did not differ significantly to an active sports and a passive control group in verbal working memory or inhibitory control (Habibi, Damasio, Ilari, Elliott Sachs, & Damasio, 2018). A stratified RCT (n = 75) found that the music group had greater improvements than the active dancing and passive control groups in response inhibition and performance on a set-shifting task; however, there were no differences in performance on verbal or visuospatial working memory, interference control or another set-shifting task (D'Souza & Wiseheart, 2018). A pilot RCT (n = 40) comparing group keyboard harmonica lessons to passive controls found the music group improved more on digit span

backwards, but not the other verbal working memory task nor the inhibitory control task (Guo, Ohsawa, Suzuki, & Sekiyama, 2018). There have been two non-randomised controlled (passive controls) intervention studies: one (n = 113) assessed 10 weeks of 'Music 'n play' musical training and found significant improvements in the music group's inhibitory control, the only EF outcome assessed (Fasano et al., 2019); the other (n = 62) assessed 16 weeks of 'In Harmony' computerised musical training and found significant improvements in visuospatial working memory, the only EF outcome assessed (Portowitz, Peppler, & Downton, 2014). There have also been various group musical experimental studies in typically developing pre-school children which have either shown improvements on some EF subtypes (Bowmer, Mason, Knight, & Welch, 2018; Bugos & DeMarie, 2017; Da Silva, Dos Santos Baldin, & Dos Santos, 2017; Janus, Lee, Moreno, & Bialystok, 2016; Kaviani, Mirbaha, Pournaseh, & Sagan, 2014; Moreno et al., 2011) or no improvement (Linnavalli, Putkinen, Lipsanen, Huotilainen, & Tervaniemi, 2018). The experimental and quasi-experimental studies on musical training and EF are summarised in Table 21.

Table 21. Table of experimental and quasi-experimental studies on musical training and executive function

Author & year	Population	Study design & timepoints	Intervention name/type (n in music group)	Intervention timing	Controls (n in control group)	EF/s & task/s	Effect size/s	Music effect
(Abrahams & van Dooren, 2018)	Residential care: ADHD, ODD and/or CD; 14-18 years; Netherlands	Pilot RCT; 3: pre, post, 3 weeks later	Musical Attention Control Training (MACT) (listening & playing) (n=2)	45-min weekly sessions x 6 weeks	Active: Non-standardised music therapy (n=2) Passive: None (n=2)	TS (TMT), VWM (DSB)	NA	None
(Bowmer et al., 2018)	TD preschool; 3-4 years; UK	Pseudo-randomised two-phase experiment; 3: pre-phase 1, post-phase 1/pre-phase 2, post-phase 2	Creative Futures group music activity (n=14)	40-min weekly sessions x 8 weeks. Repeated in phase 2.	Phase 1: Controls free play. Phase 2: Control 1 music (n=15) Control 2: art (n=12)	TS (peg tap, DCCS, trucks), IC (baby Stroop), PL (TOL), WM (spin the pots)	η2p: Peg: 0.14. PL: 0.03.	Better peg (p=0.05) & PL (p=0.05). Rest: none
(Bugos & DeMarie, 2017)	TD preschool; 4-5 years; US	RCT; 2: pre, post	Group musical training (instruments & voice) (n=18)	Twice weekly 45-min sessions x 6 weeks	Active: Lego (n=18)	IC (day/night stroop, MFFT)	Cohen's d: stroop: 0.987	Better stroop (group x time: p=0.035). MFFT: none
(Da Silva et al., 2017)	TD preschool; 5 years; Brazil	Pseudo-randomised prospective pilot; 2: pre, post	Group numeracy musical training (n=20; 10 per class)	Twice weekly 40-min sessions x 5 weeks	Passive: usual school activities (n=20)	VWM (DSB), VSWM (spatial span)	η2p: VWM: 0.18. VSWM: 0.01	Better VWM (p=0.006). VSWM: none

Author & year	Population	Study design & timepoints	Intervention name/type (n in music group)	Intervention timing	Controls (n in control group)	EF/s & task/s	Effect size/s	Music effect
(D'Souza & Wiseheart, 2018)	TD primary school; 6-9 years; Canada	RCT (stratified randomisation); 2: pre, post	Music camp (basis: Canadian national curriculum) (n=24)	120 mins/day 5 days/week x 3 weeks	Active: dance (n=26) Passive: nothing (n=25)	VWM (DSB), VSWM (VS span), IC (flanker, stroop), TS (colour-shape, quantity-identity)	Cohen's d: VWM 0.37, VWSM 0.44, flanker 0.17, stroop 0.24, colour-shape 0.23, quantity-identity 0.05	WM, stroop, Colour-shape: None. Better flanker (p=0.013) & quantity-identity (p=0.031)
(Fasano et al., 2019)	TD primary school; 8-10 years; Italy	Quasi-experimental; 2: pre, post	Music 'n' play ('MusicaInGioco') school group music training programme (n=55)	Weekly 135-min sessions x 10 weeks	Passive: usual school activities (n=58)	IC (walk no-walk stop-signal task)	NR & unable to calculate	Improved significantly (p<0.001); still worse than controls pre & post
(Flaugnacco et al., 2015)	Dyslexic children; 8-11 years; Italy	RCT (stratified randomisation); 2: pre, post	Kodaly & Orff-based group music training programme (listening & playing) (n=22)	Twice weekly 60-min sessions x 30 weeks	Active: Bruno Munari painting training (n=24)	VWM (DSB)	Cohen's d 0.32	Improved significantly more (p=0.02)
(Guo et al., 2018)	TD primary school; 6-8 years; Japan	Pilot RCT; 2: pre, post	Group keyboard harmonica lessons (n=20; groups of 10)	Twice weekly 25-min sessions x 6 weeks	Passive: free play (n=20)	VWM (DSB, LNS), IC (GNG)	η2p: DSB 0.143, LNS<0.001	DSB: better (group x time p=0.015) Rest: none

Author & year	Population	Study design & timepoints	Intervention name/type (n in music group)	Intervention timing	Controls (n in control group)	EF/s & task/s	Effect size/s	Music effect
(Habibi et al., 2018)	TD primary school; 6-7 years; US	PC-C (music: lottery); 2: pre, 2 years	'El Sistema' group string musical instrument training (n=21)	6-7 hours/week x 2 years	Active: sports (soccer/ swim) (n=23) Passive: no extra-curricular (n=24)	VWM (DSB), IC (stroop)	NR	VWM: NR IC: None
(Janus et al., 2016)	TD preschool; 4-6 years; Canada	Pseudo-RCT; 2: pre, post	Moreno's computerised classroom musical training curriculum (listening not instrumental) (n=29)	Twice daily 90-min sessions x 20 days	Active: French lessons (n=28)	VWM/TS (VF), VSWM (Corsi,) VWM (word span)	η2p: VF: 0.1	VF improved (p=0.02) (similar to controls). Rest: none
(Jaschke et al., 2018)	TD primary school; 6-8 years at start; 8-10 years at end; Netherlands	Cluster (school) RCT; 5: baseline; follow-ups 1-4 every 6 months for 2.5 years	Classroom primary school music curriculum (MOCCA expert centre) (n=44)	Weekly 60-120 mins x 2.5 years	Active 1: less music (n=44) Active 2: visual arts (n=44) Passive: no arts (n=44)	PL (TOL), VSWM (Klingberg ST & WM task), IC (GNG)	NR	PL & IC better in music groups (p's<0.05) VSWM art better (p<0.05).

Author & year	Population	Study design & timepoints	Intervention name/type (n in music group)	Intervention timing	Controls (n in control group)	EF/s & task/s	Effect size/s	Music effect
(Kaviani et al., 2014)	TD preschool; 5-6 years; Iran	RCT (matched pairs randomised); 2: pre, post	Culturally adapted Carl Orff group musical training (percussion, voice, games) (n=30)	Weekly 75-min sessions x 12 weeks	Passive: no music lessons (n=30)	VWM (DS, sentence memory) & VSWM (bead & object memory)	Cohen's d: music: 0.46, controls 0.18	Better ($p<0.01$)
(Linnavalli et al., 2018)	TD preschool; 4-5 years; Finland	PC-C (preschool: group); 4: over 2 years	Music playschool (voice, percussion, games) (n=28)	Weekly 45-min sessions for 30 weeks/year x 2 years	Active: dance (n=32) Passive: no arts (n=20)	IC & TS: NEPSY-II inhibition	NR	None ($p=0.922$)
(Moreno et al., 2011)	TD preschool; 4-6 years; Canada	Pseudo-RCT; 2: pre, post	Computerised classroom musical training (n=24)	Weekly 45-min sessions 5 days/week x 4 weeks	Active: computerised visual art training (n=24)	IC: GNG	$\eta 2p$ 0.13	Better (group x session $p=0.01$)
(Portowitz et al., 2014)	TD primary school; 9-10 years; Israel	Non-randomised controlled study (matched groups); 2: pre, post	In Harmony: 2 computerised programmes (Teach, Learn, Evaluate! & Impromptu) (n=40)	Weekly 120-min sessions x 16 weeks	Passive: no musical training (n=22)	VSWM: RCFT recall	$\eta 2p$ 0.11	Better (group x time $p<0.05$)

Key: n = number; EF = executive function; ADHD = attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder; CD = conduct disorder; RCT = randomised controlled trial; TS = task switching; TMT = trail-making task; VWM = verbal working memory; DSB = digit span backwards; NA = not applicable; TD = typically developing; UK = United Kingdom; DCCS = dimensional change card sort; IC = inhibitory control;

PL = planning; TOL = Tower of London; WM = working memory; US = United States; MFFT = Matching Familiar Figures Test; VSWM = visuospatial working memory; VS = visuospatial; NR = not reported; LNS = letter-number sequencing; GNG = go/no-go; PC-C = prospective cohort with controls; VF = verbal fluency; ST = short-term; NEPSY-II = A Developmental NEuroPSYchological Assessment Second Edition; RCFT = Rey Complex Figure Test

5.1.3. Observational studies

I now summarise the observational studies examining the association between musical training and EF. I decided to explore the observational literature too because it was more extensive than the experimental literature. Although it is only correlational data and further experimental data is needed, this observational data provides valuable early evidence supporting musical training as an intervention worth exploring further. A population-level cross-sectional educational records study (n = 112,916) found a positive association between school musical participation and academic achievement (with medium effect sizes for instrumental training and small effect sizes for vocal training) which the authors hypothesised may have been mediated by EF (Guhn, Emerson, & Gouzouasis, 2019). There have been numerous cross-sectional observational studies examining the association between musical training and EF. Below I will firstly summarise the studies in children and early-middle adolescents, then the studies in late adolescents, and finally the studies in a mixture of late adolescents and adults.

5.1.3.1. Children and early-middle adolescents

Some studies found a positive association between musical training and better phonological working memory in children and early-middle adolescents (Bergman Nutley et al., 2014; Y. S. Lee, Lu, & Ko, 2007; Ribeiro & Dos Santos, 2012; Rochette, Moussard, & Bigand, 2014; Schellenberg, 2011; Strait, Parbery-Clark, Hittner, & Kraus, 2012); others found no such association (Herrero & Carriedo, 2018; Ireland, Parker, Foster, & Penhune, 2018; Saarikivi, Putkinen, Tervaniemi, & Huotilainen, 2016; Sachs, Kaplan, Der Sarkissian, & Habibi, 2017; Zuk, Benjamin, Kenyon, & Gaab, 2014). For the EF subtypes other than phonological working memory, the evidence was less consistent. For visuospatial working

memory, some studies found a positive association (Bergman Nutley et al., 2014; Degé, Kubicek, & Schwarzer, 2011; Y. S. Lee et al., 2007), whereas others had mixed findings (Holochwost et al., 2017; Ribeiro & Dos Santos, 2012) or found no association (Strait et al., 2012). The association with inhibitory control was less consistent with half the studies finding a positive association (Degé et al., 2011; Holochwost et al., 2017; Joret, Germeys, & Gidron, 2017; Putkinen, Tervaniemi, Saarikivi, & Huotilainen, 2015) and half finding no association (Gregoire, Perruchet, & Poulin-Charronnat, 2015; Hedayati, Schibli, & D'Angiulli, 2016; Sachs et al., 2017; Schellenberg, 2011; Zuk et al., 2014). A few studies found a positive association with set-shifting (Degé et al., 2011; Saarikivi et al., 2016; Zuk et al., 2014) with one finding a mixed association (Holochwost et al., 2017) and another finding no association with either set-shifting or planning (Schellenberg, 2011).

5.1.3.2. Late adolescents

In late adolescents, studies have generally found a positive association between musical training and both phonological and visuospatial working memory (Franklin et al., 2008; George & Coch, 2011; Hou et al., 2014; Okada & Slevc, 2018). For inhibitory control, one found a positive association (Schroeder, Marian, Shook, & Bartolotti, 2016), one found a mixed association with inhibitory control and no association with set-shifting (Okada & Slevc, 2018), and one found no association with inhibitory control (Hou et al., 2014).

5.1.3.3. Late adolescents and adults

There have been numerous cross-sectional observational studies in a mixed sample of late adolescents and adults comparing EF in musicians (usually with years of musical training and current regular practice) to non-musicians (with little or no formal musical training and no current musical practice) with mixed results.

Many found a positive association with phonological working memory (Bergman Nutley et al., 2014; K. K. Clayton et al., 2016; D'Souza, Moradzadeh, & Wiseheart, 2018; Ding, Gray, Forrence, Wang, & Huang, 2018; Y. S. Lee et al., 2007; Oechslin, Van De Ville, Lazeyras, Hauert, & James, 2013; Pallesen et al., 2010; Parbery-Clark, Skoe, Lam, & Kraus, 2009; Ramachandra, Meighan, & Gradzki, 2012; Slevc, Davey, Buschkuehl, & Jaeggi, 2016; Strait et al., 2012; Suarez, Elangovan, & Au, 2016; Zuk et al., 2014). A few had mixed findings (Alain et al., 2018; Lu & Greenwald, 2016; Weiss, Biron, Lieder, Granot, & Ahissar, 2014) usually by subtype of phonological working memory and some found no association (Bailey & Penhune, 2012; Boebinger et al., 2015; Dittinger, Valizadeh, Jancke, Besson, & Elmer, 2018; Elmer, Greber, Pushparaj, Kuhnis, & Jancke, 2017; Fauvel et al., 2014; Seppanen, Pesonen, & Tervaniemi, 2012; Smayda, Worthy, & Chandrasekaran, 2018; Strait, Kraus, Parbery-Clark, & Ashley, 2010). Visuospatial working memory was less consistently associated with musical training with a few studies finding a positive association (Bergman Nutley et al., 2014; Bidelman, Hutka, & Moreno, 2013; Slevc et al., 2016; Suarez et al., 2016; Zuk et al., 2014) and a few not finding an association (Bialystok & Depape, 2009; K. K. Clayton et al., 2016; Strait, O'Connell, Parbery-Clark, & Kraus, 2014; Vassena, Kochman, Latomme, & Verguts, 2016). Complex working memory was generally not associated with musical training (Bishop, Bailes, & Dean, 2013; Posedel, Emery, Souza, & Fountain, 2012; Smayda et al., 2018); however, one study found a positive association (Y. S. Lee et al., 2007) and one found a negative association (Gelding, Thompson, & Johnson, 2015). Similarly to children and younger adolescents, findings in relation to inhibitory control were inconsistent: a few studies found a positive association (Boh, Herholz, Lappe, & Pantev, 2011;

Jentzsch, Mkrtchian, & Kansal, 2014; Lima & Castro, 2011; Slater, Azem, Nicol, Swedenborg, & Kraus, 2017; Sobierajewicz, Naskręcki, Jaśkowski, & Van der Lubbe, 2018); a few studies found a mixed association (Bialystok & Depape, 2009; D'Souza et al., 2018; Smayda et al., 2018); a few found no association (Boebinger et al., 2015; K. K. Clayton et al., 2016; Moreno, Wodniecka, Tays, Alain, & Bialystok, 2014; Seppanen et al., 2012; Slevc et al., 2016; Zuk et al., 2014). Of interest was that one study found that musicians had superior auditory inhibitory control but similar visual inhibitory control to non-musicians, suggesting that if there is an association, it might be modality-specific (Bialystok & Depape, 2009). Another found superior inhibitory control in percussionists compared to both vocalists and non-musicians, suggesting that the type of musical instrument or training might also be differentially associated with EF subtypes (Slater et al., 2017). Another suggested that timing of onset of musical training might affect performance on an Iowa Gambling Task with those who began training after 8-years-old doing better than those who began training earlier and non-musicians (Smayda et al., 2018). There were no differences in set-shifting between musicians and non-musicians in the late adolescent and adult studies (Bialystok & Depape, 2009; Boebinger et al., 2015; Slevc et al., 2016; Zuk et al., 2014).

5.1.4. Summary of musical training and executive function

There have been very few high-quality experimental studies examining the effect of musical training on EF. Most of the intervention work involved group rather than individual musical training interventions. It has not involved random assignment but rather used pseudo-random assignment and/or quasi-experimental controlled pre-post observational studies. There have been three longitudinal cohort studies with assessment at more than two time-points. Though many experimental studies

have found some improvement in certain EF subtypes, not all studies found improvement. There does not seem to be a clear pattern emerging across studies regarding which EF subtype/s might be most amenable to improvement through musical training. The cross-sectional correlational evidence is more extensive, particularly with regards to the relationship between musical training and phonological working memory, but there are almost no studies focused exclusively on adolescents. The cross-sectional nature of this evidence means that it is not possible to determine whether any group differences were pre-existing and/or causally associated with musical training. The pattern of associations that seems to emerge from this evidence is that phonological working memory is most consistently positively associated with musical training; whereas there are less consistent positive associations with visuospatial working memory and inhibition, and generally no associations with complex working memory, set-shifting and planning.

5.2. Potential effects of group drumming

Group drumming is a type of musical training intervention. Group drumming interventions have been used in a variety of populations and settings in North America, Europe, Asia, Africa and Oceania, usually aiming to improve various aspects of socioemotional functioning and behaviour but not EF or cognition. The studies in each of the following population groups are summarised in tabular format: children and adolescents with clinical, social or behavioural issues (Table 22); healthy children and adolescents (Table 23); adults with clinical or social issues (Table 24); healthy adults (Table 25). The following is a summary of the positive effects that emerged most frequently in the group drumming literature in descending order of frequency:

1. **Increased group cohesion, ‘connectedness’ or group acceptance and belonging** in:
    a. Adolescents with post-traumatic stress disorder (PTSD) (Bensimon, Amir, & Wolf, 2008)
    b. Adolescent psychiatric in-patients (Stone, 2005)
    c. Adolescents known to the juvenile justice system (Watson, Washington, & Stepteau-Watson, 2015)
    d. Healthy children and adolescents in most (Davis-Craig, 2009; Kaplan, 2000; Mackinlay, 2014) but not all studies (Wyatt, 2000)
    e. HIV-positive adult substance users (Winkelman, 2003)
    f. Adult intimate partner violence survivors (Hannigan & McBride, 2011)
    g. Adults with mood disorders (Ascenso, Perkins, Atkins, Fancourt, & Williamon, 2018)
    h. Adult psychiatric in-patients (Longhofer & Floersch, 1993)
    i. Healthy adults (Davis-Craig, 2009; G. F. Newman, Maggott, & Alexander, 2015; Stone, 2005; Venkit, Godse, & Godse, 2013)
2. **Improved mood or affect, decreased depression, increased joy, or hedonia** in:
    a. Children who are abuse survivors (Flores, 2011)
    b. Adolescents known to the juvenile justice system (B. Bittman, Dickson, & Coddington, 2009; Watson et al., 2015)

c. Healthy children and adolescents (Davis-Craig, 2009; Ho, Tsao, Bloch, & Zeltzer, 2011; Kaplan, 2000; Mackinlay, 2014)

d. Adult mental health care users (in-patients or outpatients) e.g. with mood disorders (Ascenso et al., 2018; Fancourt, Perkins, Ascenso, Atkins, et al., 2016; Fancourt, Perkins, Ascenso, Carvalho, et al., 2016; Silverman & Marcionetti, 2004) or HIV-positive adult substance users (Winkelman, 2003); however, not in adults with Parkinson's disease (Pantelyat, Syres, Reichwein, & Willis, 2016)

e. Healthy adults (B. Bittman, Bruhn, Stevens, Westengard, & Umbach, 2003; B. B. Bittman et al., 2004; Davis-Craig, 2009; G. F. Newman et al., 2015)

3. **Decreased anxiety or stress, or increased relaxation** in:

a. Adolescents with PTSD (Bensimon et al., 2008); however, not in children who are abuse survivors (Flores, 2011)

b. Healthy children and adolescents (Ho et al., 2011; Snow & D'Amico, 2010)

c. Adults with mild-moderate mood disorders (Fancourt, Perkins, Ascenso, Carvalho, et al., 2016), substance use disorders (Blackett & Payne, 2005) and intimate partner violence survivors (Hannigan & McBride, 2011)

d. Healthy adults (G. F. Newman et al., 2015; C. Smith, Viljoen, & McGeachie, 2014; Venkit et al., 2013)

4. **Improved self-esteem or decreased negative self-evaluation** in:
    a. Children who are abuse survivors (Flores, 2011)
    b. Adolescents known to the juvenile justice system (B. Bittman et al., 2009)
    c. Healthy children and adolescents in many (Mackinlay, 2014; Snow & D'Amico, 2010; Wood, Ivery, Donovan, & Lambin, 2013) but not all studies (Wyatt, 2000)
    d. Adult psychiatric in-patients (Longhofer & Floersch, 1993; Silverman & Marcionetti, 2004)
5. **Improved concentration or EF, or decreased inattention** in:
    a. Children who are abuse survivors (Flores, 2011); however, not in children with attention problems (Chacona, 2007) (decreased impulsivity but not inattention) or emotional, learning and behavioural disorders (Montello & Coons, 1998)
    b. Healthy adolescents (Ho et al., 2011)
    c. Healthy adults (G. F. Newman et al., 2015)
6. **An inclusive, equalising effect** in:
    a. Adolescent psychiatric in-patients (Stone, 2005): “Being joined by rhythm transcended and often erased barriers between us. Drumming made me feel good about myself and others.”
    b. Healthy adolescents (Faulkner, Wood, Ivery, & Donovan, 2012)
    c. Adults with substance use disorders (Blackett & Payne, 2005)

d. Healthy adults (G. F. Newman et al., 2015; Stone, 2005)

7. **Increased sense of purpose or motivation** in:

    a. Children with emotional, learning and behavioural disorders (Montello & Coons, 1998)

    b. Adolescents known to the juvenile justice system (Watson et al., 2015)

    c. Healthy children and adolescents (Mackinlay, 2014; Snow & D'Amico, 2010)

    d. Adult psychiatric in-patients (Longhofer & Floersch, 1993)

8. **Decreased anger or aggression** in:

    a. Adolescents with PTSD (Bensimon et al., 2008)

    b. Adolescents known to the juvenile justice system (B. Bittman et al., 2009)

    c. Children with emotional, learning and behavioural disorders (Montello & Coons, 1998)

    d. Healthy adolescents (Snow & D'Amico, 2010)

    e. Adult psychiatric in-patients (Silverman & Marcionetti, 2004)

9. **Increased energy or decreased tiredness** in:

    a. Adolescents known to the juvenile justice system (Watson et al., 2015)

    b. Adults with mild-moderate mood disorders (Fancourt, Perkins, Ascenso, Carvalho, et al., 2016)

c. Healthy adolescents and adults (Davis-Craig, 2009; G. F. Newman et al., 2015)

10. **Emotional release or expression** in:

    a. Adults who are intimate partner violence survivors, HIV-positive substance users, or psychiatric in-patients (Hannigan & McBride, 2011; Silverman & Marcionetti, 2004; Winkelman, 2003)

    b. Healthy adults (G. F. Newman et al., 2015)

11. **Connection to cultural tradition or ancestors** in:

    a. Adolescent psychiatric in-patients (Stone, 2005)

    b. Healthy adolescents and adults (Davis-Craig, 2009; Stone, 2005)

12. **Increased confidence** in:

    a. Healthy children and adolescents (Mackinlay, 2014; Snow & D'Amico, 2010)

    b. Healthy adults (Venkit et al., 2013)

13. **Increased engagement** in:

    a. Healthy adolescents (Faulkner et al., 2012)

    b. Adults who are intimate partner violence survivors or have mood disorders (Ascenso et al., 2018; Hannigan & McBride, 2011)

Other less frequent positive effects, each emerging in only two studies, included: increased agency or sense of control (Ascenso et al., 2018; Bensimon et al., 2008); increased prosocial behaviour or empathy (Flores, 2011; G. F. Newman et al., 2015); improved general well-being or quality of life (Fancourt, Perkins, Ascenso,

Carvalho, et al., 2016; Pantelyat et al., 2016); increased cooperation (Hannigan & McBride, 2011; Wood et al., 2013); sense of accomplishment (Ascenso et al., 2018; G. F. Newman et al., 2015); and decreased burnout (B. Bittman et al., 2003; B. B. Bittman et al., 2004).

Pertinent potential effects which appeared once only in the group drumming literature included: increased functional connectivity on functional MRI between key brain regions (Amad et al., 2017); increased salivary oxytocin, a hormone important for social bonding, amongst in-patients with emotional problems (Yuhi et al., 2017); and decreased salivary cortisol, a stress hormone, and certain pro-inflammatory cytokines in adults with mood disorders (Fancourt, Perkins, Ascenso, Atkins, et al., 2016).

In summary, most of the existing studies on group drumming as an intervention have been small and/or uncontrolled quantitative or qualitative studies. They have generally found immediate and/or short-term benefits for socio-emotional well-being, particularly a sense of belonging and acceptance within the drumming group, improved mood, and decreased anxiety. The few larger RCTs, i.e. the highest quality evidence thus far, have found quantitative improvements in mood (B. Bittman et al., 2003; B. Bittman et al., 2009; B. B. Bittman et al., 2004). Although additional large-scale, randomised studies are needed, the preliminary evidence is promising. Therefore, I decided group drumming was an intervention worth exploring further. In the following chapter, I describe the development and initial testing of a group drumming intervention aiming to improve EF and socio-emotional wellbeing in HIV-positive adolescents.

Table 22. Table of group drumming studies in children and adolescents with clinical, social or behavioural issues

Reference	Intervention	Target population	Controls	Measure	Finding
(Bensimon et al., 2008)	Group music therapy drumming x 16 x weekly 90-min session	Adolescent soldiers with post-traumatic stress disorder (n=6), Israel	None	Qualitative content analysis from video recordings	↑ group cohesion & belonging ↓ anger ↓ anxiety ↑ sense of control
(B. Bittman et al., 2009)	HealthRHYTHMS group hand drumming weekly 60-min sessions x 6 weeks	Adolescents in a juvenile justice residential treatment programme (n=52), US	Randomised controlled crossover trial. Controls: normal routine therapeutic & educational programmes	1. Child and Adolescent Functional Assessment Scale 2. Reynolds Adolescent Depression Scale 2nd edition 3. Adolescent Anger Rating Scale	Improved school/work role performance ↓ depression ↓ negative self-evaluation ↓ instrumental aggression
(Chacona, 2007)	World Music Drumming x 30-mins twice a week x 7 weeks	Primary school children & adolescents with attention problems (n=30), US	Passive i.e. no additional activity (n=30)	Continuous performance task	↓ impulsivity Unchanged inattention
(Flores, 2011)	Group djembe drumming weekly 40-50-min sessions x 4 months	Children with a history of abuse & high levels of psychiatric comorbidity (n=16), South Africa	None	Beck Youth Inventories: self-concept, anxiety, depression, anger & disruptive behaviour. Qualitative analysis of video-recorded sessions	No quantitative effects: depression, anger, disruptive behaviour. ↑ anxiety. Qualitative: ↑ self-esteem, prosocial behaviour, affect & concentration
(Montello & Coons, 1998)	School-based active group hand drumming music	Children with emotional, learning &	Crossover with school-based passive listening-	Teacher Report Form (TRF):	Both groups: ↑ motivation ↓ hostility

	therapy, weekly 45-min sessions x 12 weeks	behavioural disorders (n=16), US	based group music therapy	attention, motivation, hostility	Unchanged attention
Reference	**Intervention**	**Target population**	**Controls**	**Measure**	**Finding**
(Stone, 2005)	Group hand drumming weekly x 6 months	Adolescent mostly African-American & Latino psychiatric in-patients (n=31) & staff, US	None	Qualitative observation by drum facilitator	4 themes: 1. community 2. equality 3. family 4. connection to culture / ancestors
(Watson et al., 2015)	Spir-rhythms group drumming x 6 weeks	African American adolescent males known to the juvenile justice system (n=34), US	None	Qualitative observation as a participant-observer	↑ peer & mentor relationships ↑ energy ↑ joy ↑ sense of purpose
(Yuhi et al., 2017)	Group Taiko-ensou drumming x 1 session	Pre-adolescents and adolescents with emotional problems in a therapeutic facility (n=28), Japan	None	Pre-post salivary oxytocin (role in social bonding)	↑ oxytocin

Key: US = United States

Table 23. Table of group drumming studies in healthy children and adolescents

Reference	**Intervention**	**Target population**	**Controls**	**Measure**	**Finding**
(Amad et al., 2017)	Group drumming, 3 x 30-mins x 8 weeks	Healthy adolescents, UK (n=15)	Passive (n=16)	fMRI	↑ FC in bilateral STG & various key brain regions
(Davis-Craig, 2009)	Group drumming & dancing	Multigenerational African-American adolescents & adults (n=15 for interview & focus groups; n=70 for participant observation), US	None	Qualitative: 2 focus groups; 9 interviews (3 open-ended; 6 history); participant observation x 4 weeks	6 themes: 1. African tradition 2. family 3. communication 4. support 5. energy

					6. shared enjoyment
Reference	**Intervention**	**Target population**	**Controls**	**Measure**	**Finding**
(Ho et al., 2011)	School-based complex group drumming with counselling activities, 40-45-mins weekly x 12 weeks	Low-income mostly Latino primary school students (n=54), US	Class as usual (n=47)	Child Behaviour Checklist Teacher's Report Form	↓ depression ↓ anxiety ↓ inattention
(Kaplan, 2000)	Group drumming in groups of six, single 35-min session led by an experienced drumming facilitator	Healthy adolescent undergraduate students (n=304 in all 4 arms), US	4-arm RCT with 3 active control groups: aerobic exercise, music listening, and cooperative Origami paper folding task	Profile of Mood States – Bipolar Version Group cohesiveness scale (Zaccaro)	Improved mood ↑ group cohesion
(Mackinlay, 2014)	School-based 'Bam Bam' group drumming, weekly 40-min sessions x 6 months	Primary school students (n=22), Australia	None	Narrative, arts-based & creative analytic process (CAP) ethnographic data collection by teacher/ facilitator	↑ excitement & joy ↑ self-esteem ↑ confidence ↑ social relationships & unity Sense of purpose
(Snow & D'Amico, 2010)	Alternative secondary school-based music therapy drumming circle	"At risk" adolescents (n=9), Canada	None	Verbal analysis of 6 video-recorded sessions by co-facilitator reviewed by educational psychologist. Written session observations by an educational psychologist → thematic analysis.	↑ self-esteem ↑ openness ↓ stress ↓ anger ↑ motivation ↑ confidence

				Open-ended questions in participant questionnaire.	
Reference	**Intervention**	**Target population**	**Controls**	**Measure**	**Finding**
(Wood et al., 2013) (Faulkner et al., 2012)	Holyoake DRUMBEAT (Discovering Relationships Using Music, Beliefs, Emotions, Attitudes, & Thoughts) school-based group hand drumming programme incorporating socio-emotional themed discussions	Adolescents “at risk” of poor social and health outcomes (n=180), Australia	None	1. Rosenberg self-esteem scale 2. School records: behavioural incidents, school attendance. 3. Teacher-rated Behavioural Observation Scale. 4. Mid- & post-intervention feedback questionnaire (perceptions, learning, enjoyment)	↑ self-esteem ↓ behavioural incidents ↑ school attendance ↑ co-operation Non-threatening engagement tool Facilitator as positive Indigenous role model Inclusiveness of circle
(Wyatt, 2000)	Group drumming music therapy, 10 55-min sessions twice weekly x 6 weeks	Healthy high school students (n=20), US	Normal class (n=19)	1. Rosenberg self-esteem scale 2. Index of Peer Relations	Unchanged self-esteem & peer relations

Key: UK = United Kingdom; fMRI = functional magnetic resonance imaging; FC = functional connectivity; STG = superior temporal gyrus; US = United States; RCT = randomised controlled trial

Table 24. Table of group drumming studies in adults with clinical or social issues

Reference	Intervention	Target population	Controls	Measure	Finding
(Blackett & Payne, 2005)	Health Rhythms group drumming x 7 sessions	Substance misuse treatment programme outpatients, UK (n=7)	None	1. Self-report change assessment questionnaires 2. Semi-structured interviews	Inclusion in group ↓ stress
(Fancourt, Perkins, Ascenso, Atkins, et al., 2016)	Group drumming, weekly 70-mins x 6 weeks in groups of 15-20	Mental health care users with mild to moderate mood disorders, UK (n=31)	None	1. Hospital Anxiety and Depression Scale 2. Warwick-Edinburgh Mental Wellbeing Scale 3. Connor-Davidson Social Resilience Scale 4. Visual analogue scales: stress, happiness, relaxation, energy, tiredness 5. Pro-inflammatory cytokines 6. Salivary cortisol 7. Interviews 8. Focus group discussion	Long-term: ↓ Depression ↑ Well-being ↑ Social resilience ↓ Pro-inflammatory cytokines Immediate: ↑ Relaxation / ↓ stress ↑ Happiness ↑ Energy / ↓ tiredness ↓ Salivary cortisol See below for interview & focus group data
(Fancourt, Perkins, Ascenso, Carvalho, et al., 2016) (Ascenso et al., 2018)	Group drumming, 10 weeks in groups of 15-20	Mental health care users, UK (n=30)	Regular community-based non-musical social activities (n=15)	1. Pro-inflammatory cytokines 2. Salivary cortisol 3. Hospital Anxiety and Depression Scale (HADS) 4. Interviews 5. Focus group discussion	↓ Pro-inflammatory cytokines ↓ Salivary cortisol ↓ Anxiety ↓ Depression Themes: 1. Hedonia 2. Agency 3. Accomplishment 4. Engagement through focus & flow

					5. Renewed identity with ↑ self-awareness 6. Connectedness
Reference	**Intervention**	**Target population**	**Controls**	**Measure**	**Finding**
(Hannigan & McBride, 2011)	Group drumming (therapists had 6-18 years of experience; mean 9.4 years)	Intimate partner violence survivors, Canada	None	Case study with therapists running groups	↑ Group cohesion ↑ Cooperation ↑ Engagement ↑ Emotional expression ↑ Relaxation
(Longhofer & Floersch, 1993)	Voluntary group drumming, 50-mins weekly x 6 months	Adult mental health care facility in-patients (n=45), US	None	Reflective qualitative data from group facilitator	Meaningful group role ↑ Self-esteem Supportive peer group
(Pantelyat et al., 2016)	West African group drumming, 45-60-mins twice-weekly x 6 weeks	Adults with Parkinson's disease (n=10), US	Usual care (n=10)	Geriatric Depression Scale Parkinson Disease Questionnaire-39	Unchanged depression ↑ Perceived quality of life (not maintained)
(Perkins, Ascenso, Atkins, Fancourt, & Williamon, 2016)	Group hand drumming, weekly 90-min sessions x 6/10 weeks	Adult mental health care users & carers (n=39), UK	None	Interpretative phenomenological analysis of qualitative data from individual interviews & focus groups	3 themes: 1. Drumming 2. Group 3. Learning
(Silverman & Marcionetti, 2004)	Single session of group drumming	Adult psychiatry in-patients (n=48), US	None	Likert scales 1-10: self-esteem, ability to express self, anger management, mood, symptoms	↑ Self-esteem ↑ Expression ↓ Anger Improved mood

Reference	Intervention	Target population	Controls	Measure	Finding
(Venkit et al., 2013)	Group drumming x 8 sessions	Female commercial sex workers in a rehabilitation programme (n=76), India	None	3 independent observers: session participant observation.	↓ Stress ↑ Confidence ↑ Concentration ↑ Group cohesion
(Winkelman, 2003)	Voluntary group drumming	HIV-positive substance users (n not reported), US	None	Participant-observer at drumming sessions	↑ Joy Emotional release ↑ Connectedness

Key: UK = United Kingdom; US = United States

Table 25. Table of group drumming studies in healthy adults

Reference	Intervention	Target population	Controls	Measure	Finding
(B. Bittman et al., 2003)	HealthRHYTHMS group drumming, weekly 60-min sessions x 6 weeks	Long-term care workers (n=112), US	Randomised controlled cross-over study	1. Maslach Burnout Inventory 2. Profile of Mood States	↓ burnout Improved mood
(B. B. Bittman et al., 2004)	HealthRHYTHMS group drumming, weekly 60-min sessions x 6 weeks	Nursing students (n=75), US	Randomised controlled cross-over study	1. Maslach Burnout Inventory 2. Profile of Mood States	↓ burnout Improved mood
(G. F. Newman et al., 2015)	Workplace group drumming, 30-min 3 times/week	Child and adolescent mental health unit workers, South Africa	None	Questionnaire (6 open-ended questions): thematic analysis	Themes: ↑ connectedness non-verbal emotional expression ↓ anxiety ↑ concentration ↑ empathy ↑ energy skills development improved mood equalising ↑ sense of accomplishment & self-concept
(C. Smith et al., 2014)	Single session of group djembe drumming	Healthy young (n=17) & middle-aged adults (n=17), South Africa	None	Stress Anxiety Index	↓ stress
(Wachi et al., 2007)	Single 60-min session of HealthRHYTHMS group drumming	Male corporate employees (n=20), Japan	Crossover study with 6-month interval (n=20)	1. NK cell activity 2. IL-γ & IL-10 gene expression 3. Profile of Mood States	↑ NK cell activity Altered IL gene expression Improved mood

Key: US = United States; NK = natural killer; IL = interleukin

Chapter 6: Study 4, the Adolescent HIV Executive Function and Drumming (AHEAD) study, a feasibility trial of a group drumming intervention

6.1. Background

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6.1. Background

6.1.1. Need for intervention and rationale for music training

In Chapter 2, I demonstrated that there is a dearth of evidence-based interventions shown to improve EF in HIV-positive adolescents and that there is an urgent need for interventions to improve EF, particularly working memory, in this group. In Chapter 5, through a review of the existing literature, it was evident that musical training may be a potential intervention to improve EF, particularly working memory, in children and adolescents. In this chapter, I describe the rationale and hypothesised theory of change, the development and initial testing of a music intervention comprising short-term group hand drumming which aims to improve EF in HIV-positive adolescents in rural South Africa. The thesis hypotheses tested in this chapter are:

Baseline data:

1.2.1. Markers of more advanced disease or uncontrolled disease are associated with poorer EF in HIV-positive adolescents.

2.1. EF deficits are associated with increased risky substance use in adolescents.

2.2. EF deficits are associated with lower adherence to ART in HIV-positive adolescents.

Baseline and endline post-intervention data (using a controlled design):

3.1. A short-term group drumming programme is a feasible and acceptable intervention in HIV-positive adolescents in rural South Africa.

3.2. Participation in a short-term group drumming intervention improves EF in HIV-positive adolescents in rural South Africa.

3.3. Participation in a short-term group drumming intervention improves depression and anxiety symptoms in HIV-positive adolescents in rural South Africa.

It is appreciated that hypotheses 3.2 and 3.3 cannot be tested fully in this feasibility study because it is not powered to detect a small or medium effect; however, the study does examine whether there is signal for an effect on EF and depression and anxiety symptoms and provides an estimate of the variability of these outcomes.

6.1.2. Rationale for group hand drumming

There are various reasons justifying group hand drumming as the musical intervention of choice for this feasibility study. Some of the reasons relate to efficacy and the multiple components of the complex intervention which mechanistically have potential to improve EF directly (through progressively increasing EF demands) and through improving socio-emotional well-being. The other reasons relate to its likely acceptability and feasibility in a rural African context. The reasons are summarised below.

6.1.2.1. Potential mechanisms

Direct EF training and neuroplasticity

Learning to play a percussive instrument like the drum may train working memory as well as other EFs e.g. inhibitory control. Correlational data supports an association between superior inhibitory control and playing a percussive instrument; however, whether this is causal remains to be tested (Slater, Ashley, Tierney, & Kraus, 2018; Slater et al., 2017). Group drumming that incorporates two or more simultaneous rhythms places demands on the core EFs of working memory, task switching or cognitive flexibility, and inhibitory control through rhythmic memorisation, switching from one memorised rhythm to another on demand, creating one's own rhythms through improvisation, as well as inhibition of the impulse to copy or be distracted from one's current rhythm by the counter-rhythm/s being played simultaneously by other participants. It is possible to build up the executive function demands of the musical content progressively over the course of a few weeks or months by:

1. Increasing working memory load through an increasing number, length and complexity of rhythms requiring memorisation and playing in an individual session.
2. Increasing inhibitory control demands by introducing competing rhythm/s played by other participants within the circle simultaneously, initially splitting the group into two semicircles playing competing rhythms but later separating participants playing the same rhythm.
3. Increasing task switching demands by introducing and then increasing the regularity of switching from one rhythm to another by subgroups when cued by the facilitator.

There is neuroimaging evidence suggesting that drum training is able to induce neuroplasticity in both healthy and clinical populations. A short group drumming programme (three 30-minute sessions a week for eight weeks) in healthy adolescents (n = 15) found increased functional connectivity between the posterior part of bilateral superior temporal gyri and various key brain regions on functional magnetic resonance imaging (fMRI) post-intervention relative to a control group (n = 16) (Amad et al., 2017). Similarly, in a small clinical population of adults with Huntington's disease (n = 10), a neurodegenerative disorder associated with worsening EF, two months of Bongo hand drumming at home (15 minutes per day, five days a week) was associated with increased functional connectivity between bilateral prefrontal cortices on fMRI and improved EF on behavioural testing in those who completed the intervention (Metzler-Baddeley et al., 2014).

EF effects through effects on mental health

Group drumming can reduce depressed mood and anxiety symptoms (see Chapter 5, Section 5.2), which may improve the EF deficits associated with these symptoms in adolescents (Ajilchi & Nejati, 2017; Sommerfeldt et al., 2016). It may also improve self-esteem, self-efficacy and social connectedness, all of which could play a role in improving EF (Campbell et al., 2006; Diamond & Lee, 2011).

Rhythm denotes a pulse or beat with quasi-periodicity or repetition at a relatively steady interval and the organisation of repetitive events into smaller hierarchical chunks which follow rules in relation to their subdivision and relative emphasis of subcomponents (Tecumseh Fitch, 2012). Rhythmical music-making, like group drumming, may facilitate entrainment, both attentional and social. Clayton defines entrainment as the process of interaction [coupling] between independent [self-sustaining] rhythmical [oscillatory] processes which may lead to synchronisation or

stabilisation of the relationship between the processes (M. Clayton, 2012). Human rhythmic entrainment can occur at an intra-individual level (e.g. entrainment of neuronal oscillator networks during metrical perception and selective attention) and an inter-individual level (e.g. co-ordinated playing within musical ensembles) (M. Clayton, 2012; Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008). Intra-individual entrainment is an important mechanism in attentional control and thus EF. It involves the synchronisation of the brain's neuronal excitability oscillations (rhythms) to the rhythm detected in the task or sensory stimulus that is the focus of attention (Calderone, Lakatos, Butler, & Castellanos, 2014; Lakatos et al., 2008). Congruency (matching) of different simultaneous sensory inputs (e.g. auditory and tactile inputs during hand drumming) enhances entrainment and attentional control (van Ee, van Boxtel, Parker, & Alais, 2009). Intra-individual entrainment is thus likely a key mechanism through which playing the drum could enhance EF. Inter-individual entrainment or social synchronisation is a potential mechanism through which synchronised music-making might exert some of its positive socio-emotional effects. In most cultures throughout history, groups of people have gathered for rituals involving singing, dancing and often drumming together where they will entrain to a repetitive isochronous pulse or beat and synchronise their voices and movements to this pulse (Merker, Madison, & Eckerdal, 2009). People tend to make music in groups which requires synchronisation of their actions through communication, interaction and imitation or mirroring. Yet it allows individual expression and leadership. It can therefore be a powerful social learning experience (Overy & Molnar-Szakacs, 2009). This social synchronisation can form an important bonding and relationship-building exercise.

From a cognitive neuroscience perspective, synchronised music-making may be facilitated by the mirror neuron system (Koban, Ramamoorthy, & Konvalinka, 2019) and is associated with increased between-brain oscillatory couplings with cortical phase synchronisation on electroencephalogram i.e. people's brain rhythms start to synchronise with each other (Lindenberger, Li, Gruber, & Müller, 2009). Group drumming may, like other behavioural synchronisation, result in increased activity in the caudate nucleus, part of the reward pathway (Kokal, Engel, Kirschner, & Keysers, 2011) and endogenous opioid (endorphin) release which can have a euphoria-inducing effect (E. E. Cohen, Ejsmond-Frey, Knight, & Dunbar, 2010). Music listening itself is a highly pleasurable activity associated with activation of the brain's dopaminergic reward system (Gebauer, Kringelbach, & Vuust, 2012; Vuust & Kringelbach, 2010). These mechanisms may lead to increased positive affect.

Inter-individual or social synchronisation promotes social cohesion (Hove & Risen, 2009; Marsh, Richardson, & Schmidt, 2009), empathy (Behrends, Müller, & Dziobek, 2012), altruism (Valdesolo & Desteno, 2011) and prosocial behaviour towards those within the synchronising group (Anshel & Kipper, 1988; Kirschner & Tomasello, 2010; Wiltermuth & Heath, 2009) perhaps through increasing social attachment and blurring the self-other distinction (Hove & Risen, 2009).

Social cohesion and group belonging are particularly crucial during adolescence when there is elevated sensitivity to social reward (Foulkes & Blakemore, 2016). During adolescence, peer group membership is protective against various emotional and behavioural problems (B. M. Newman, Lohman, & Newman, 2007). Positive peer relationships are also an important predictor of life satisfaction (Oberle, Schonert-Reichl, & Zumbo, 2011). Social exclusion, which may be more

common in adolescents with a stigmatised disease like HIV, can result in worse EF (Campbell et al., 2006; L. Cluver, Gardner, & Operario, 2009). Drumming groups could counteract this.

6.1.2.2. Evidence for potential efficacy

The literature describing the association between musical training and EF, including efficacy of music interventions in improving EF, is summarised in Chapter 5, Section 5.1. Qualitative and quantitative studies of group drumming interventions have suggested improvements in attention, behaviour and emotional wellbeing in various healthy populations and populations with clinical or social issues. See Chapter 5, Section 5.2 for a summary of the potential effects of participation in group drumming interventions described in the literature.

6.1.2.3. Likely acceptability

Hand drumming can be learnt quickly and easily. It does not require high levels of fine motor coordination, making it accessible and non-intimidating to people without prior musical training or experience (Fancourt, Perkins, Ascenso, Atkins, et al., 2016; Petersen, 2012; Stone, 2005). The structure of the drum circle is non-hierarchical, making it accessible and encouraging feelings of equality and unity amongst all participants and the facilitator regardless of differences (Fancourt, Perkins, Ascenso, Atkins, et al., 2016; Skeef, 1999; Stevens, 2003).

The use of an African drum as an intervention emphasises the value of Indigenous knowledge systems and makes this an Afrocentric intervention of African origin rather than an external import. Drums are an important component of many African traditional cultural rituals. This may increase the likelihood of drumming being

viewed as a culturally valid and acceptable intervention amongst African adolescents.

The social nature of the drum circle should increase the appeal of this intervention for adolescents. The facilitation of the circle by a young adult should also increase acceptability by providing a more accessible role model who can be viewed as a peer mentor rather than as a teacher or elder. An older facilitator might invoke fear and deference due to the social hierarchy based on age within the Shangaan Tsonga culture.

Drumming circles are fun and engaging for adolescents (Stone, 2005). Local songs and rhythms that are popular amongst the particular group of adolescents can be incorporated flexibly to keep the adolescents engaged.

6.1.2.4. Likely feasibility

Hand drumming is quick to learn, making it feasible for a short-term intervention and possible to be implemented by a trained layperson. This is crucial in an overburdened health care system with staff shortages and resource constraints. A group intervention (rather than an individual intervention) led by a trained layperson (rather than a highly qualified health care worker) is likely to cost less, which is important in LMICs for it to be feasible, and potentially sustainable and scalable.

6.1.3. Theory of Change

I used a Theory of Change (ToC) framework to summarise how and why I thought change to EF in HIV-positive adolescents would occur as a result of implementing a group drumming programme in a rural South African context. ToC is a comprehensive approach that is useful for developing and evaluating complex interventions in LMICs so that they are rooted in the local context and therefore

more likely to be effective, sustainable and scalable (De Silva et al., 2014). By identifying the rationale (based on evidence from relevant literature), underlying assumptions, interventions or intervention components, and indicators to measure change (outcome measures) at each point along the proposed causal pathway, this framework is useful for mapping a complex system and the key levers for change.

For this intervention study, the required human resources are: the research unit staff, project manager, assessment fieldworkers, clinic staff, and intervention fieldworkers. The research unit staff and project manager are responsible for project management and fieldworker supervision throughout the participant identification and treatment phases of the study. Clinic staff help identify and refer potential participants during the identification phase and provide ongoing clinical management with referral for specialised care when necessary during the treatment phase. The assessment fieldworkers inform, screen, recruit and assess participants. The long-term outcomes are the study's primary and secondary outcomes with the potential impact being decreased risky behaviour, better adherence to treatment and disease control, improved academic attainment and employability, and enhanced quality of life, assuming that improved EF transfers to these distal outcomes. Interventions include fieldworker training, regular supervision and quality control, referral of cases (e.g. depression) requiring treatment, treatment of such cases, and the drumming sessions themselves. See Figure 44 and the associated Table 26 for the full ToC map and assumptions, interventions, rationale, and indicators in this study.

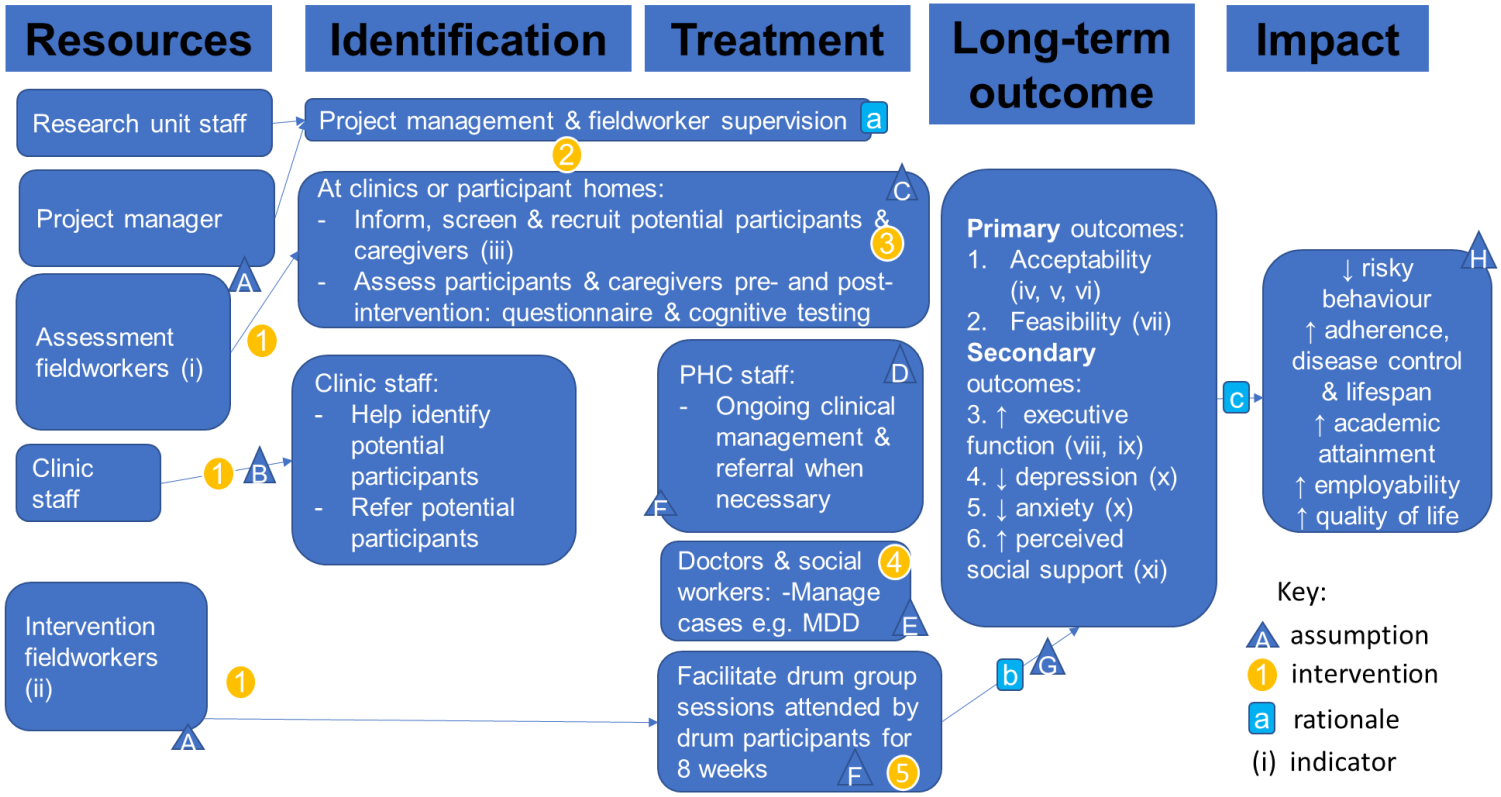


Figure 44. AHEAD Study Theory of Change map summarising the assumptions, rationale, interventions and indicators at each stage of implementation of this complex group drumming intervention aiming to improve executive function. PHC = primary health care. MDD = major depressive disorder.

Table 1. AHEAD Study Theory of Change framework assumptions, interventions, rationale, and indicators as demonstrated in Figure 44 above.

Assumptions	Interventions
A. Potential project manager & fieldworkers with suitable characteristics & potential are interested, apply & take up roles. B. Clinic staff willing to identify & refer potential participants. C. Participants & caregivers interested & willing to enrol & participate. D. Clinic staff willing to manage 'additional work' identified by study screening. E. Doctors & social workers willing to accept additional cases. F. Logistics enable programme implementation & participant interest & schedules allow programme completion. G. 8 weeks of hour-long fieldworker-led drum group sessions is a sufficient dose & potency/quality of musical training to improve EF. H. Improved EF will transfer to behavioural & other outcomes.	1. Fieldworker training → key skills 2. Regular supervision & monitoring of quality of data collection 3. Refer if red flag on assessment (SRQ-20≥13/suicidal) 4. Clinical cases receive appropriate additional care 5. Intervention arm receives 8 drum group sessions

Rationale	Indicators
a. Task shifting can be effective only if ongoing supervision (Kakuma et al 2001) b. Short-term musical training can → ↑ EF (Moreno et al.). Drumming has → ↑ EF & ↑ PFC connectivity in clinical populations with EF deficits (Metzler-Baddeley et al.) & induced neuroplasticity in healthy adolescents (Amad 2017) Group drumming has → ↑ self-reported attention (Wood et al 2013, Faulkner et al 2012, Ho et al 2011), ↓ depression (Fancourt et al 2016), ↓ anxiety (Fancourt et al 2016), ↑ quality of life (Pantelyat et al 2016) in various clinical & at-risk populations c. EF associated with adherence in HIV-affected populations (e.g. PHACS AMP cohort – Nichols et al, Sirois et al.)	i. 3 intervention fieldworkers trained & 1 chosen (top score: trainer assessment) ii. 3 assessment fieldworkers trained (additional training if <70% on test) iii. CONSORT flow diagram: numbers informed, screened & enrolled iv. Attendance rate v. Acceptability questionnaire vi. Number of adverse events, if any vii. Rate of logistical problems viii. Change in performance on 7 EF tasks ix. Change in SRQ-20 score x. Change in MSPSS score

6.1.4. Objectives

Primary objective:

- To assess, in a rural South African context, the intervention's:
    - feasibility of implementation
    - acceptability to:
        - potential adolescent users
        - potential intervention facilitators i.e. lay fieldworkers, clinic staff, school teachers

Secondary objectives:

- To assess, in HIV-positive adolescents, the association between EF and:
    - markers of disease progression i.e. CD4 count
    - markers of disease control i.e. viral load
    - risky substance use
    - adherence to treatment
- To assess the intervention's effect on:
    - EF
        - Core cool: verbal and visuospatial working memory, inhibition, set-shifting
        - Hot: inhibition, decision-making in the context of risk
        - Higher: planning or sequencing
    - socio-emotional well-being and behaviour including:
        - adolescent:
            - depressed mood and total depressive and anxiety symptoms

- perceived social support
- frequency of alcohol use
- illicit drug use
- self-reported forgetting to take treatment

- caregiver: depressive and anxiety symptoms

6.2. Methods

6.2.1. Scoping visits: community entry and intervention development

I conducted two scoping visits to South Africa and a few Skype meetings with South Africa-based collaborators.

6.2.1.1. Intervention design meetings

The first visit included a multidisciplinary team meeting with my South Africa-based supervisor who has extensive experience at the MRC/Wits Agincourt Research Unit (hereafter referred to as 'Agincourt') and my two South Africa-based music collaborators, Dr Sonkanise Nkosi, a djembe performer and creative arts education lecturer at the University of Johannesburg with a doctorate in Modern African Classical Drumming, and Dr Andeline dos Santos, a music therapist and lecturer at the University of Pretoria with a doctorate in the use of group drumming to develop empathy in adolescents with aggression.

I introduced principles from Diamond's review on EF interventions that would be adapted to be the foundation for designing this intervention (Diamond & Ling, 2016): choosing and training a drumming facilitator with the right personal characteristics who believes in the programme and its potential efficacy and can serve as a mentor and role-model; achieving local community support or buy-in;

aiming to make sessions enjoyable and engaging; direct EF training by challenging EF progressively (e.g. through progressively increasing the number and complexity of rhythms and the frequency of switching between subgroups and rhythms); indirectly improving EF through positive socio-emotional effects (e.g. increasing joy, social support, reducing depression and anxiety) which can be achieved by the facilitator establishing a good rapport with the group, treating the participants with a positive, empowering, accepting and encouraging attitude, and building group cohesion.

We discussed the choice of hand drum. Dr Nkosi suggested that using the djembe, the prototypical single membrane African hand drum might be better than using the local traditional drum because there would be no specific cultural or gendered associations with this drum. The djembe originates with the Maninka and Susu tribes in West Africa. It is now used globally for drumming circles. It is a popular choice of hand drum because of its wide dynamic and melodic range, enabling greater emotional expressivity. It is used for Modern African Classical Drumming in Southern Africa.

In order to develop EF, we decided that there should be increasing complexity and number of rhythms and counter-rhythms to challenge EFs through starting with one rhythm per song (four main songs in total) to memorise; then introducing a second rhythm per song initially played separately and then simultaneously with the first rhythm in subgroups; then the subgroups switching rhythms; then introducing a third and fourth rhythm per song which would initially be played separately and then simultaneously with the group split into subgroups; then the subgroups switching rhythms again; and then progressively switching between the first and second sets of rhythms with subgroups switching. The curriculum would

include a combination of taught and improvised rhythms. Taught rhythms would be notated for replication by facilitators, but all participant teaching and learning would be aural through imitation. Dr dos Santos suggested that improvisation encourages creativity and allows participants to “find their voice”. She suggested incorporating local songs, dances, and games to engage the adolescents. She suggested having a drum-making activity using local materials near the end of the programme to help achieve sustainability and so that adolescents realised they did not need a djembe drum specifically to continue drumming. Both music collaborators felt that there should be a concert or showcase after programme completion so that participants would have a goal to work towards as well as experience a sense of accomplishment. The showcase would need to be carefully prepared and be limited to a small audience to minimise the risk of confidentiality breaches.

We discussed the key role of the group facilitator in creating an inclusive and welcoming environment that would be enjoyable and engaging for adolescents but also feel safe with appropriate supervision to deter bullying or teasing. We decided on the necessary intervention fieldworker characteristics: respectful, empathetic, engaging, affirming, empowering, good listening skills, confident, flexible, and adaptable. We felt that prior drumming or other musical experience would be preferable. We decided that 40 hours of training in how to facilitate a drumming group with a final assessment would be sufficient for the intervention fieldworker and decided on the structure of the facilitator training programme and the flexible 8-week drumming curriculum for the adolescents.

6.2.1.2. Exploratory scoping visit to the Agincourt HDSS study site

Objectives

1. To determine the prevalence, participation, and significance of musical activities for adolescents in the region.
2. To elucidate the perceived acceptability of using a local traditional drum versus introducing the *djembe* drum as an intervention amongst adolescent boys and girls in the region.
3. To decide whether to subdivide the drumming arm participants into groups based on age, sex, or geographic location.
4. To determine the appropriate sampling frame for participants.

Focus group discussions while developing Drum-Assisted Recovery Therapy for Native Americans (DARTNA) in North America revealed that participants believed drumming was “sacred medicine” with multiple benefits but that culturally, only men drummed while women sang along but did not drum themselves. The Indigenous elders felt that allowing women to drum could be considered in the future (Dickerson, Robichaud, Teruya, Nagaran, & Hser, 2012). This highlights the importance of cultural sensitivity and appropriate exploration of potential attitudinal barriers (e.g. gender norms) that might decrease acceptability of a potential drumming intervention amongst a particular cultural group. Having a mixed group of boys and girls and allowing girls to drum might help to challenge the inequitable gender norms which can predispose to risky sexual behaviour through disempowering girls and making it difficult for them to negotiate condom use in sexual relationships (Marston & King, 2006; Wechsberg et al., 2008; A. L. Wilkinson, Fleming, Halpern, Herring, & Harris, 2018).

Methods

I conducted an exploratory study using:

- participant-observation of performers and community members taking part in a Sunday *muchongolo* traditional dancing event, a school choir rehearsal and a local church service;
- semi-structured interviews with seven school principals or creative arts teachers, two church leaders, the head of the district Community Arts Centre and the provincial Community Arts Centre Forum, a local drum-maker who sells traditional drums and shields for the *muchongolo*, and two local youth non-governmental organisation managers;
- a focus group discussion with the MRC/Wits Agincourt Research Unit's community advisory board (CAB).

A purposive sampling technique was used to recruit participants from schools, churches, non-governmental organisations (NGOs) and the community in the following seven villages: Kildare A; Kildare B; Cunningmoore A; Cunningmoore B; Xanthia; Agincourt A; Agincourt B. Seven of nine secondary schools approached agreed to participate and their principal, deputy principal and/or creative arts teachers were interviewed.

Results and discussion

Objective 1: Adolescent musical activities in the region

Singing is ubiquitous in educational, religious and community settings and traditional dancing is popular and common. The *muchongolo* seems to be the most popular dance form and mainly involves males dancing with a small section where

women dance and sing. Other local traditional dance forms include: *xibavhana* (where women drum on basins), *makhwaya* and *xibelana*. Modern dance forms include: gumboot dancing, and dancing from the musical 'Sarafina'. When it is available, a single bass drum is often used to accompany singing or dancing. Musical activities taking place in secondary schools include: singing hymns in assemblies; traditional dancing often accompanied by drumming during 'Creative Arts' classes in the first two years of secondary school; worship songs and clapping at Student Christian Organisation meetings; school choirs (in some schools) accompanied by a melodica; drum majorette groups (in the past or on special occasions annually); concerts for special events or cultural days. There are many (often 10-15) churches in each village and these all incorporate singing, sometimes with a worship band or mass choir. Some of the traditional Zionist Christian Churches incorporate traditional cow-skin drums and a slow circular dance. More modern churches tend to use European instruments e.g. keyboard with some also having a drum kit and guitar. The youth NGOs are not currently running musical activities. There is a community youth choir in one of the villages and a marimba band in another. One of the villages has a community hall where regional arts festivals are hosted. These showcase choral verse and traditional dances from different tribes including: Tsonga *muchongolo*, Mapulana *dinaka*; Pedi *makgagase* and *dipepetlwana*; *xipenda*; Mozambican *makhwaya*; and *mthimba*. Most traditional dances are accompanied by a single drummer playing a large bass drum (*xigubu)* or a few smaller drums (*xintumbhana* or *xingomana*). The exception is the *ntwasa* traditional healer graduation ceremony when many people of different ages and genders play leadwood drums in a circle simultaneously.

Muchongolo takes place weekly in different villages. It is very popular and a great source of pride in the Shangaan Tsonga culture, bringing people joy and building a sense of community. Some expressed fear that traditional instruments would die out due to lack of interest from the youth which would be problematic because “Indigenous knowledge systems should be preserved”.

Boys and girls may play drums, but boys more commonly show interest and learn to play the drums. Although males play the drums for most of the traditional dance styles, for the *xibavhana* dance, the women drum.

Perceived benefits of participation in musical and dancing activities for adolescents included: co-ordination; collaboration; a sense of connectedness, belonging or community; and sharpening the mind.

Objective 2: Drum choice

The local traditional drums are used in different contexts and not confined to a certain player. The introduction of a new drum, the *djembe*, to the region would be acceptable and exciting; although easy availability within the village/s after the study would have been preferable.

Objective 3: How to subdivide drumming participants into groups

The CAB felt that distance from the drumming venues would be a barrier for drum group attendance so forming groups based on participants’ locations would be the best method of subdivision.

Objective 4: Appropriate sampling frame

The CAB was concerned that having HIV-positive participants only would be problematic because it might expose their HIV status, by virtue of the study being known as an 'HIV study'. One member suggested that the *djembe* drum might then become associated with HIV and become stigmatised. They stressed that HIV is still highly stigmatised in these villages. They preferred the suggestion of a sample of adolescents with a mixed set of chronic diseases (e.g. diabetes mellitus, asthma, HIV) attending the clinic. That way, participants would not automatically be identified as having HIV.

Conclusion

Although musical activities are common and valued as a vital source of cultural pride and community-building, hand drumming is not common. The study intervention would thus be adding a new musical activity. Due to the perceived acceptability and lack of existing gendered or cultural associations, I decided to use the djembe drum for the intervention. The study team also decided to follow the CAB's recommendations to subdivide the drumming participants into groups based on their locations and to broaden the sampling frame to include any adolescents with chronic diseases attending the clinics, provided they knew their HIV status or had recently been tested and were willing to share their HIV status with the study team.

6.2.2. Study design

The study was a feasibility individually randomised controlled trial with a non-blind, parallel group, two-arm design with 1:1 allocation ratio and a passive control arm (receiving no intervention) nested within the Agincourt HDSS (registration number:

PACTR201804003332337). The Agincourt Public Engagement Office assisted with community entry and informed key community members via the CAB when the study commenced. Simple random allocation occurred with the field supervisor blindly drawing lots from a sealed envelope following consent and enrolment. Full blinding of the assessors would have been preferable; however, due to resource constraints, it was not possible to have separate fieldworkers for recruitment (and informing participants of their allocation) and for the assessments. Passive controls (no intervention or alternative programme) were included to assess the willingness of participants to be randomised and potentially receive no drumming intervention, to allow testing for intervention effects on EF and mental health, and to control for learning effects on the EF measures in which pre-post improvement may be due to task familiarity. A health facility-based sampling frame was used to target this clinical population. The assessment fieldworkers recruited and assessed participants at four primary health care facilities (known locally as 'clinics') in the southern HDSS study site villages. The study focused on early and middle adolescence (12-19-year-old age range) because earlier intervention is preferable for preventing adverse outcomes. HIV-positive adolescents were eligible regardless of route of transmission (i.e. perinatally or behaviourally acquired) because route of transmission is not routinely recorded in clinical records at South African public health facilities. All study documentation and questions were available in the local language Tsonga. The baseline (pre-intervention) and endline (post-intervention) assessments of the adolescent and the caregiver were conducted by trained fieldworkers. The intervention arm participants were assessed by an independent assessment fieldworker post-intervention to minimise

the risk of bias. I supervised the fieldworkers, randomised each participant after enrolment, and performed the clinical record reviews.

6.2.3. Study participant eligibility criteria

Inclusion criteria:

- 12-19-year-old male or female adolescent with a chronic disease (e.g. HIV, diabetes mellitus, asthma) attending the clinic.
- Participant is willing and able to give informed consent (18-19-years-old) or assent (12-17-years-old).
- Primary caregiver is willing to give informed consent for participation in the study on behalf of 12-17-year-old participants.
- Participant's HIV status is known (i.e. positive or tested negative within the last three months).
- Participant or caregiver is willing to share adolescent's HIV status with the study team.
- The participant must currently live in or be attending a clinic in the Agincourt HDSS villages and plan to remain in the area for the next 6 months.

Exclusion criteria:

- profound hearing loss or deafness
- current severe infective illness
- another uncontrolled medical condition
- cerebral palsy
- known intellectual disability due to another cause
- epilepsy with a history of seizures in the last seven years

- recent central nervous system infections
- current or previous brain malignancies
- a previous stroke
- history of a significant head injury
- currently more than four months' pregnant

6.2.4. Recruitment

At trial initiation, the clinic data clerks assisted us with compiling lists of all the 12-19-year-old adolescents on chronic treatment and their contact details. Some participants were referred directly by the nursing staff at the facility when they came for clinic appointments. Other potential participants and their caregivers were initially approached and informed about the study telephonically using the study phones and invited to an appointment for screening if they were interested and not ineligible based on this initial telephone call.

The assessment fieldworkers mostly met with potential participants and caregivers in a private office at the clinics to maintain confidentiality; however, they met participants at their homes if participants requested this due to difficulty coming to the clinic. Participants were reimbursed for their transport fares for all study visits. Potential participants and caregivers who agreed to be screened were given a verbal explanation of the eligibility screening process and written screening participant information sheets with different versions for caregivers of minors, and minor participants of different ages (see examples in Appendix 9: AHEAD Study screening information sheet for minor participants aged 12-14 years old and Appendix 10: AHEAD Study screening information sheet for caregivers of minor participants (younger than 18 years old)). If they agreed to be screened,

participants signed the screening consent and assent forms which included consent to access medical records and were then screened against the eligibility criteria using a REDCap (Research Electronic Data Capture) tablet-based questionnaire (see Appendix 11: AHEAD Study participant eligibility screening questionnaire) and medical record screening if there was uncertainty regarding aspects of the medical history. Unaccompanied minors who were interested in being screened were asked to return to the clinic with their caregivers for screening. 18-19-year-old participants who were unaccompanied by a caregiver were asked to return with a caregiver if they were comfortable with a caregiver also completing assessments. Refusal to enrol with a caregiver did not preclude participation of 18-19-year-old participants. Eligible adolescents were invited to receive full information and enrol in the study.

6.2.5. Informed consent

Potential participants and caregivers were told that participation was voluntary and non-participation would not affect their treatment. Assessment fieldworkers gave them a detailed verbal explanation of the study and full participant information sheets (as appropriate for minor vs non-minor, and caregiver of minor vs non-minor; see examples in Appendix 12: AHEAD Study full participant information sheet for participants aged 15 to 17 years old and Appendix 13: AHEAD Study full information sheet for caregivers of participants younger than 18 years old). They were informed of potential risks and benefits, the randomisation process and what exactly participation would involve depending on group allocation. They were given the opportunity to ask questions and time to consider participation. Once participants decided to enrol, they signed consent and/or assent forms based on age and caregivers signed separate consent forms.

6.2.6. Details of the intervention

The intervention was comprised of eight hour-long, weekly sessions over eight weeks. Intervention sessions took place in a clinic adolescent room or one of two church halls with the venues spread across three villages to accommodate participants living in different villages. The intervention arm was subdivided into four subgroups based on proximity to the venues with each group meeting on a different weekday afternoon. Participants were given telephonic reminders by the intervention fieldworker the day before their sessions to confirm arrangements each week. The participants stayed in the same subgroup throughout the programme. Each participant was given a healthy snack (2-3 items of fruit) and beverage (fruit juice and/or water) at each drumming session. The drumming programme was facilitated by a trained intervention fieldworker. I attended sessions as a participant-observer. The fieldworker kept an attendance register at each session. Participants who arrived early for sessions could socialise and practise drumming, singing and dancing.

Each participant chose a djembe drum at the start of each session. The participants, facilitator and I sat on chairs with our drums in a circle facing inwards. The first session involved introductions, setting norms together as a group, becoming acquainted with posture and drum positioning (drum resting on the floor tilted slightly away from the player and gripped between the legs), and learning (through listening and imitation) the technique for playing the three basic tones with their hands. The tones were taught with associated vocalisations to assist learning: bass tone (‘du’), high tone (‘ke’) and slap tone (‘pa’). The participants then learnt a basic rhythmic accompaniment, melody and lyrics for a greeting song (‘Avuxeni’ meaning ‘Hello’) for greeting each other at the start of each session. They then

played an ‘Introductions’ rhythmical game where each person had to introduce herself/himself by stating her/his name, village and favourite song or singer while the group kept playing a background rhythm. We then went around the circle with each participant contributing a norm that she/he wanted the group to uphold throughout the programme. If the following norms had not already been mentioned by participants, the facilitator added them:

- Respect one another.
- Listen to one another.
- No mobile phone use during sessions.
- What happens in the group stays in the group (i.e. confidentiality).
- There is no wrong answer.
- Care for one another.
- We are not competing. We are a team. Work together for the group to be better.

The first session ended by singing and learning a rhythm to accompany the farewell song (‘Wahamba nathi’ meaning ‘You walked with us’) and the facilitator recommending that the participants practised what they had learnt at home.

The basic structure of sessions from the second week onwards was: open the session with the greeting song; play a game or icebreaker sometimes followed by an improvisatory ‘call and response’ game; learn and practise the core rhythms (1-3 per song) for each of their three different songs (based on their favourite songs suggested in Week 1); and close the session with the farewell song. The facilitator started to introduce core rhythms of increasing complexity to accompany each song. Initially these rhythms were played in series switching from Rhythm 1 to

Rhythm 2 and Rhythm 3 as a group. In later sessions, the facilitator gradually introduced playing of different rhythms in parallel combining two and eventually three or four rhythms simultaneously in each song with subgroups switching rhythms when cued by the facilitator. See Appendix 14: AHEAD Study drumming programme weekly schedule, Appendix 15: AHEAD Study notated rhythms of songs and games and Appendix 16: AHEAD Study song lyrics.

6.2.7. Outcomes measures

Primary outcome measures:

- The attendance rates, attrition rates, reasons for non-attendance, and number of logistical problems (as indicators of intervention feasibility).
- The attendance rates and acceptability ratings from the early drop-out and endline acceptability questionnaires (as indicators of intervention acceptability to participants).

Secondary outcome measures:

The difference between the intervention and control groups on the endline mean scores (controlling for baseline scores, highest level of education and socio-economic status) for:

- Seven cognitive task scores (see Appendix 3: OCS-EF task descriptions for details):
    - Five Oxford Cognitive Screen - Executive Function (OCS-EF) tasks, as described in Chapter 3 but with minor modifications to three tasks (see Appendix 18: AHEAD OCS-EF cognitive task modifications) (Rowe et al., 2019):

        - Trails switching proportion accuracy cost, a measure of planning/sequencing and set-shifting
        - Iowa Gambling Task net score, an affective EF measure of decision-making in the context of risk
        - Rule-finding accuracy, a measure of visuospatial pattern recognition/problem-solving and set-shifting
        - Emotional go/no-go d-prime, a measure of affective inhibition
        - Digit span backwards, a measure of verbal working memory
    - Two Rapid Assessment of Cognitive and Emotional Regulation (RACER) tasks, tablet-based tasks which have been designed for and used in various LMIC or humanitarian settings implemented by trained laypeople (Ford, Kim, Brown, Aber, & Sheridan, 2019) (see Appendix 19: AHEAD RACER cognitive task descriptions for full task descriptions):
        - Dot location recall accuracy difference, a measure of visuospatial working memory
        - Simon task reaction time difference, a measure of non-affective inhibition

After each cognitive task, the fieldworker selected a test condition from a pre-defined list (as described in Chapter 3, Section 3.2.2), on-screen (OCS-EF) or in a logbook (RACER). The participant's task data were only included if the test condition was marked 'no issue'. If there were any issues which made the test invalid (e.g. interruptions or the examiner skipping a task by mistake), the participant's task data were excluded. The following socio-emotional and

behavioural questionnaires or questions were included to assess secondary outcomes:

- The World Health Organisation's Self-Reporting Questionnaire 20 (SRQ-20) was included as a measure of depression and anxiety symptoms. It is a twenty-item questionnaire with binary response format. It may be self-administered or administered by an interviewer. It was designed by comparing four other screening tools, including the General Health Questionnaire (GHQ) (Beusenberg & Orley, 1994; Goldberg et al., 1997; Goldberg & Hillier, 1979). It was developed for use as a screening instrument for symptoms of common mental disorders (including depressive, anxiety and somatoform disorders) in primary care settings by workers with limited mental health training, particularly in LMICs where it has commonly been used (Ali, Ryan, & De Silva, 2016; Beusenberg & Orley, 1994). It has been validated for use in South Africa (Cherian, Peltzer, & Cherian, 1998; van der Westhuizen, Wyatt, Williams, Stein, & Sorsdahl, 2016). Deriving subscales is not recommended because the factor structure has varied significantly by setting.
- Multidimensional Scale of Perceived Social Support (MSPSS), a 12-item questionnaire used to assess perceptions of support received from three sources: family, friends, and a significant other (Zimet, Dahlem, Zimet, & Farley, 1988). There are four items per subscale. It has been validated for use amongst adolescents in South Africa (Bruwer, Emsley, Kidd, Lochner, & Seedat, 2008).

- The World Health Organisation's Alcohol Use Disorders Identification Test (AUDIT) questionnaire (Babor, de la Fuente, Saunders, & Grant, 1992)), a ten-item screening tool used to assess alcohol consumption, drinking behaviours, and alcohol-related problems. It has been validated for use amongst adolescents in South Africa (Young & Mayson, 2010). The first item was used to assess frequency of alcohol use.
- Illicit or recreational drug use: a single question with a binary response format was used at baseline (ever used) and endline (used in last three months).
- Forgetting to take treatment: adolescents were first asked a binary question about forgetting to take their treatment ever (baseline) or in the last three months (endline). This was followed by a Likert-style question assessing the frequency of forgetting treatment.

6.2.8. Baseline assessments

All questions and instructions were translated into Tsonga from English by an Agincourt permanent staff member or one of the assessment fieldworkers who was fluent in both English and Tsonga with another assessment fieldworker checking the translation. The two fieldworkers discussed any sentences where they disagreed on the translation until they agreed on the final translation. Questionnaires were all administered using REDCap, hosted at the University of Witwatersrand.

Household socio-economic status (SES) data was obtained by linking participants to the Agincourt HDSS census data and obtaining their household's latest asset index data (see Appendix 20: AHEAD Study MRC/Wits Agincourt Health and Socio-demographic Surveillance System asset index form). The participant

baseline pre-intervention assessment consisted of tablet-based cognitive tasks (completed before the questionnaire if they were performed on the same day) and fieldworker-assisted questionnaire (see Appendix 21: AHEAD Study adolescent baseline questionnaire). The questionnaire included medical, socio-demographic, mental health, alcohol and substance use screening, and behavioural questions. A paper-based pre-cognitive testing checklist (see Appendix 17: AHEAD Study participant pre-cognitive testing checklist) was completed by the fieldworker to check that it was suitable to perform cognitive testing on a participant on that particular day. The cognitive tasks included five OCS-EF tasks: trails; Iowa Gambling Task; rule-finding; emotional go/no-go; digit recall. These tasks are described in detail in Chapter 3 and Appendix 3: OCS-EF task descriptions. There were a few minor adaptations to OCS-EF for this study (see Appendix 18: AHEAD OCS-EF cognitive task modifications). In addition, two RACER tasks were completed on an Android tablet with finger input. I decided to replace two of the original OCS-EF tasks, selection and figure drawing with the single RACER dot location recall task because I felt it was a purer visuospatial working memory task. I also chose to add the cool, non-affective inhibition task from RACER because the OCS-EF only measures hot or affective inhibition. These two sets of tasks complement each other well and form a comprehensive set of EF tasks assessing both hot and cool EF, visuospatial and verbal working memory, as well as all three core EFs, yet they could still all be administered in approximately 30 minutes. Both cognitive tools have been used in LMICs before with the OCS-EF having been used in the Agincourt HDSS previously (see Chapters 3 and 4) (Ford et al., 2019; Rowe et al., 2019).

Primary caregivers completed a tablet-based questionnaire (see Appendix 22: AHEAD Study caregiver baseline questionnaire) containing socio-demographic, personal mental health (SRQ-20), and emotional and behavioural questions about their child using REDCap with the assistance of the fieldworker.

The standardised questionnaires listed in section 6.2.7 were chosen because they have previously been used successfully in South Africa in adolescents or young adults and are open access tools.

I used the REDCap clinical data extraction form (see Appendix 23: AHEAD Study clinical data extraction form) to obtain the following HIV-related clinical information from the HIV-positive participants' health records at the local clinic:

- Diagnosis: date of last HIV test; HIV-testing method/s; test result; age
- WHO clinical stage: at diagnosis
- History of previous HIV encephalopathy
- Treatment-related: ever treated with ART; date of ART initiation; ART duration (exclude months of interruption); current ART regimen (relevant because efavirenz can have neuropsychological side effects); previous ART regimen/s; any reported neuropsychiatric side effects; previous virological failure episodes; episodes of non-adherence reported or suspected
- Laboratory investigations:
    - CD4+ T-cell count and CD4%: nadir (lowest recorded); most recent
    - HIV RNA viral load: peak (highest recorded); most recent

6.2.9. Subsequent visits and endline assessments

If not already done, the baseline assessment was completed at the second visit. For participants allocated to the intervention arm, a paper-based pre-intervention

expectations questionnaire (see Appendix 24: AHEAD Study pre-intervention expectations questionnaire) was completed upon arrival at the first drumming session. The next eight visits were the intervention sessions for those in the intervention arm. If any participants or caregivers (in the case of minors) decided to withdraw from the drumming groups early, an early study exit tablet-based questionnaire (see Appendix 25: AHEAD Study early study exit questionnaire) was completed by participants with an independent assessment fieldworker (to minimise bias and increase the likelihood of receiving honest answers) to assess their experience of study participation and their reason/s for leaving the study early, if they were willing to share this.

When the drumming programme was complete, all participants (regardless of trial arm) completed an endline questionnaire covering recent medical history, emotional and behavioural history, perceived social support, and substance use behaviour (see Appendix 26: AHEAD Study adolescent endline questionnaire). The same standardised questionnaires used at baseline were repeated at endline: AUDIT, SRQ-20, and MSPSS. Caregivers completed the SRQ-20 (own recent mental health) (see Appendix 27: AHEAD Study caregiver endline questionnaire). Intervention arm participants completed a retrospective acceptability questionnaire (see Appendix 28: AHEAD Study drumming participant endline acceptability questionnaire) in which they rated their overall perception of and satisfaction with the programme. Questions included: whether (and if yes, how often) they practised drumming at home; whether they thought participation affected their cognitive task performance, concentration at school or work, and overall mood or feelings; whether they would recommend the programme; whether they would continue participating if they were given the opportunity to do so; aspects of the programme

that they liked; aspects of the programme that they did not like; any problems experienced due to participation; reasons for missed sessions; suggestions for improvement of the programme; anything else they wanted to share about their experience of participation.

All participants completed the same tablet-based cognitive tasks again under similar testing conditions to the baseline assessment. After their final visit, participants and caregivers were given a simple summary of the adolescent's individual cognitive task results and certificates to thank them for their participation.

6.2.10. Withdrawal of study participants

Participants who did not attend drumming sessions were called to remind them about the programme, check that they had not experienced any adverse events due to participation, and to find out if they wanted to remain in the drumming programme or not. Participants who attended less than four (half the) drumming sessions completed early study exit questionnaires at endline. Every participant had the right to withdraw from the study at any time. Participants could also be withdrawn if it was deemed necessary, for example due to:

- Ineligibility (either arising during the study or having been overlooked at screening)
- Significant protocol deviation (e.g. a control arm participant inadvertently being exposed to the intervention)
- Withdrawal of consent
- Loss to follow up
- Intercurrent acute severe illness or diagnosis with one of the medical conditions constituting exclusion criteria

6.2.11. Fieldworker recruitment and training

Three fieldworkers (fluent in English and Tsonga) were recruited through Agincourt (see Appendix 29: AHEAD Study fieldworker job advertisement content and Appendix 30: AHEAD Study fieldworker interview questions). They underwent five days of assessment training by me (see Appendix 31: AHEAD Study assessment fieldworker training) and five days of intervention training by Dr Nkosi (see Appendix 32: AHEAD Study group drumming facilitation training for the objectives, schedule and photographs). One fieldworker was selected as the intervention fieldworker based on her post-training musical assessment by Dr Nkosi (including a mock drum circle facilitation) and her continuous assessment during drum training by me (see Appendix 33: AHEAD Study intervention fieldworker assessment schedules). The intervention fieldworker also functioned as an assessment fieldworker at baseline, but not endline post-intervention assessment. She was loaned a djembe drum for the duration of the study so she could practise at home. She received an additional half-day of training by me in the practicalities of running each drum session: the attendance register, snacks, transport fare reimbursement, checking participants' hands had no sores prior to sessions.

In order to promote sustainability if the programme proved to be acceptable and beneficial, we invited and trained six local schoolteachers and the regional hospital occupational therapy technician in group drumming facilitation. The teachers' schools were each given a drumming textbook (containing musical scores), a djembe drum and drum bag after study completion. The hospital's Rehabilitation Department was also given a djembe drum and bag. After the drumming showcases at the end of the intervention, a social worker from the local HIV-related NGO 'Right To Care' who showed interest in the drumming groups and attended

the showcases, expressed the desire to use the drums in adolescent support groups they were starting at local clinics. She and two other members of their psychosocial team were therefore also trained by me for a day in the basics of drumming group facilitation.

6.2.12. Data analysis

Deriving variables for analysis

The OCS-EF cognitive task scores were derived in the same way as described in Chapter 3 and Appendix 3: OCS-EF task descriptions. The RACER cognitive task scores were derived as described below:

- Dot location recall accuracy difference: the difference between the mean accuracy on high-load, long-delay trials and low-load short-delay (100 trials, a measure of visuospatial working memory: working memory score = [mean distance from target on low-load short-delay trials] – [mean distance from target on high-load long-delay trials]
- Simon task reaction time difference (difference between mean reaction time in milliseconds on congruent and incongruent trials), a measure of cool or non-affective inhibition: inhibitory control score = [mean congruent trial reaction time] – [mean incongruent trial reaction time]

The asset index items were recoded (so that higher values corresponded with a higher SES), standardised (so that each item took on a value of 0-1), grouped into five subcategories with standardisation within each subcategory, and then summed and standardised to create an asset index (range 0-1 with higher values representing a higher SES) (Kabudula et al., 2016).

Statistical analysis

Statistical analysis was performed in Stata Version 14 by an independent analyst, Julia Ruiz Pozuelo, who was not involved with study design and data collection. I re-ran the analysis for thesis purposes and to check for errors in the code. The balance across the two arms was assessed by comparing the baseline adolescent and caregiver characteristics of the two trial arms using student's t test, Wilcoxon rank-sum, Kruskal-Wallis or X^2 tests, as appropriate depending on the nature and distribution of each variable. Due to the exploratory nature of this feasibility study, we also looked at the baseline pairwise correlations between sociodemographic, cognitive and socio-emotional variables across the full sample.

The intervention acceptability was analysed using simple descriptive summary statistics, including the proportion of participants who fell in each response category for each question in the acceptability questionnaires, reasons given for non-attendance, and reflexive thematic analysis of the qualitative open-ended questions in the acceptability and endline adolescent questionnaires (Braun, Clarke, Hayfield, & Terry, 2018). After familiarising myself with the content of the responses, I used an inductive, semantic approach to thematic analysis in which coding and theme development were directed by the explicit content of the data. I then reviewed the initial themes that were generated and named them. Simple descriptive statistics of the attendance rates, drop-out rates, and the number of logistical problems encountered per week during implementation were used to assess the feasibility of the programme.

Quantitative outcomes were analysed by comparing the mean differences between intervention and control arm in EF and socio-emotional scale scores at endline controlling for baseline scores, SES quantiles (low, middle, high) based on asset index, and education level (primary school completion) using a multivariable linear

regression. The following assumptions were checked and met before deciding to use the ordinary least squares family of linear models:

1. A linear relationship was present between the dependent variable and the independent variables.

This assumption was checked using scatterplots to check whether relationships were linear. They were all linear with no curvilinear relationships observed.

2. There was multivariate normality of the residuals of the regression i.e. the errors between the observed and the predicted values had a normal distribution.

This assumption was checked by looking at histograms of the residuals of each regression.

3. No multicollinearity was present between the independent variables.

This assumption was checked using a pairwise Pearson's correlation matrix between the independent variables. None of the independent variables was highly correlated (Pearson's correlation coefficients were all < 0.80).

4. There was homoscedasticity or similar variances of the error terms across the values of the independent variables.

This assumption was checked using residual-vs-fitted values plots which showed no clear distributional pattern.

The treatment outcomes were analysed using a per-protocol analysis with the minimum dose being set at six sessions (i.e. 75% attendance). Participants in the intervention arm with an attendance rate of less than 75% (i.e. those who missed more than two drumming sessions) were excluded from the analysis. Outcome

data were analysed after study completion. Secondary outcomes were analysed in a similar way.

Due to this being a feasibility study, it was not powered to do a formal efficacy analysis. We aimed to recruit at least 50 HIV-positive participants, 25 per trial arm. To account for potential attrition and the broader sampling frame, we aimed to oversample by approximately 30% (i.e. recruit 65-70 participants).

All reported probability values are two-tailed p values.

6.2.13. Data management and quality assurance

The study's data management plan and quality assurance procedures are described in Appendix 34: AHEAD Study data management and quality assurance procedures.

6.2.14. Ethical considerations

The University of Oxford Tropical Research Ethics Committee (OxTREC), the University of Witwatersrand Human Research Ethics Committee (Medical) and the Mpumalanga Provincial Health Research committee approved the final study protocol. For further details regarding the ethical considerations in this study, see Appendix 35: AHEAD Study ethical considerations.

6.3. Results

6.3.1. Participant and caregiver characteristics

Potential participants and their caregivers were either approached telephonically; or referred directly by the clinic nursing staff. 121 families were initially given information about the study prior to screening. Some were found to be ineligible at this stage and others declined to be screened or participate. Reasons for declining included: final secondary school exams; caregiver had not yet disclosed the

adolescent's HIV status to them; travel distance or safety concerns; no perceived benefit of participation if randomised to the control arm; and lack of interest. Other reasons for not screening included: cancelled appointments due to service delivery protests; missed appointments. Of the 100 (83% of those informed) considered eligible for screening, 77 (77%) consented to and underwent formal eligibility screening. Of those screened, 72 (94%) were eligible for inclusion (see Figure 46). Of those eligible for inclusion, 69 (96%) enrolled with 68 caregivers and underwent randomisation to the intervention (n = 34) and control (n = 35) arms. There was one early loss to follow-up (1%) with no further study attrition; the study retention rate was 99%.

Participants came from 17 different villages within the Bushbuckridge Municipality. All participants were black Africans and spoke Tsonga as their home language. Randomisation resulted in a successfully balanced sample in terms of participant sociodemographic characteristics and musical experience (see Table 27) and caregiver sociodemographic and clinical characteristics (see Table 28). All participants were HIV-positive with 61 (89.7%) having perinatally acquired HIV. Sixty-seven (98.5%) were currently on ART and one control arm participant restarted ART upon study enrolment after six months of defaulting from treatment. 34 (50%) had at least one episode of non-adherence recorded in their clinical folders. 17 (25%) had a recorded history of past virological failure. The most common first-line regimen that this cohort had been exposed to was abacavir, lamivudine, and efavirenz. The second most common first-line regimen was tenofovir, emtricitabine and efavirenz as a fixed dose combination in those who had initiated ART more recently. The two arms were also balanced in terms of perinatal and psychiatric history (see Table 29) and disease-related characteristics

(see Table 30). The sample had a low median CD4 cell count (429 copies/millilitre) with low rates of virological suppression (only 19.1% had an undetectable viral load; 61.8% had a viral load < 1000 copies/millilitre).

Invalid test conditions for the cognitive testing (see Chapter 3, Section 3.2.2) were balanced across the trial arms at baseline and endline and are presented in Table 31 and Table 35. The summary statistics of the cognitive characteristics at baseline for both arms are presented in Table 32. The two arms were balanced except for the intervention arm having lower scores on affective inhibition (go/no-go d-prime) than the control arm at baseline (see Table 32). The summary statistics of the socioemotional scales at baseline for both arms are presented in Table 33 and the frequency of behavioural outcomes in Table 34. The two arms were balanced across both sets of outcomes. The baseline internal consistency coefficients were acceptable (Cronbach's alpha > 0.70) (Cronbach, 1951; Tavakol & Dennick, 2011) for the adolescent self-reported MSPSS ($\alpha = 0.71$) and SRQ-20 ($\alpha = 0.72$), and the caregiver-rated SRQ-20 ($\alpha = 0.89$). A pairwise correlation matrix of cognitive, socio-emotional and behavioural outcomes at baseline in participants from both trial arms with valid test conditions on all cognitive tasks is presented in Table 36. Cohen's operational definitions were used to assess the strength of the correlations (small: $r = 0.10$; moderate: $r = 0.30$; strong: $r = 0.50$) (J. Cohen, 1988). The highly significant ($p < 0.001$) correlations between adolescent variables included: a moderate positive correlation between performance on the digit span forwards and the digit span backwards ($r = 0.47$, $p = 0.0003$), and a moderate positive correlation between depressed mood and frequency of alcohol use ($r = 0.49$, $p = 0.0002$). There was no correlation between frequency of alcohol use and EF (Table 36) which does not support the hypothesised relationship between EF

and risky behaviour (thesis hypothesis 2.1). Other significant ($p < 0.01$) correlations between adolescent variables included: a moderate negative correlation between verbal short-term memory and self-reported depression and anxiety symptoms ($r = -0.36$, $p = 0.0071$), a moderate negative correlation between verbal working memory and self-reported forgetting to take treatment ($r = -0.37$, $p = 0.0065$) and (an unexpected) moderate negative correlation between perceived social support and rule-finding performance ($r = -0.38$, $p = 0.0052$). The association between poorer verbal working memory and more self-reported forgetting of treatment partially supports the hypothesised association between EF deficits and lower adherence to treatment (thesis hypothesis 2.2). The lack of association between self-reported forgetting of treatment and other EF variables suggests that the association may be limited to verbal working memory (Table 36). Markers of current advanced or uncontrolled disease were not associated with EF performance which does not support the hypothesised association (thesis hypothesis 1.2.1).

Table 27. AHEAD Study participant baseline sociodemographic characteristics

Variable	Total (n=68)	Intervention arm (n=34)	Control arm (n=34)	χ^2	t	p
Age in years, mean (SD)	15.4 (2.4)	15.5 (2.3)	15.3 (2.4)	-	-0.26	0.79
Female, n (%)	46 (67.7)	24 (70.6)	22 (64.7)	0.27	-	0.60
Married, n (%)	1 (1.5)	1 (2.9)	0 (0.0)	1.01	-	0.31
Country of birth:				1.01	-	0.31
South Africa, n (%)	67 (98.5)	33 (97.1)	34 (100.0)			
Mozambique, n (%)	1 (1.5)	1 (2.9)	0 (0.0)			
Socio-economic status:				0.13	-	0.94
Low	23 (34.9)	12 (36.4)	11 (33.3)			
Middle	32 (48.5)	16 (48.5)	16 (48.5)			
High	11 (16.7)	5 (15.2)	6 (18.2)			
Education:						
Attending school, n (%)	64 (94.1)	32 (94.1)	32 (94.1)	0.00	-	1.00
Repeated grade, n (%)	44 (64.7)	22 (64.7)	22 (64.7)	0.00	-	1.00
Completed primary, n (%)	39 (57.4)	20 (58.8)	19 (55.9)	0.06	-	0.81
Completed secondary, n (%)	4 (5.9)	2 (5.9)	2 (5.9)	0.00	-	1.00
Musical experience:						
Played instrument, n (%)	11 (16.2)	5 (14.7)	6 (17.6)	0.11	-	0.74
Plays instrument, n (%)	8 (11.8)	4 (11.8)	4 (11.8)	0.00	-	1.00
Choral experience, n (%)	32 (47.1)	15 (44.1)	17 (50.0)	0.24	-	0.63
Dancing experience, n (%)	22 (32.4)	10 (29.4)	12 (35.3)	0.27	-	0.60

Key: n = number; t = t-statistic from two-samples t test; * p<0.10; ** p<0.01; *** p<0.001

Table 28. AHEAD Study caregiver baseline sociodemographic and clinical characteristics

Variable	Total (n=67)	Intervention arm (n=34)	Control arm (n=33)	χ2	z	p
Age in years, m (SD)	48.1 (13.7)	47.9 (11.0)	48.3 (16.0)	-	-0.21	0.89
Female, n (%)	62 (91.2)	33 (97.1)	29 (85.3)	2.92	-	0.09*
Relationship:				10.19	-	0.34
Mother, n (%)	27 (40.3)	15 (44.1)	12 (36.4)			
Grandmother, n (%)	16 (23.9)	8 (23.5)	8 (24.2)			
Other, n (%)	24 (35.8)	11 (32.4)	13 (39.4)			
Country of birth:				0.50	-	0.48
South Africa, n (%)	59 (88.1)	29 (85.3)	30 (90.9)			
Mozambique, n (%)	8 (11.9)	5 (14.7)	3 (9.1)			
Married, n (%)	26 (38.8)	12 (35.3)	14 (42.4)	0.36	-	0.55
Currently employed, n (%)	6 (9.0)	3 (8.8)	3 (9.0)	0.00	-	0.97
Education:						
Completed primary, n (%)	33 (49.3)	15 (44.1)	18 (54.6)	0.73	-	0.39
Completed secondary, n (%)	13 (19.4)	5 (14.7)	8 (24.2)	0.97	-	0.32
Psychiatric:						
Psychiatric diagnosis, n (%)	5 (7.5)	3 (8.8)	2 (6.1)	0.19	-	0.67
SRQ-20 score, m (SD)	4.94 (4.83)	5.47 (5.14)	4.39 (4.51)	-	-0.83	0.41

Key: m = mean; SD = standard deviation; z = z-statistic from the Wilcoxon rank-sum test; * p<0.10; ** p<0.01; *** p<0.001

Table 29. AHEAD Study participant perinatal and psychiatric history

Variable	Total (n=68)	Intervention arm (n=34)	Control arm (n=34)	χ2	z	p
Perinatal:						
Antenatal drug or alcohol exposure, n (%)				2.14	-	0.34
Yes	2 (3.0)	1 (2.9)	1 (3.0)			
Unknown	8 (11.9)	6 (17.7)	2 (6.1)			
No	57 (85.1)	27 (79.4)	30 (90.9)			
Preterm birth, n (%)				2.25	-	0.32
Yes	5 (7.5)	3 (8.8)	2 (6.1)			
Unknown	2 (3.0)	2 (5.9)	0 (0.0)			
No	60 (89.6)	29 (85.3)	31 (93.9)			
Perinatal hospital admission, n (%)				3.48	-	0.18
Yes	6 (9.0)	4 (11.8)	2 (6.1)			
Unknown	6 (9.0)	4 (11.8)	2 (6.1)			
No	55 (82.1)	29 (85.3)	26 (78.8)			
Psychiatric:						
Psychiatric diagnosis	2 (2.9)	1 (2.9)	1 (2.9)	0.00	-	1.00
On psychotropics	2 (2.9)	1 (2.9)	1 (2.9)	0.00	-	1.00

Key: n = number; z = z-statistic from the Wilcoxon rank-sum test; * p<0.10; ** p<0.01; *** p<0.001

Table 30. AHEAD Study participant disease-related characteristics

Variable	Total (n=68)	Intervention arm (n=34)	Control arm (n=34)	χ2	z	p
HIV-positive, n (%)	68 (100.0)	34 (100.0)	34 (100.0)			
Route of HIV transmission, n (%)				0.16	-	0.69
Perinatal	61 (89.7)	31 (91.1)	30 (88.2)			
Behavioural	7 (10.3)	3 (8.8)	4 (11.8)			
Full HIV disclosure to adolescent at baseline, n (%)	52 (76.5)	25 (73.5)	27 (79.4)	0.33	-	0.57
Age at last HIV test, n (%)				7.91	-	0.16
1-3 years old	3 (4.4)	2 (5.9)	1 (2.9)			
3-5 years old	9 (13.2)	6 (17.7)	3 (8.8)			
5-10 years old	18 (26.5)	8 (23.5)	10 (29.4)			
10-15 years old	20 (29.4)	12 (35.3)	8 (23.5)			
>15 years old	9 (13.2)	5 (14.7)	4 (11.8)			
Unknown	9 (13.2)	1 (2.9)	8 (23.5)			
WHO disease stage at diagnosis, n (%)				5.48	-	0.24
1	34 (50.0)	14 (41.2)	20 (58.8)			
2	15 (22.1)	10 (29.4)	5 (14.7)			
3	11 (16.2)	6 (17.7)	5 (14.7)			
4	2 (2.9)	2 (5.9)	0 (0.0)			
Unknown	6 (8.8)	2 (5.9)	4 (11.8)			
ART regimen, n (%)				1.27	-	0.53
NNRTI-based						
Efavirenz	51 (75.0)	26 (76.5)	25 (73.5)			
Nevirapine	1 (1.5)	1 (2.9)	0 (0.0)			
PI-based (Lopinavir/ritonavir)	16 (23.5)	7 (20.6)	9 (26.5)			
Regimen number, n (%)						
First	32 (47.1)	18 (52.9)	14 (41.1)			
Second	24 (35.3)	13 (38.2)	11 (32.4)			
Third or more	12 (17.6)	3 (8.8)	9 (26.5)	3.64	-	0.06*
History of non-adherence, n (%)				0.24	-	0.63
Yes	34 (50.0)	18 (52.9)	16 (47.1)			
No	34 (50.0)	16 (47.1)	18 (52.9)			
Past virological failure, n (%)				1.04	-	0.60
Yes	17 (25.0)	7 (20.6)	10 (29.4)			

No	44 (64.7)	24 (70.1)	20 (58.8)			
Unknown	7 (10.3)	3 (8.8)	4 (11.8)			
Variable	**Total (n=68)**	**Intervention arm (n=34)**	**Control arm (n=34)**	**χ2**	**z**	**p**
History of neuropsychiatric side effects, n (%)						
Clinical folder review	6 (8.8)	2 (5.9)	4 (11.8)	0.73	-	0.39
SRQ-20 frequent headaches	31 (45.6)	15 (44.1)	16 (47.1)	0.06	-	0.81
Biological data						
Nadir CD4 count (cells/mm3), md (IQR)	276 (153 – 398)	294 (168 – 428)	251 (144 – 366)	-	- 1.02	0.31
Current CD4 count (cells/mm3), md (IQR)	429 (271 – 630)	429 (290 – 740)	426 (238 – 577)	-	- 0.47	0.64
Peak viral load (copies/ml), md (IQR)	898 (119 – 49418)	1795 (95 – 25450)	444 (145 – 99000)	-	0.26	0.79
Current viral load (copies/ml), md (IQR)	199 (49 – 2430)	147 (49 – 2300)	274 (49 – 12700)	-	0.40	0.69
Viral load < 1000 copies/ml, n (%)	42 (61.8)	21 (61.8)	21 (61.8)	2.17	-	0.34
Viral load undetectable < 40 copies/ml, n (%)	13 (19.1)	6 (17.7)	7 (20.6)	2.10	-	0.35
ART duration (years), md (IQR)	4.0 (2.1 – 7.5)	3.9 (1.2 – 7.1)	4.3 (2.4 – 7.5)	-	0.95	0.34

Key: md = median; IQR = interquartile range; n = number; z = z-statistic from the Wilcoxon rank-sum test; * p<0.10; ** p<0.01; *** p<0.001

Table 31. AHEAD Study proportion with invalid test conditions at baseline in each trial arm with reasons

Cognitive task, n (%)	**Total (n=68)**	**Intervention arm (n=34)**	**Control arm (n=34)**	**χ2**	**p**
Digit recall	1 (1.5)	0 (0.0)	1 (2.9) interruptions	2.06	0.357
Trails	3 (4.4)	1 (2.9) interruptions	2 (5.9) 1 x technical problem 1 x examiner error	3.02	0.389
Rule-finding	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Iowa Gambling	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Go/no-go	5 (7.4)	4 (11.8) interruptions	1 (2.9) interruptions	1.94	0.163
Dot recall	5 (7.4)	4 (11.8) 2 x interruptions 2 x other	1 (2.9) interruptions	2.47	0.290
Simon	5 (7.3)	2 (5.9) 1 x examiner error 1 x other	3 (8.8) 2 x interruptions 1 x other	3.02	0.389

Key: n = number; * p<0.10; ** p<0.01; *** p<0.001

Table 32. AHEAD Study baseline summary statistics of cognitive tasks of participants in both trial arms with adequate conditions of test

Cognitive task (m, SD)	Total (n=68)	Intervention arm (n=34)	Control arm (n=34)	Difference	t	z	p
Digit span forwards	5.00 (1.09)	4.97 (1.19)	5.03 (0.98)	-0.06	0.22	-	0.824
Digit span backwards	3.16 (1.19)	3.18 (1.11)	3.15 (1.28)	0.03	-0.09	-	0.932
Trails baseline accuracy	0.75 (0.24)	0.74 (0.23)	0.77 (0.24)	-0.03	-	0.80	0.421
Trails switch accuracy	0.36 (0.22)	0.40 (0.23)	0.33 (0.22)	0.07	-1.22	-	0.226
Trails switch accuracy cost	0.50 (0.28)	0.53 (0.27)	0.46 (0.29)	0.07	-1.05	-	0.299
Rule-finding task	0.37 (0.17)	0.40 (0.19)	0.35 (0.14)	0.05	-1.32	-	0.191
Iowa Gambling Task net	0.07 (0.28)	0.09 (0.33)	0.05 (0.23)	0.04	-0.48		0.632
Go/no-go d-prime	2.67 (1.10)	2.41 (1.06)	2.90 (1.10)	-0.49	1.77	-	0.082 *
Dot recall	-134.86 (50.96)	-135.28 (52.13)	-134.47 (50.67)	0.72	0.06	-	0.951
Simon	-14.30 (58.74)	-11.26 (51.27)	-17.45 (66.28)	-3.04	-0.41	-	0.681

Key: m = mean; SD = standard deviation; t = t-statistic from two-samples t test; z = z-statistic from the Wilcoxon rank-sum test; * p<0.10; ** p<0.01; *** p<0.001

Table 33. AHEAD Study baseline summary statistics of socioemotional scale scores of participants in both trial arms

Variable, m (SD) unless indicated	Total	Intervention arm	Control arm	Difference	t	z	χ2	P
Adolescent-rated	n=68	n=34	n=34					
SRQ depr	0.10	0.15	0.06	0.09	-	-	1.43	0.231
SRQ-20	3.90 (3.04)	4.32 (3.13)	3.47 (2.93)	0.85	-	-1.20		0.232
MSPSS	3.48 (0.52)	3.43 (0.63)	3.54 (0.39)	0.11	0.89	-		0.375
Caregiver-rated	N=67	n=34	n=33					
SRQ-20	4.94 (4.83)	5.47 (5.14)	4.39 (4.51)	1.08	-	-0.83	-	0.405

Key: m = mean; SD = standard deviation; t = t-statistic from two-samples t test; z = z-statistic from the Wilcoxon rank-sum test; SRQ = Self-Reporting Questionnaire 20; depr = depressed mood item; MSPSS = Multidimensional Scale of Perceived Social Support; * p<0.10; ** p<0.01; *** p<0.001

Table 34. AHEAD Study baseline frequency of behavioural outcomes in both trial arms

Behavioural outcome, n (%)	**Total (n=68)**	**Intervention arm (n=34)**	**Control arm (n=34)**	**χ2**	**z**	**P**
Frequency of alcohol use				1.02	-	0.602
Never	61 (89.7)	30 (88.2)	31 (91.2)			
Monthly or less	6 (8.8)	3 (8.8)	3 (8.8)			
2-4 times a month	1 (1.5)	1 (2.9)	0 (0.0)			
Ever used illicit drugs	0 (0.0)	0 (0.0)	0 (0.0)	-		-
Forgets treatment	20 (29.4)	10 (29.4)	10 (29.4)	0.00	-	1.000
Frequency of forgetting treatment				3.67	-	0.598
Once a year	1 (1.5)	1 (2.9)	0 (0.0)			
Once a month	8 (11.8)	4 (11.8)	4 (11.8)			
A few times a month	4 (5.9)	3 (8.8)	1 (2.9)			
Once a week	6 (8.8)	2 (5.9)	4 (11.8)			
A few days per week	1 (1.5)	0 (0.0)	1 (2.9)			
Never	48 (70.6)	24 (70.6)	24 (70.6)			
Past non-adherence (clinic record)	34 (50.0)	16 (47.1)	18 (52.9)	0.24	-	0.628
Recorded episodes of non-adherence, m (SD)	2.4 (4.1)	3.2 (4.7)	1.6 (3.3)	-	-1.02	0.308

Key: m = mean; SD = standard deviation; n = number; z = z-statistic from the Wilcoxon rank-sum test; * p<0.10; ** p<0.01; *** p<0.001

Table 35. AHEAD Study proportion with invalid test conditions at endline in each trial arm with reasons

Cognitive task, n (%)	**Total (n=68)**	**Intervention arm (n=34)**	**Control arm (n=34)**	**χ^2**	**p**
Digit recall	7 (10.3)	5 (14.7) 1 x technical problem 4 x interruptions	2 (5.9) interruptions	1.81	0.404
Trails	1 (1.5)	1 (2.9) interruption	0 (0.00)	1.01	0.314
Rule-finding	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Iowa Gambling	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Go/no-go	1 (1.5)	0 (0.0)	1 (2.9) interruption	1.02	0.314
Dot recall	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Simon	1 (1.5)	1 (2.9) interruption	0 (0.0)	0.99	0.321

Key: * p<0.10; ** p<0.01; *** p<0.001

Table 36. AHEAD Study baseline cognitive, socioemotional and behavioural outcome pairwise correlation matrix

	DF	DB	TB	TS	Rule	IGT	d'	Dot	Simon	SRQA	Depr	SRQC	PSS	Forgot	EtOH	CD4	VL
DF	1.00																
DB	0.47***	1.00															
TB	0.29*	0.15	1.00														
TS	0.01	0.03	-0.19	1.00													
Rule	0.22	0.15	0.26	-0.19	1.00												
IGT	-0.12	-0.10	-0.08	-0.10	-0.01	1.00											
d'	-0.04	0.19	0.29*	0.05	0.22	-0.23	1.00										
Dot	0.20	0.08	0.18	0.12	0.01	0.01	0.15	1.00									
Simon	-0.09	0.21	-0.09	0.13	0.20	0.07	0.31*	0.26	1.00								
SRQA	-0.36**	-0.22	-0.16	-0.17	-0.07	0.17	-0.07	0.04	0.25	1.00							
Depr	-0.20	-0.19	-0.09	0.04	0.12	0.17	0.11	0.06	-0.04	0.26	1.00						
SRQC	0.23	0.22	0.11	-0.02	0.20	-0.14	-0.03	0.10	-0.06	0.09	0.27*	1.00					
PSS	0.25	0.32*	-0.05	0.12	-0.38**	-0.26	-0.07	-0.04	-0.13	-0.19	-0.34*	-0.09	1.00				
Forgot	-0.02	-0.37**	0.12	-0.01	-0.08	0.22	-0.14	0.03	0.01	0.16	-0.01	0.09	-0.12	1.00			
EtOH	-0.03	-0.00	-0.04	0.09	-0.00	-0.07	0.22	0.25	0.19	0.17	0.49***	0.13	-0.08	-0.04	1.00		
CD4	-0.25	-0.11	-0.11	-0.11	0.14	0.01	0.14	0.03	-0.08	0.24	0.25	0.17	-0.18	-0.14	0.09	1.00	
VL	0.04	-0.08	-0.19	0.19	-0.26	-0.12	-0.15	0.09	0.16	-0.04	-0.06	0.00	0.05	0.17	-0.05	-0.13	1.00

Key: All values are Pearson's correlation coefficients. * p<0.05; ** p<0.01; *** p<0.001; DF = digit span forwards; DB = digit span backwards; TB = trails baseline; TS = trails switch proportion accuracy cost; Rule = rule-finding; IGT = Iowa Gambling Task net score; d' = d-prime; Dot = dot recall; SRQA = Self-Reporting Questionnaire 20 (SRQ-20) adolescent total score; Depr = adolescent SRQ-20 depressed mood; SRQC = SRQ-20 caregiver total score; PSS = multidimensional scale of perceived social support total score; Forgot = self-reported history of forgetting to take treatment; EtOH = frequency of alcohol use; CD4 = CD4 cell count; VL = viral load

6.3.2. Attendance and retention

68 participants and 67 caregivers underwent both the baseline and endline assessments (i.e. 100% of those with baseline assessments were re-assessed at endline). For the intervention arm drumming sessions:

- 22 (65%) participants attended 6-8 drumming sessions (≥75% attendance therefore data analysed in per-protocol analysis)
- 12 (35%) attended <75% of sessions
    - four (12%) attended 4-5 sessions,
    - three (9%) attended 1-2 sessions,
    - five (15%) attended none.

Adolescents who attended < 75% of the intervention ("non-compliers") were significantly more likely than those who attended ≥75% of the intervention ("compliers") to have behaviourally acquired HIV, less likely to be school-enrolled and reported marginally more frequent alcohol use (see Table 37). They were also generally older and more likely to have completed primary school (see Table 37). There were no differences in EF between compliers and non-compliers (see Table 37). The reasons for non-attendance were often logistical (e.g. distance, transport issues or other commitments) or due to acute illness or fatigue (see Figure 46).

There was an initial drop-off rate of 21% of participants who attended no sessions or only the first session. This was largely due to logistical issues impeding attendance e.g. relocating to the city (3%), schedule clashes with academic (e.g. final school examination study camp) or extra-curricular (e.g. football practice) commitments (9%), caregiver concern regarding safety of travel to the venue due to high crime rates (3%). One participant attended two sessions only; the caregiver

raised concerns about the safety of the participant taking a minibus taxi to the sessions, and the risk of inadvertent HIV status disclosure to the community through being seen at the clinic weekly.

There were a few participants who regularly came late to sessions which will have decreased the effective intervention dose that they received. Amongst the participants who attended at least half the sessions, the following reasons for missed sessions were cited by adolescents: illness or physical ailments; providing childcare; fatigue; travel; attending a clinic appointment; forgetting about the session; hunger; attending a school event; unable to find the venue.

Overall participant retention was good. See Figure 45 for a plot of attendance rate at each of the eight formal intervention sessions and a ninth informal ‘showcase’ session.

Table 37. AHEAD Study comparison of baseline characteristics of intervention arm compliers (attended 75% or more) versus non-compliers (attended < 75%)

Variable, m (SD) unless indicated	Total (n=34)	Compliers (n=22)	Non-compliers (n=12)	t	z	χ2	p
Age	15.46	14.99 (2.22)	16.31(2.43)	1.56	-	-	0.134
Female (%)	70.59	72.73	66.67	-	-	0.14	0.711
Behavioural HIV (%)	8.82	0.00	25.00	-	-	6.03	0.014 *
Primary (%)	58.82	50.00	75.00	-	-	2.00	0.157
School-enrolled (%)	94.12	100.00	83.33	-	-	3.90	0.048 *
SES (asset index)	0.73 (0.11)	0.71 (0.11)	0.75 (0.09)	1.05	-	-	0.303
SRQ-20	4.32 (3.13)	4.05 (2.57)	4.83 (4.04)	-	0.20	-	0.841
Depressed (%)	14.71	13.64	16.67	-	-	0.06	0.812
MSPSS	3.43 (0.63)	3.41 (0.73)	3.46 (0.41)	0.22	-	-	0.830
Frequency of alcohol use	0.15 (0.44)	0.05 (0.21)	0.33 (0.65)	-	1.77	-	0.076 *
Digits forwards	4.97 (1.19)	4.91 (1.38)	5.08 (0.79)	0.47	-	-	0.643
Digits backwards	3.18 (1.11)	3.18 (1.33)	3.17 (0.58)	- 0.05	-	-	0.964
Trails baseline	0.74 (0.23)	0.77 (0.23)	0.69 (0.23)	-	- 0.99	-	0.325
Trails switch	0.53 (0.27)	0.49 (0.28)	0.60 (0.26)	1.11	-	-	0.279
Rule-finding	0.40 (0.19)	0.40 (0.23)	0.40 (0.11)	- 0.03	-	-	0.975
Iowa Gambling	0.09 (0.33)	0.12 (0.37)	0.03 (0.25)	-	- 1.30	-	0.195
D-prime	2.41 (1.06)	2.17 (1.02)	2.77 (1.05)	1.55	-	-	0.134
Dot recall	135.28 (52.13)	-142.93 (52.20)	-123.81 (52.10)	0.98	-	-	0.335
Simon	-11.26 (51.27)	-8.90 (55.99)	-15.77 (42.96)	- 0.39	-	-	0.703

Key: m = mean; SD = standard deviation; t = t-statistic from two-samples t test; z = z-statistic from the Wilcoxon rank-sum test; behavioural HIV = behaviourally acquired HIV; SES = socio-economic index (asset index); SRQ = Self-Reporting Questionnaire; Depressed = adolescent SRQ-20 depressed mood item; MSPSS = Multidimensional Scale of Perceived Social Support; * p<0.10; ** p<0.01; *** p<0.001

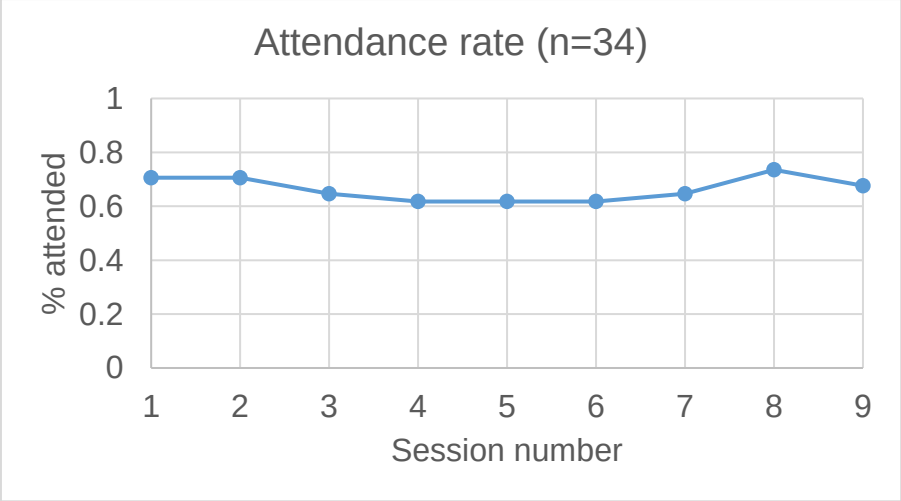


Figure 45. AHEAD Study plot of drumming session attendance rate over time including both the formal intervention sessions in Weeks 1-8 and the optional showcase session in Week 9

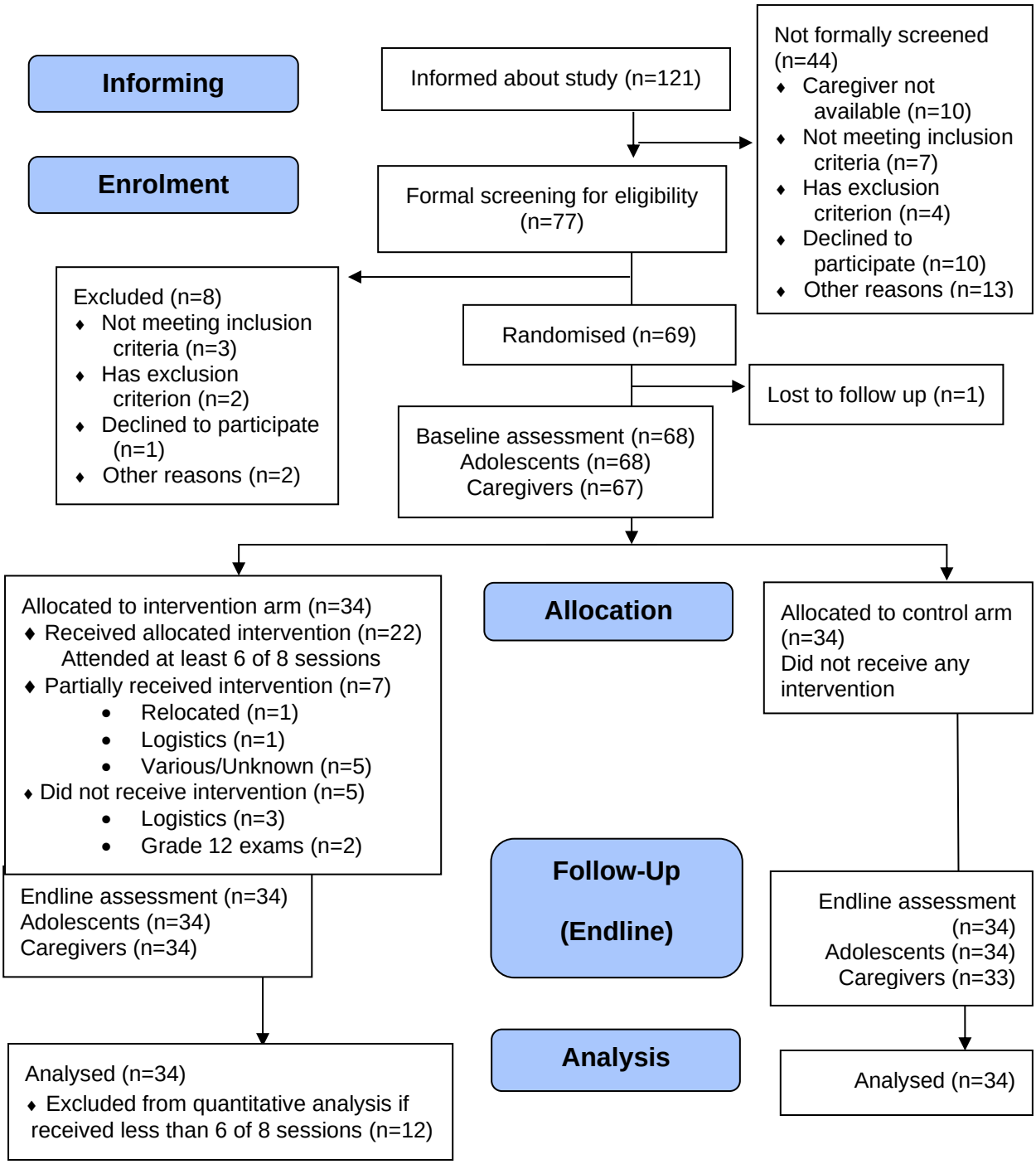


Figure 46. AHEAD Study CONSORT flow diagram

6.3.3. Acceptability and qualitative outcomes

6.3.3.1. Pre-intervention expectations: intervention arm

Participants who attended at least one drumming session (n = 29) completed a paper-based pre-intervention expectations questionnaire before their first session. The intervention fieldworker explained the questions to them, but they completed the questionnaire alone and handed completed questionnaires to me. On a scale from 0 (not at all excited) to 10 (very excited), most were very excited about the upcoming drumming programme (median 9.9; IQR 6.0-10.0). Most participants felt positive (45%) or very positive (48%) towards the upcoming programme with the minority feeling neutral (7%). No one expressed feeling negative towards the upcoming programme.

6.3.3.2. Post-intervention acceptability questionnaire: intervention arm

Overall attitudes towards the programme after completion (n = 34) were: 35% very positive; 59% positive; 6% neutral; none were negative. Satisfaction ratings on a visual analogue scale from 1 (”not at all enjoyable”) to 10 (”highly enjoyable”) were also high (median 9.2; IQR 8.2-9.3). 88% of those who attended at least four drumming sessions reported practising drumming: two-thirds practised once a week; one-third practised more than once a week. Perceived programme effects (in participants who attended at least half the sessions) on:

- Ability to do cognitive tasks: 88% felt it helped a lot; 12% felt it helped a little.
- Ability to concentrate at school or work: 77% felt it helped a lot; 15% felt it helped a little; 4% felt it made no difference; 4% felt it made it worse.
- Overall mood or feelings: 73% felt it helped a lot; 23% felt it helped a little; 4% felt it made no difference.

Recommendation of the programme: 82% would recommend the programme to other people their age; 6% might recommend it; 12% would not recommend it.

Continuation or repetition of the programme: All except one participant would continue or take part again if they had the chance.

Adverse effects of participation: 91% had none; 9% were unsure but could not list any negative experiences attributed to participation. Two participants had concerns expressed during the programme: one regarding time away from homework and the potential effects on academic performance; the other regarding her caregiver getting angry due to time away from housework or chores. One participant cited a negative element of the programme in the endline questionnaire: feeling judged by the facilitator and other participants for joking too much in the sessions.

Participant suggestions for improvement in future drumming programmes:

Most participants had no suggestions for improvement. Two participants suggested incorporating more dancing or traditional dancing while another suggested adding drama. One participant suggested including other youth who are experiencing problems. Another participant suggested extending the duration of the programme to make it longer than two months and finding other good leaders to facilitate the drumming groups. A participant who was unable to attend any sessions suggested adding a drumming venue closer to home, so she could travel alone to the venue.

6.3.3.3. Endline adolescent questionnaire: intervention and control arm participants

Impact of study participation on their problems: In the intervention arm, significantly more participants felts that their problems were better from study participation than those in the control arm (82% vs 53%; p = 0.036). No drumming participants felt that their problems were worse, while 21% of the control arm felt their problems were worse. More than 85% of participants in each arm felt that taking part in the study was helpful. If participants felt it was helpful, they were asked to explain why or how they found it helpful. Their responses were incorporated into the qualitative themes described below.

Qualitative outcomes

A word frequency cloud generated from the open-ended question feedback revealed that 'enjoy' was the most common word mentioned (see Figure 47).



Figure 47. AHEAD Study word frequency cloud generated in NVivo 12 using drumming participant feedback in the endline acceptability questionnaire

The following recurring themes emerged from the inductive, semantic approach to reflexive thematic analysis of the drumming participants' qualitative data:

1. Enjoyment of the drumming group

Enjoyment of the musical elements of drumming and singing was a common theme, with some mentioning feelings of excitement and anticipation about sessions:

"It's like waiting for Christmas. The excitement and looking forward to it. It's nice to have something to look forward to. It feels good to be here." – Female #1.

2. Finding acceptance and belonging in the circle

This social theme was very common. Many mentioned finding the circle non-judgemental and a space where they felt accepted. It was a space for solidarity and friendship. Some also mentioned wanting to expand the group and include others. Some of the participants' comments are below:

"I'm happy to be in the group. I feel loved and enjoy being around the people." – Female #2.

"I enjoy being here with all the girls. I believe it is improving my self-esteem. It makes me happy to be with the group. I was struggling to make friends before but now I feel like I have friends. It makes me happy. I enjoy the sessions." – Female #3.

"I am very happy to be part of the group. It makes me feel good about myself being around people that don't judge me." – Female #4.

"It is nice to finally find a group of friends that accept me as I am." – Female #5.

3. Decreased internalised stigma

Feeling less stigmatised (abnormal, isolated and/or judged by others) with associated improvements in self-worth or self-esteem was another common theme.

“Give thanks to the study for giving me courage to keep going and not to commit suicide which I was considering before. I did not value myself before the study because of my status but now I value myself more. I'm not alone with this chronic disease. There are many other people living with the disease.” – Female #6.

4. Improving emotional well-being and resilience

The final theme that emerged was improved emotional well-being and resilience. Many described feelings of happiness and improved quality of life, with others describing less anxiety in general or less anxiety about their HIV status. One participant (Female #1) explained: “It helps us forget about other things going on in our lives.” Others felt more energised since taking part. A few also mentioned decreased suicidality.

Some control group participants also reported perceived benefits from study participation with the following themes emerging:

1. Finding a confidant

The most common theme to emerge was finding a non-judgemental confidant whom they could trust and talk to about their disease or other concerns. As one participant (Female #7) described: “I was given a chance to talk to someone.” Another participant (Female #8) explained: “I found people that spoke to me in a good way despite my situation.”

2. Disease ownership

The other theme that emerged was an increased sense of responsibility for managing their own disease with some also mentioning improved knowledge about their disease and others mentioning improved adherence to treatment since study participation.

6.3.3.4. Assessment of specific intervention components by drumming facilitator and myself, the participant-observer

The following two tables summarise the non-musical (see Appendix 36: AHEAD Study facilitator post-intervention feedback on non-musical components of intervention) and musical (see Appendix 37: AHEAD Study drumming facilitator post-intervention feedback on musical components of the intervention) components of the intervention and feedback about the implementation and acceptability of each component by me and the drumming facilitator.

6.3.3.5. Group drumming facilitator daily reflection and feedback

The drumming facilitator performed daily reflection and assessment of her own performance and development (summarised in Appendix 38: AHEAD Study summary of drumming facilitator reflection on the facilitation process), and that of each of the participants which she then shared with me (see assessment rubric in Appendix 39: AHEAD Study drumming facilitator participant continuous assessment rubric and the weekly group mean scores of the drum session attendees on the assessed criteria in Appendix 40: AHEAD Study drumming facilitator participant continuous assessment weekly group mean scores on the assessed criteria).

6.3.3.6. Perceived demand for the intervention

Additional drum session attendees

One of the drumming groups had six additional peer attendees (close friends and family members of participants) join over the course of the programme and a professional nurse (designated clinic adolescent lead) who attended one full session. Two of the other groups had visiting attendees at a single session. This expansion to include non-participants occurred spontaneously. Some of the

reasons cited by participants: feeling safer travelling to the venue with someone; wanting to share and enjoy the experience with friends.

Showcases

We held two optional showcases (two groups at each showcase) the week after drumming programme completion. They gave the adolescents closure and created opportunities to engage the local clinic, health-related NGO, *Right To Care*, and the Agincourt staff. The adolescents initially met and made percussive instruments from recycled materials before performing their songs and exercises. The showcases were well attended by the adolescents: 79% of adolescents who attended an intervention drumming session attended a showcase. Everyone in attendance seemed to enjoy the showcase and many expressed the desire to continue with the drumming groups after the study. A social worker from *Right To Care* suggested that they could use the drums to engage adolescents for the adolescent support groups they were planning to start in collaboration with the clinics.

6.3.4. Feasibility

6.3.4.1. Logistical issues encountered

I kept a log of logistical issues or incidents arising during study implementation (see Table 38).

Table 38. Logistical issues encountered during AHEAD Study implementation

Study stage	Number of issues	Problem categories	Examples	Seriousness (1-10) of each	Avoidability of incidents	Suggestions for future project manager
Preparation	3	-Asset acquisition	-Drum order incorrect -Cash payment method	3, 3, 5	3 potentially	-Confirm order & payment details close to collection date.
Training	6	-Resource availability -Catering	-Venue cables, electricity, data projector -Food order incorrect -Insufficient food	2, 3, 3, 2, 4, 2	5 definitely 1 potentially	-Confirm all venue resources in advance. -Confirm trainer resource requirements in advance. -Confirm dietary requirements with caterer directly. -Use caterer for all training days.
Recruitment and baseline	11	-Resource availability -Staff transportation -Community impact -Study assets -Recruitment strategy	-Seating at clinic -Car maintenance -Service delivery protests blocking road -Taxi delays -Car damage & repair -Fence damage & repair -Stationery loss	2, 3, 5, 5, 2, 8, 8, 7, 7, 3, 3	6 definitely 1 potentially 4 unavoidable	-Confirm resources at venue in advance. -Use unit vehicle. -Driving test for all drivers. -Label stationery. -Use professional handyman with own transport for repairs.
Intervention	5	-Venue -Study assets	-Venue not opened -No fan -Phone damage	5, 4, 5, 3, 5	4 potentially 1 unavoidable	-Re-confirm repeat arrangements with venue. -Portable study fan. -Phone cover/case.

6.3.4.2. Training

Dr Nkosi travelled from another province to train the drumming circle facilitators. I ran additional drum training after programme completion for the *Right To Care* NGO psychosocial team who showed interest in learning so they could use drumming in adolescent support groups. The limited availability of trainers locally is a potential constraint for scalability and sustainability of this intervention.

6.3.4.3. Venues for drum training and intervention sessions

The drumming venues mostly had very basic amenities (one had a pit latrine and no running water) but they had fans (important in the hot climate). We provided pre-paid electricity vouchers, toilet paper, and bottled water. All venues were easily accessible by public transport but far from home for some participants. Distance to the venue and concerns particularly about younger female participants travelling alone on minibus taxis, which carried up to 12 people simultaneously, were barriers to session attendance. Having a venue in each village would likely facilitate attendance and reduce travel costs and safety concerns in a full-scale RCT.

6.3.4.4. Transport

Most participants walked to the study venues or used taxis with transport fare reimbursement in cash. Covering transport costs facilitated attendance particularly for low-income households. Transport was provided by a staff car for some participants for whom the journey took too long by taxi. We used research unit transport for one day during a minibus taxi strike. Private transport is reliable but costly and not scalable. Staff transport was also by minibus taxi or private transport.

6.3.4.5. Communication

We had two study mobile phones for calling participants to set up appointments and for session reminders. Mobile communication was not fully sustainable because some participants or caregivers lost or changed their mobile phone numbers or sold their mobile phones during the study making them difficult to contact.

6.3.4.6. Timing of sessions

Following clinic staff recommendation, we also recruited on weekends because most adolescents attended clinic then; however, intervention sessions were held on weekday afternoons after school. An advantage of weekday sessions is that the adolescents generally have a more structured daily routine which can make it easier to remember to come to the drumming sessions. Attendance rates dropped slightly during school examinations and vacation (see Figure 45). Almost every week, some attendees arrived early (especially those in primary school or those who attended school close to the venue) and some arrived late (usually in secondary school, and/or went to school far from the venue).

6.3.5. Quantitative outcome analysis

The achieved power (calculated using G*Power 3.1.9.4) (Faul, Erdfelder, Buchner, & Lang, 2009) was 0.82 to detect a large effect size (Cohen's d = 0.8); however, it was only 0.43 to detect a medium effect size (Cohen's d = 0.5) and 0.11 (i.e. insufficient) to detect a small effect size (Cohen's d = 0.2). There was no intervention effect on EF in multivariable regression analyses controlling for baseline EF, socioeconomic status, and education level (see Table 39). There was an intervention effect on the adolescent SRQ-20 depressed mood item (beta = -0.15; 95% CI -0.29, -0.02; p = 0.030) and a marginal effect on caregiver total SRQ-

20 depression and anxiety symptoms score (beta = -2.33; 95% CI -4.82, 0.17; p = 0.067) in multivariable regression analyses controlling for baseline scores, socioeconomic status and education level. There were no intervention effects on adolescent total SRQ-20 or MSPSS scores (see Table 40). There were no intervention effects on frequency of alcohol use (beta = 0.03; 95% CI -0.11, 0.18; p = 0.642), illicit drug use (beta = -0.03; 95% CI -0.10, 0.05; p = 0.494) or self-reported forgetting to take treatment (beta = -0.14; 95% CI -0.36, 0.08; p = 0.213) (see Table 41).

Table 39. AHEAD Study results of multivariable regression analysis of executive function outcomes

Variables	DF	DB	TB	TS	Rule	IGT	d’	Dot	Simon
Intervention	0.06	0.28	0.04	0.03	-0.06	-0.01	-0.09	6.78	-23.14
	[0.4]	[0.4]	[0.1]	[0.09]	[0.0]	[0.09]	[0.3]	[10.9]	[15.1]
1.primary education	0.53	0.48	0.03	0.05	-0.00	0.06	-0.18	10.67	3.52
	[0.4]	[0.5]	[0.1]	[0.09]	[0.0]	[0.08]	[0.2]	[10.8]	[15.3]
2.middle SES	0.15	-0.23	-0.01	-0.05	-0.01	0.07	0.41	6.30	0.28
	[0.4]	[0.5]	[0.1]	0.09	[0.0]	[0.10]	[0.3]	[12.1]	[16.4]
3. high SES	1.12**	0.89	0.08	0.11	0.00	0.17	0.09	21.96	22.69
	[0.5]	[0.6]	[0.1]	[0.13]	[0.1]	[0.13]	[0.4]	[16.7]	[25.1]
Baseline EF score	0.12	0.40*	0.38***	0.19	0.55***	0.28*	0.70***	0.37***	0.23*
	[0.2]	[0.2]	[0.1]	[0.16]	[0.1]	[0.15]	[0.1]	[0.1]	[0.1]
Constant	4.17***	2.10***	0.50***	0.36	0.22***	-0.04	1.03**	-101.51***	-28.98*
	[0.9]	[0.6]	[0.1]	[0.12]***	[0.0]	[0.09]	[0.4]	[19.7]	[15.1]
Observations	47	47	49	49	54	54	49	49	48
R-squared	0.18	0.23	0.21	0.10	0.37	0.09	0.52	0.31	0.13

Key: DF = digit span forwards; DB = digit span backwards; TB = trails baseline; TS = trails switch cost; Rule = rule-finding; IGT = Iowa Gambling Task; d’ = d-prime; Dot = dot recall; SES = socio-economic status; EF = executive function; values are regression coefficients with standard errors in brackets unless otherwise specified; * p<0.10; ** p<0.05; *** p<0.01.

Table 40. AHEAD Study results of multivariable regression analysis of socioemotional scale outcomes

Variables	SRQC	SRQA	Depr	PSS
Intervention	-2.33*	-0.44	-0.15**	-0.16
	[1.2]	[0.7]	[0.1]	[0.1]
1.primary education	-1.03	1.72**	0.05	-0.26*
	[1.3]	[0.7]	[0.1]	[0.1]
2.middle SES	2.07	-0.59	-0.02	0.04
	[1.3]	[0.8]	[0.1]	[0.1]
3. high SES	-1.28	-0.20	-0.07	-0.06
	[1.8]	[1.1]	[0.1]	[0.2]
Baseline score	0.68***	0.57***	0.38***	0.35**
	[0.1]	[0.1]	[0.1]	[0.1]
Constant	2.86**	1.45	0.09	2.58***
	[1.3]	[0.9]	[0.1]	[0.4]
Observations	53	54	54	54
R-squared	0.41	0.34	0.25	0.21

Key: SRQA = Self-Reporting Questionnaire 20 (SRQ-20) adolescent total score; Depr = adolescent SRQ-20 depressed mood; SRQC = SRQ-20 caregiver total score; PSS = multidimensional scale of perceived social support total score; values are regression coefficients with standard errors in brackets unless otherwise specified; * p<0.10; ** p<0.05; *** p<0.01.

Table 41. AHEAD Study results of multivariable regression analysis of behavioural outcomes

Variables	EtOH	Drug	Forgot
Intervention	0.03	-0.03	-0.14
	[0.07]	[0.04]	[0.11]
1.primary education	0.08	0.03	-0.07
	[0.07]	[0.04]	[0.11]
2.middle SES	-0.12	0.03	-0.01
	[0.08]	[0.04]	[0.12]
3. high SES	-0.14	-0.01	0.24
	[0.11]	[0.06]	[0.16]
Baseline score	0.15	0	0.21*
	[0.14]	NA	[0.11]
Constant	0.09	0.00	0.15
	[0.08]	[0.04]	[0.12]
Observations	54	54	52
R-squared	0.11	0.04	0.14

Key: EtOH = frequency of alcohol use in the last three months; Drug = illicit drug use in the last three months; Forgot = self-reported forgetting to take treatment in the last three months; NA = not applicable

6.3.6. Referrals

Five caregivers (three with adolescents in the intervention arm; two with adolescents in the control arm) and three adolescents (two in the intervention arm who received < 75% of intervention; one in the control arm) were referred to the clinic professional nurse and the social worker for mental health concerns. One participant (intervention arm) also required referral to the hospital's psychiatric clinic for further management. Two participants (control arm) were referred to the clinic counsellor or a professional nurse for adherence counselling. Three participants on second-line treatment with potential virological failure on clinical record review (two in the intervention arm; one in the control arm) were discussed with the clinic professional nurse for referral to the local hospital for HIV genotypic resistance testing[17] to inform the choice of potential third-line ART.

6.3.7. Sustainability

Dr Nkosi and I trained an occupational therapy technician, secondary school teachers and the *Right To Care* NGO psychosocial team in drum circle facilitation so that they would have the basic knowledge and skills to continue using the drums effectively when they received them after the study. When I met with a participating clinic facility head close to the end of the programme, she was very supportive of the intervention and stated that using drums in adolescent support groups would fit in well with the Department of Health's policy to make every clinic an 'Adolescent- and Youth-friendly facility'; however, she voiced some concerns about the feasibility of sustaining the intervention. She mentioned the following

[17] HIV genotypic resistance testing involves sending a patient's blood sample to be tested for HIV genetic mutations conferring resistance to antiretroviral therapy. It gives the treating doctor a drug resistance profile and shows antiretroviral drugs to which the patient's HIV strain is still sensitive, allowing the doctor to tailor an antiretroviral therapy regimen for a particular patient.

potential barriers to implementation: human resource constraints (the clinic staff are already overburdened and have to prioritise their clinical work; the HIV counsellors are on strike because they want to be formally incorporated government employees); the clinic's inability to provide participant transport, snacks and session reminders (facilitating factors) without additional funding. Another potential path to sustainability is to train some of the adolescents to run the groups themselves as a peer-led programme. HIV-positive adolescents have successfully been trained to lead interventions for their peers in Zimbabwe (Kidia, Ndhlovu, Jombo, Abas, & Makadzange, 2015).

6.3.8. Scalability and replicability

Certain non-musical (e.g. norms) and musical (e.g. rhythms) intervention components are standardised and easier to replicate across contexts; however, there are other components (e.g. specific melodies and lyrics used) that would need to be adapted to make the intervention more acceptable to the particular group, population, and context. It is difficult to predict whether the programme will translate well to other contexts. I hypothesise that it will translate well to similar rural Southern African contexts if local musical content is incorporated.

The greatest challenges to scalability and replicability will probably be skilled human resource constraints and maintaining the quality of the intervention and its facilitation at scale. The willingness and availability of a drumming trainer to run an adequate training programme for the drumming facilitators will be crucial. It will also be necessary to find and recruit potential drumming facilitators with the right key characteristics and motivation to learn, and the time to prepare and practise for sessions (30-90 minutes prior to each session was spent in this study). In this

study, fieldworkers underwent five days of training followed by a formal assessment of their ability to facilitate by the trainer.

6.4. Discussion

6.4.1. Main findings

6.4.1.1. Summary of main findings

I found that a short-term group drumming intervention was feasible and acceptable amongst HIV-positive adolescents in a rural South African context, providing support for thesis hypothesis 3.1. There was a 77% uptake to formal eligibility screening amongst potentially eligible participants informed about the study. There was a 96% enrolment rate of those found to be eligible and a 99% study retention rate. 77% of intervention participants attended at least 50% of the intervention sessions with 65% attending 75% or more. These rates suggest that progression to a pilot and full-scale RCT would likely be worthwhile.

There was no signal for an effect on EF, the quantitative outcome which would have been the primary outcome analysing efficacy in a full-scale RCT (evidence against thesis hypothesis 3.2). There was an effect on depressed mood which was supported by the qualitative data (partial support for thesis hypothesis 3.3). There were various perceived socio-emotional benefits described in the qualitative data including finding acceptance and belonging in the circle, decreased internalised stigma, and improved emotional well-being and resilience with improved mood and decreased anxiety. These findings provide evidence to support thesis hypothesis 3.3. The baseline data did not support an association between EF and markers of advanced or uncontrolled disease (thesis hypothesis 1.2.1) or EF and frequent alcohol use (thesis hypothesis 2.1). Baseline data did partially support an

association between forgetting to take treatment (one of the causes of poorer adherence) and poorer EF; the association was limited to poorer verbal working memory (thesis hypothesis 2.2).

6.4.1.2. Reason for lack of an effect on EF

The hypothesis that EF in HIV-positive adolescents could be improved through short-term group drumming was based on several underlying assumptions, with varying degrees of evidence to support these assumptions:

1. Short-term (few weeks) musical training can improve EF in adolescents.

2. Short-term (few weeks) group drumming can improve EF in adolescents.

3. Short-term (few weeks) group drumming can improve EF in adolescents in a rural African setting with multiple threats to EF development.

4. Musical training by a trained layperson can improve EF in adolescents.

5. EF is malleable to change in HIV-positive adolescents even in the presence of ongoing systemic inflammation and neuroinflammation.

6. EF outcome measures used are sensitive enough to detect change if change occurs.

Based on these assumptions, I hypothesised that eight weeks of one-hour fieldworker-led group drumming sessions would be a sufficient dose (duration) and potency (quality) of musical training to improve EF in HIV-positive adolescents (see Theory of Change Figure 44 and Table 26); however, any one or more of these assumptions may be incorrect and the reason for the lack of effect. Assuming that long-term (many months or years) musical training can improve EF, eight weeks with 6-8 hours of musical training might be an insufficient dose (too few hours of

training) to improve EF in adolescents. Generally longer EF training interventions have shown better results (Diamond & Ling, 2016; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008), possibly because they allow time for training-induced reorganisation of the brain's neural networks to allow more efficient processing (Bamidis et al., 2015). There is a possibility that group hand drumming, as a type of musical training, would not result in EF improvements at any dose or that it would only result in near transfer to improved rhythmical or tonal working memory (not measured in this study), more specific to musical training, but not verbal or visuospatial working memory or other EF subtypes (Diamond & Ling, 2016). It is also possible that short-term, and possibly longer-term, group drumming is insufficient to improve EF in adolescents in a rural African context against a background of multiple threats to EF development. Perhaps a single positive or supportive factor (e.g. musical training in the form of group drumming) is insufficient to change EF unless other negative developmental factors (e.g. poor nutrition, a low quality of education) are also addressed.

The facilitator was faithful to the intervention programme in all the sessions I observed; therefore inadequate quality of facilitation is unlikely to be a reason for the lack of effect; however, I cannot rule out that having a recently trained, relatively inexperienced drummer (rather than a highly trained music therapist or drumming circle facilitator with years of experience) as the facilitator might have affected the outcome. EF may be less malleable in HIV-positive adolescents in the presence of ongoing neuroinflammation which may be contributing to their poorer EF. EF may only improve if neuroinflammation is also treated. The chosen EF task measures (mostly accuracy scores) may not be sufficiently sensitive to detect change or be

demanding enough to reveal between-group differences (Diamond & Ling, 2016). Duration or reaction time measures might have been more sensitive.

6.4.1.3. Socio-emotional effects

The intervention had positive effects on certain socioemotional constructs which were included as secondary outcomes. These socio-emotional outcomes were included because they are highly associated with EF and they are important in their own right. There were improvements in adolescent depressed mood supported by the quantitative and qualitative data. There was no significant change in overall depressive and anxiety symptoms on the SRQ-20, possibly because the sample's total SRQ-20 score was low at baseline; however, an improvement in depressive and anxiety symptoms was an emergent theme in the qualitative data suggesting that it may have improved both depressive *and* anxiety symptoms in the few participants experiencing both symptoms. The inter-individual synchronisation involved in the group drumming process may have exerted a positive effect on mood by promoting social cohesion and a sense of belonging (Hove & Risen, 2009; Marsh et al., 2009) with associated increases in dopamine release in the reward pathway (Kokal et al., 2011), endorphin release (E. E. Cohen et al., 2010) and oxytocin release (Yuhi et al., 2017). A new-found sense of peer acceptance is likely to have had a particularly powerful effect on improving mental health in those adolescents with depressed mood related to experiences of isolation, rejection and stigmatisation due to HIV. Listening to music is generally a highly pleasurable activity in and of itself (Gebauer et al., 2012; Vuust & Kringelbach, 2010) and may thus have induced a positive mood. Music listening is associated with activation of the brain's dopaminergic reward system (Gebauer et al., 2012; Vuust & Kringelbach, 2010).

There were marginal improvements in depressive and anxiety symptoms in the caregivers of intervention arm participants although there was no difference in contact time between caregivers of participants in different trial arms. This may be because caregivers in the intervention arm were relieved that their children were receiving an intervention which they perceived as beneficial for the adolescents. It may have decreased some of their anxiety centred around concerns for the adolescent's well-being.

The qualitative data suggested that the intervention improved adolescents' sense of social belonging and peer acceptance through solidarity experienced in the group with associated decreases in internalised stigma and improvements in self-esteem. These effects might have served as a buffer or protective factor which increased resilience to stress (S. Cohen & Wills, 1985; Collishaw et al., 2016). Despite these qualitative findings, there were no significant changes in the quantitative measure of perceived social support, possibly because the intervention only improved perceived social support in a small proportion of the adolescents or because the measure was not sensitive enough to detect small changes in perceived social support by peers (only four of the scale's twelve items focused on friends).

Qualitative data suggested that control arm participants also experienced non-specific effects from study participation, with perceived benefits of having the fieldworker as a confidant and experiencing an increased sense of disease ownership and responsibility. This suggests that this population of adolescents living with a chronic, stigmatised disease like HIV, some of whom are still adjusting to the diagnosis or have recently had their diagnosis fully disclosed to them, seem to benefit from increased one-to-one contact time with someone they can trust and

talk to about their concerns. Participants from both trial arms and their caregivers could have benefited from the increased contact time with screening for and identification of depression and anxiety, and referral to clinic staff, social workers, counsellors and the hospital when necessary (see Section 6.3.6. Referrals).

6.4.2. Strengths

To my knowledge this was the first feasibility study assessing a potential cognitive rehabilitation programme aiming to improve EF exclusively focused on HIV-positive adolescents in a LMIC. It tested an African 'homegrown' solution in which the intervention was designed and co-created by a South African team of collaborators. It used a theory of change framework to map out contextual factors, role players, underlying assumptions and rationale, and levers for change. It included a more comprehensive battery of EF tasks than has been used in previous intervention studies in HIV-affected children and adolescents, including both affective and non-affective tasks. It is also one of the first studies to evaluate group drumming as a potential mental health intervention rigorously using mixed methods and randomisation. It also considered potential sustainability from the design stage through to training and evaluation.

6.4.3. Limitations

There were several study limitations. The first limitation relates to sample size. It was a feasibility study; therefore, it had a relatively small sample size and was underpowered to detect intervention effects, particularly small or medium effect sizes. It was therefore not able to formally assess efficacy using the study results. The second limitation was related to multiplicity. There were multiple quantitative outcomes measured which increases the risk of Type I errors. Normally one would adjust for this; however, the feasibility study was exploratory in nature and

adjustment for multiplicity is thus not expected. Thirdly, there were a few limitations related to measures and measurement. The study did not include a detailed subjective measure of EF in real-life contexts (e.g. the Behavioural Rating Inventory of Executive Function) or an in-depth measure of mood measuring positive affective states (e.g. the Positive and Negative Affect Schedule); however, it would be possible to include these in a future pilot and full-scale RCT. Although all these measures had been validated in a South African context, the Tsonga versions had not all been validated. The cognitive testing was not done in a strictly controlled laboratory environment and it was performed by less experienced testers. Although theoretically this could have increased the likelihood of measurement error, it was unlikely to have been significant in this study because the tools are designed to be easy to administer in a standardised way with design features to minimise the potential effects of human error. I also performed random spot checks for quality control purposes. The study had limited open-ended qualitative questions in the questionnaire. Obtaining funding to include in-depth interviews, focus group discussions or drum session video recordings with independent ratings of the quality of facilitation, the interactions and the participants could provide richer qualitative data in a future pilot RCT. Fourthly, the study used a health facility-based sampling frame meaning that the sample may not be representative of the HIV-affected population at large because it only included those already linked to care. Finally, there were a few limitations in the study design. The study did not have an independent blinded quantitative assessment fieldworker due to resource constraints. The feasibility assessment did not include a cost-effectiveness analysis. There was no measure of risky sexual behaviour in this 8-week study, an important distal behavioural outcome. There

was no delayed follow-up round of data collection to assess the maintenance of any effects.

6.4.4. Conclusion and next steps

Despite these limitations, this feasibility study adds valuable evidence to the body of literature on interventions aiming to improve EF in HIV-positive adolescents and to the music intervention literature more broadly. It demonstrated the feasibility of this fieldworker-delivered intervention in a small-scale study setting in rural South Africa. It also showed high acceptability amongst HIV-positive adolescents, the local drumming facilitator, clinical and NGO psychosocial team staff. Although there was no signal detected for an intervention effect on EF, there were promising qualitative findings with some supporting quantitative findings to suggest positive socio-emotional effects on mood, internalised stigma, self-esteem and peer group belonging and acceptance within the drum circle. Skilled human resource and financial constraints will likely be the main challenges to scalability and replicability. There could be more challenges with implementation in a real-world setting, particularly with regards to mobilisation of the necessary resources to ensure it can be implemented successfully. Overall, the high screening, enrolment, attendance, study retention and adolescent-rated acceptability rates as well as the promising socio-emotional effects suggest that this intervention should be considered for progression to a formal pilot with subsequent full-scale RCT with a sample size sufficient to detect small and medium effect sizes. The primary outcome will likely shift to depressive symptoms rather than EF. If EF is kept as a secondary outcome, the intervention dose (duration) may need to be increased e.g. to 10 or 12 weeks, a common duration for group drumming interventions used in the literature.

Chapter 7: General discussion and conclusions

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7.1. Introduction

In this chapter, I provide an overview of the thesis as a whole and discuss and integrate the main findings from the empirical chapters. I also discuss broader issues that emerged in earlier chapters. After describing the strengths and limitations of the work, I discuss thesis contributions and remaining research gaps. Finally, I present implications for clinical practice and policy before concluding the thesis.

In this thesis, I firstly explored the relationship between EF and HIV in children and adolescents more generally through performing a systematic review of the existing literature from a global perspective. I then narrowed my focus to the specific region of interest, rural South Africa, due to its high HIV prevalence particularly amongst adolescent females. I performed a validation of OCS-EF, a novel, tablet-based tool

for use by trained laypeople, to confirm that it could be used to measure EF reliably amongst adolescents in this context. I then specifically explored the relationship between EF, HIV and other important risky behavioural outcomes linked to HIV transmission in late adolescent females. Finally, I co-developed and conducted a feasibility trial of a complex musical training programme as an intervention aiming to improve EF and related socio-emotional outcomes and behaviours in HIV-positive adolescents.

7.2. Main findings

Below I will summarise the main findings and then discuss them in light of each thesis hypothesis (printed in Italics).

I found that despite treatment with ART, perinatal HIV infection is associated with EF deficits. There is a specific pattern of EF deficits in perinatally acquired HIV. EF deficits in perinatally acquired HIV are more marked when compared to HIV-unaffected controls than HIV-affected controls, suggesting that the association between HIV and EF deficits is likely due to the combined contribution of biological and psychosocial risk factors that cluster in HIV-affected households. A history of advanced disease, during early critical periods of cognitive development, is generally associated with poorer EF; however, current markers of disease progression (serum CD4 cell count) and disease control (serum viral load) had mixed associations with EF varying by EF subtype.

Adolescents with less advanced HIV, acquired behaviourally in the last few years (i.e. much later during their cognitive development), seem to have limited, if any, EF deficits. This suggests that EF is affected by the timing and severity of HIV infection. Factors found to be associated with EF deficits that might be potential

risk factors, outcomes, or both, included: poorer academic performance, adolescent and caregiver depression or emotional distress, poorer adherence to treatment and increased risk-taking behaviour.

These associations suggested that interventions to improve EF and depression might lead to better outcomes through an association with less risk-taking and better adherence to treatment. Due to the lack of evidence-based interventions that might be feasible, acceptable and scalable to target EF and depression in a resource-limited setting like rural South Africa, and evidence to support the potential efficacy and likely acceptability of musical training, I co-developed and tested an African group drumming intervention amongst HIV-positive adolescents in rural South Africa. I found that it was acceptable and feasible within a study context. There was no evidence for an effect on EF or distal behavioural outcomes. There were positive effects on adolescent depressed mood although not total depressive and anxiety symptoms. Qualitative data also supported the finding of mood improvements and suggested that for some adolescents, drumming group participation helped reduce their internalised stigma through increasing their sense of peer acceptance, belonging, and self-worth. Self-reported forgetting to take treatment improved but not significantly more than in the control group. There were no effects on alcohol or illicit drug use.

I thus found evidence to support some but not all my original thesis hypotheses. There were two thesis hypotheses for which the evidence was either generally not supportive or inconclusive:

1. the association between HIV and EF deficits in adolescents with behaviourally acquired HIV;

2. the potential for short-term musical training to improve EF in HIV-positive adolescents.

The thesis hypotheses and their associated findings are described below in more detail in the context of the existing literature.

1. The relationship between HIV and EF in adolescents with HIV

1. EF deficits are more common in HIV-positive adolescents.

The evidence was generally supportive of this overarching hypothesis in the context of adolescents with perinatally acquired HIV on antiretroviral therapy; however, this was not the case in slow progressors with perinatally acquired HIV or adolescents with behaviourally acquired HIV. This demonstrates the heterogeneity present in the overall population of HIV-positive adolescents (Laughton, Cornell, Boivin, & Van Rie, 2013). There are important differences between subpopulations affecting their likelihood of having EF deficits. These include the route of transmission, the timing of infection, the rate and severity of disease progression, and the timing of access to antiretroviral therapy (Crowell et al., 2014; Laughton et al., 2013).

1.1. These EF deficits are greater if infection occurred early in the course of cognitive development; therefore, adolescents with vertically transmitted HIV acquired perinatally will have larger and more global deficits than adolescents with later behaviourally acquired HIV.

The evidence from the systematic review and case-control study generally supported this sub-hypothesis. Children and adolescents with perinatally acquired HIV seem to have more extensive EF deficits affecting multiple EF subtypes (see hypothesis 1.3). The evidence in adolescents with behaviourally acquired HIV was,

however, much more limited (see hypothesis 1.4). There were also no primary studies directly comparing the two subpopulations.

1.2. EF deficits arise partly due to the direct neurological effects of this neurotropic virus on the brain and partly due to associated risk factors that are commonly found in HIV-affected households.

1.2.1. Markers of more advanced disease (i.e. low CD4 count) *or uncontrolled disease* (i.e. high viral load) *are associated with poorer EF in HIV-positive adolescents.*

There were mixed findings with regards to this hypothesis. In perinatally acquired HIV (Study 1), current CD4 count was positively associated with working memory and inhibitory control but not associated with planning or global EF (Malee et al., 2017; Martin et al., 2006; Nachman et al., 2012; Nagarajan et al., 2012; Ruel et al., 2012). In less advanced behaviourally acquired HIV (Study 3), CD4 count was generally not associated with EF performance except for an unexpected association between a higher CD4 cell count (≥ 350 cells/mm3) and poorer rule-finding performance, perhaps due to a confounder not controlled for e.g. current antiretroviral therapy.

Past advanced disease defined clinically (an AIDS-defining condition), potentially during an earlier critical period of cognitive development, was associated with poorer EF (Study 1). The meta-analysis demonstrated poorer working memory, inhibitory control and set-shifting in those with perinatally acquired HIV with a history of advanced disease (an AIDS-defining condition) than in those without such a history. This supports the element of hypothesis 1.2 that HIV itself has direct neurological effects, which contribute to risk of EF deficits.

Current viral load was associated with some, but not all aspects of EF in perinatally acquired HIV (Study 1), but there was no association in adolescents with behaviourally acquired HIV (Study 3). In perinatally acquired HIV (Study 1), a higher viral load was negatively associated with working memory, inhibitory control, planning and parent-reported global EF (Kapetanovic et al., 2010; Malee et al., 2017; Martin et al., 2006; Nichols et al., 2015; Ruel et al., 2012; Ruisenor-Escudero et al., 2015). There were no associations with set-shifting or global EF (Bangirana et al., 2016; J. Hoare et al., 2019; Nagarajan et al., 2012; R. N. Robbins et al., 2019).

Serum disease markers, rather than CSF markers, are generally used because they are much less invasive to obtain. There are limitations of using serum markers rather than CSF markers as a proxy for disease activity in brain tissue. Antiretroviral drugs have varying degrees of CNS penetration effectiveness based on their ability to cross the blood-brain barrier and suppress the CSF viral load (Crowell et al., 2014; Letendre et al., 2008). Sometimes there are discrepancies between the different body compartments e.g. ‘CSF viral escape’ where there is a detectable CSF viral load despite undetectable or suppressed serum viral load (Edén et al., 2010; Joseph et al., 2016). CSF viral load is likely a better proxy marker of brain HIV activity and perhaps more closely linked to cognitive function (Ellis et al., 2002; Peluso et al., 2012; Smurzynski et al., 2011). This is understudied in HIV-positive children and adolescents due to the need for lumbar puncture but studies are now underway (Joseph et al., 2016).

1.2.2. EF deficits in HIV-positive adolescents are more marked when compared to HIV-unaffected controls than when compared to HIV-affected controls.

The systematic review was able to compare children and adolescents with perinatally acquired HIV with both HIV-affected (perinatally HIV-exposed or living in HIV-affected households) and HIV-unaffected HIV-negative controls. Effect sizes were larger when compared to HIV-unaffected controls than when compared to HIV-affected controls. This supports the element of hypothesis 1.2 stating that psychosocial risk factors contribute to the risk of EF deficits.

1.2.3. PHEU and/or PHU adolescents living in HIV-affected households have mild EF deficits compared to healthy HIV-unaffected adolescents.

The evidence was mixed with regards to this sub-hypothesis. When perinatally HIV-exposed uninfected children and adolescents were compared with perinatally HIV-unexposed uninfected controls, effect sizes were small and not significant (Study 1). There were certain EF subtype deficits found in some cohorts or contexts though (Boivin et al., 1995; Milligan, 2016; Milligan & Cockcroft, 2017; Puthanakit et al., 2013). This suggests that there is a small additive risk from psychosocial risk factors in certain contexts and that HIV-affected subpopulations fall on a spectrum or gradient of risk: those with perinatally acquired HIV are most at risk and those living in HIV-affected households have some additional risk compared to HIV-negative children and adolescents not living in HIV-affected households.

1.3. Perinatally acquired HIV is associated with a distinct pattern of EF deficits with effect sizes varying by EF component.

The systematic review found evidence to support this hypothesis. Effect sizes are largest for verbal and visuospatial working memory, smaller for inhibitory control

and planning, and smallest for set-shifting. These deficits are greater in extent but similar to the pattern seen in adults with behaviourally acquired HIV where a recent meta-analysis found larger effect sizes for working memory and hot inhibition (decision-making in the context of risk) than for cool inhibition and set-shifting (K. A. Walker & Brown, 2018). The effect sizes for working memory and inhibition were larger in perinatally acquired HIV (compared to HIV-unaffected controls) than the effect sizes seen in adults with behaviourally acquired HIV (K. A. Walker & Brown, 2018). The pattern of EF deficits seen may be related to the brain regions where neuropathology is evident. In adults with behaviourally acquired HIV, working memory deficits have been linked to abnormalities in fronto-striatal and fronto-parietal circuit function (Chang et al., 2001; Tomasi, Chang, Caparelli, Telang, & Ernst, 2006) and inhibitory control deficits linked to abnormal subcortical function (du Plessis et al., 2015). In adolescents with perinatally acquired HIV, better working memory and set-shifting have been positively associated with fractional anisotropy and axial diffusion (markers of white matter integrity) in the external capsule, cerebral peduncle, and superior and inferior fronto-occipital fasciculi (J. Hoare et al., 2019; Uban et al., 2015). Abnormal levels of glial functioning markers have been negatively associated with working memory in children and adolescents with perinatally acquired HIV and adults with behaviourally acquired HIV (Ernst, Chang, & Arnold, 2003; Van Dalen et al., 2016) (see Chapter 2, Table 4). These findings also lend support to the first part of hypothesis 1.2 i.e. that EF deficits arise partly due to the direct neurological effects of this neurotropic virus on the brain.

1.4. Behaviourally acquired HIV is associated with a distinct pattern of EF deficits with effect sizes varying by EF component.

There was insufficient data in adolescents with behaviourally acquired HIV to suggest a consistent pattern of EF deficits in support of this hypothesis. The data was limited for behaviourally acquired HIV because in the adult medical literature, 18-24-year-olds were often analysed with adults aged 25-55-years-old without disaggregated adolescent data. My meta-analysis (Study 1) did not find set-shifting deficits; however, the data were limited. The case-control study (within Study 3) found poorer verbal working memory in behaviourally acquired HIV than in HIV-negative controls. More research focused on adolescents is needed to see whether their developing brains have a similar pattern of EF deficits to adults with behaviourally acquired HIV.

2. The relationship between EF and risk-taking behaviour in adolescents

2.1. EF deficits are associated with increased risky sexual behaviour and substance use.

The systematic review found a small study (n = 44) examining the association between EF and risk-taking behaviour in HIV-positive adolescents and HIV-negative controls. This US study of mostly male adolescents with behaviourally acquired HIV found no association between verbal working memory or set-shifting and risky sexual or substance use behaviour (Baker et al., 2014). In Study 3 in adolescent females, I found that better verbal working memory and planning were generally associated with a lower risk of risky sexual behavioural outcomes. Better affective inhibition (emotional go/no-go) was only associated with a lower risk of transactional sex. Better planning ability was also associated with a lower risk of risky substance use and binge drinking. Like the US study, I found no association between set-shifting ability and risky behavioural outcomes. Possible reasons that

the US study found no association with verbal working memory included sample size (n = 44), sex of participants, context or measures. Overall the findings suggest that EF does not have global associations with risk-taking behaviour, but that different EF subtypes may relate differently to risky behavioural outcomes in adolescents, with verbal working memory and planning ability possibly being more strongly associated with risk-taking; however, more research is needed.

2.2. EF deficits are associated with lower adherence to ART in HIV-positive adolescents.

There were mixed findings with regards to this hypothesis with some studies finding no association and others finding associations limited to certain EF subtypes. The systematic review found two studies examining the association between adherence and EF. In the Spanish CoRISPeS[18] cohort, no cool EF subtypes were associated with adherence (Garcia-Navarro et al., 2013). In the US PHACS AMP[19] cohort, only self-reported behavioural regulation[20] was associated with adherence (Garcia-Navarro et al., 2013; Garvie et al., 2017). Other EFs were not related to adherence. In the AHEAD Study, there was an association between better verbal working memory and lower self-reported forgetting to take medication; however, there were no associations with other EF subtypes. Forgetting to take medication is one potential reason for adherence difficulties; however, there are many other potential reasons. Other reasons include: adverse effects of medication; reluctance to be seen collecting medication at the clinic; and

[18] CoRISpeS: Cohort of the Spanish Paediatric HIV Network
[19] PHACS AMP: Paediatric HIV/AIDS Cohort Study Adolescent Master Protocol
[20] Measured with the BRIEF (Behavioural Rating Inventory of Executive Function) index behavioural regulation index: comprised of the Inhibit, Shift, and Emotional Control scales

fear of people discovering their medication at home and finding out their status this way. It should be noted that adherence to medication is difficult to measure, particularly in adolescents (Hodes, Cluver, Toska, & Vale, 2018). Differences in definitions and measures of adherence may account for some of the differences in findings between studies.

3. The development and testing of an intervention aiming to improve EF in HIV-positive adolescents

3.1. A short-term group drumming programme is a feasible and acceptable intervention in HIV-positive adolescents in rural South Africa.

The high screening and enrolment rates, moderate and consistent attendance rates, and high retention rates, as well as high acceptability ratings and qualitative data suggested that this intervention was acceptable to HIV-positive adolescents and their caregivers. They also suggest, along with the low rate of mostly minor logistical issues encountered, that it was feasible. The evidence therefore supported this thesis hypothesis.

3.2. Participation in a short-term group drumming intervention improves EF in HIV-positive adolescents in rural South Africa.

There was no evidence for an effect on EF in multivariable analyses. The evidence did not support this thesis hypothesis. There were also no effects detected on distal behavioural outcomes hypothesised to be related to EF e.g. frequency of alcohol use, illicit drug use, forgetting to take treatment. Possible reasons for the lack of effect are discussed in detail in Chapter 6 section 6.4.1.2. If the underlying assumption that long-term (many months or years) musical training can improve EF is correct, eight weeks (6-8 hours) of musical training might be an insufficient

dose (too few hours) to improve EF in adolescents. Longer EF training interventions have generally had superior results (Diamond & Ling, 2016; Jaeggi et al., 2008). There is a possibility that group hand drumming, as a type of musical training, would not result in EF improvements at any dose. It is also possible that a higher dose of group drumming might result in near transfer to improved rhythmical or tonal working memory (not measured in the AHEAD study), more specific to musical training, but not other EF subtypes (Diamond & Ling, 2016). It may be that group drumming is insufficient as an isolated supportive factor to improve EF in adolescents in a low-income context where adolescents are facing multiple threats to EF development (e.g. HIV, food insecurity, low-quality education). EF may also be less malleable in HIV-positive adolescents in the presence of ongoing neuroinflammation which may be contributing to their poorer EF. EF may only improve if neuroinflammation is also treated. In summary, some of the more likely potential reasons for the lack of effect on EF are the low intervention dose and the indeterminate malleability of EF in HIV-positive adolescents in the context of ongoing low-grade systemic inflammation and neuroinflammation and multiple other threats to EF development (see Section 7.3.1. Malleability of executive function).

3.3. Participation in a short-term group drumming intervention improves depression and anxiety symptoms, playing a supportive role in improving EF, in HIV-positive adolescents in rural South Africa.

There were positive effects on adolescent's depressed mood but not total depression and anxiety symptoms. Qualitative data also supported the finding of mood improvement and suggested that for some adolescents, drumming group participation helped reduce their internalised stigma through increasing their sense

of peer acceptance, belonging, and self-worth. These findings are consistent with findings from other controlled group drumming studies in adolescents and adults with clinical and/or social issues (Ascenso et al., 2018; B. Bittman et al., 2009; Fancourt, Perkins, Ascenso, Carvalho, et al., 2016). The findings thus partially supported this hypothesis.

7.3. Emerging issues

There were a few broader issues raised by the thesis.

7.3.1. Malleability of executive function

The lack of signal for an intervention effect in the feasibility study raises the question of whether EF is less malleable in a clinical population in which ongoing low-grade systemic inflammation and neuroinflammation promote negative neuroplasticity and contribute to EF deficits (Blokhuis et al., 2019; J. Hoare et al., 2019; Kim-Chang et al., 2019; Vance, 2010). Perhaps psychosocial interventions will only be useful when neuroinflammation is also targeted and the balance is pushed in favour of factors promoting positive neuroplasticity (Cody & Vance, 2016). More broadly, it raises the question of EF malleability in adolescents with short-term musical training interventions. Most of the experimental data supporting EF malleability with short-term musical training interventions comes from younger pre-school or primary-school aged children (see Chapter 5, Section 5.1.2). The only effective experimental study including adolescents was much longer and saw improvements after 60 sessions (60 hours) (Flaugnacco et al., 2015). This suggests that musical training interventions need to be longer (i.e. a higher minimum effective dose) to change EF in adolescents.

7.3.2. Measurement challenges and opportunities

Another broad issue that emerged was the importance of triangulation. Different methods or data sources may have inconsistent findings. Triangulation involves using multiple data sources or methods to study the same phenomenon in order to validate or verify the findings by comparing and integrating them (M. Q. Patton, 1999). It helps to balance the inherent biases present in each measure or method (Hodes et al., 2018). Inconsistencies between different sources or methods may not mean that the findings are invalid. It may serve to highlight the measurement challenges and the nuances, heterogeneity or complexity of the phenomenon being studied (Hodes et al., 2018; M. Q. Patton, 1999). In the AHEAD Study, I used triangulation of methods (qualitative and quantitative) to study socio-emotional outcomes. Findings from the different methods did not always correspond as expected. For example, the qualitative data suggested improved depression and anxiety symptoms; whereas, there was no effect on the total SRQ-20, only the depressed mood item. There were also themes emerging from the qualitative data that I had not attempted to measure quantitatively. For example, the qualitative data suggested that the intervention might have reduced internalised stigma. No quantitative measures of stigma were included. This reiterates the importance of including qualitative methods alongside quantitative scales, particularly in feasibility studies of complex psychosocial interventions, to:

- detect new or unexpected effects or constructs that may be hard to measure quantitatively using the chosen scales,
- explore effects that may only be present in a subset of participants, and
- to inform the future choice or development of quantitative measures for further studies in the context.

The inclusion of qualitative methods may highlight weaknesses in the chosen quantitative scales when used in the cultural and linguistic context and remind one of the difficulties in measuring social constructs such as perceived social support or social belonging cross-culturally. For replicability and comparability, one should strive to use similar measures globally; however, sometimes to measure a similar construct in a different context and language, the measure requires adaptation and the careful piloting of translated measures in the process of local validation. For example, in future, the Tsonga version of the MSPSS should be validated locally prior to use to be sure that it is reliable to use in this population and context.

EF is also challenging to measure, particularly longitudinally or pre- and post-intervention due to developmental and learning effects. This made the inclusion of a control group to control for these effects in the feasibility study vital. Accuracy outcome measures may have limited variability and a high potential for ceiling effects. Although accuracy outcome measures were chosen for the trails, rule-finding, figure recall and selection tasks for comparability and fidelity to the OCS-EF developers' original measures, efficiency, a measure combining accuracy and duration, is a useful measure to explore in the future. It could provide a parsimonious and more sensitive measure to detect change and differences, particularly when examining and attempting to train EF in healthy adolescent populations. By combining accuracy (often negatively skewed in young, healthy people) with duration (often positively skewed), it also provides a measure more likely to be normally distributed and suitable for use with parametric methods.

7.3.3. Complexity, context and change

Another issue emerging from the thesis is the challenge of developing complex interventions to target levers for change in a particular context. Behavioural change

is difficult to achieve in any context and thus often calls for complex interventions. Using a Theory of Change (ToC) framework in the AHEAD Study helped to map the change landscape more clearly; however, it could not fully predict how the intervention would interact with the population and context to produce or not produce change/s. The Context and Implementation of Complex Interventions (CICI) is another framework that can be used when developing and evaluating complex interventions. It describes seven contextual domains (geographical, epidemiological, socio-cultural, socio-economic, ethical, legal, and political) occurring at the micro, meso and macro levels (Pfadenhauer et al., 2017). All these contextual factors may influence the intervention implementation and whether it changes the desired outcomes. If group drumming is acceptable in a particular socio-cultural context, it may have the potential to improve adolescent mood and perceived social support; however, in isolation it may be insufficient for certain individuals in particular socio-economic and political contexts. For example, it may be insufficient in a malnourished adolescent living in a low-income household struggling with food insecurity because her family are immigrants who are not only facing xenophobia and ostracization by the community but also unable to access government social grants. Changing a single behavioural determinant (e.g. EF) may be insufficient to result in behavioural change. For example, improving EF may make it easier for an adolescent to resist the impulse to drink too much alcohol; however, if he finds himself in a socio-cultural context in which the group leader say he can no longer be part of the friendship circle if he does not get drunk with them, he may still choose to binge drink to protect his social reputation and maintain his membership in the friendship circle. Behavioural change in general is a difficult outcome to achieve because there are multiple intrinsic and extrinsic

factors influencing behaviour. Behavioural change thus calls for complex interventions targeting multiple potential behavioural determinants. Multiple components of complex interventions may interact to result in emergent properties that are more than the sum of their parts. If the interventions do effect change, it can be difficult to identify the active component or combination of components required to replicate the effect. The component/s required may also differ by context. There may thus be tensions between fidelity to the original intervention and flexible adaptation to ensure feasibility, acceptability and efficacy in the context when replicating or scaling up complex interventions. One needs to identify and balance the global/generalisable components and the local/specific components needed in the context.

7.4. Strengths

The body of work presented in this thesis has several strengths relating to its context, methodology and resources used. In relation to context, three of the four studies are based in a rural African context. This is representative of the context where most of the world's HIV-affected populations live yet is generally under-represented in the literature. This means that this work is more likely to be applicable to other high HIV prevalence rural African contexts.

There are various methodological strengths. Firstly, the work was highly interdisciplinary and collaborative in nature. Bringing together people with different theoretical backgrounds, assumptions, and approaches challenged our different specialised ways of thinking about problems and thus strengthened the work. It allowed us to approach the complex problem of measuring EF and changing EF in HIV-positive adolescents from multiple angles and to generate innovative approaches to measurement, in the form of OCS-EF, and intervention, in the form

of AHEAD. Related to this, a variety of methodologies (e.g. qualitative and quantitative) and sources (caregiver and adolescent; full sample and a nested case-control sample) were combined to capture the problem more fully and strengthen the findings. Secondly, Studies 2 and 3 had a large sample size, increasing the likely representativeness of the sample and thus the generalisability of the work to the population. Thirdly, the studies acknowledged the complexity of EF being both unified and diverse by examining the various EF subtypes, including EF in affective contexts which is understudied in the context of HIV-positive adolescents. This allowed us to examine specific associations between EF subtypes, HIV, and behaviour. This was important because, as we found, EF subtypes may be differentially affected in HIV-positive populations and relate to behavioural outcomes differently. Fourthly, the thesis did not address cognition in isolation, but looked at it in the context of and in relation to emotions and behaviour. This helped to demonstrate the interrelationships and relevance of EF to behaviour.

Finally, the limited resources available to fund the work meant that it used open-access tools and required greater creativity and resourcefulness in its design and implementation. This means that it is more likely to be relevant and replicable in other resource-constrained settings.

7.5. Limitations

There were also several limitations to this body of work. Limitations were related to potential bias and confounding, the nature of the data (including its complexity and heterogeneity), and the availability of resources.

There was potential for bias at various stages of each study. Publication bias was prevalent in the systematic review and meta-analysis. Selection bias may mean that the samples were not fully representative. The most vulnerable and high-risk adolescents were potentially excluded due to the eligibility criteria (e.g. at baseline, Study 3 excluded adolescent girls who were pregnant or had already dropped out of school) and/or the sampling strategy (e.g. Study 4 recruited at health facilities and thus only recruited those already linked to care). Studies 2-4 were also fully or predominantly female decreasing the applicability to males in the population. There is a possibility that procedural bias might have been present e.g. subconscious pressure to complete tasks and questions quickly if completed at the end of the day. Various forms of measurement bias might have been present e.g. interviewer bias, instrument bias, social desirability bias or order bias (in the AHEAD acceptability questionnaires). Researcher bias and positionality could have influenced the analysis of the data. This was minimised by using an independent analyst for the feasibility trial quantitative data. The extent to which I could examine and control for potential confounders also varied e.g. meta-regression was not performed in the meta-analyses due to low numbers of studies. I was wary of overadjustment or adjustment for intermediate variables on the causal pathway which might have biased results towards the null (Breslow, 1982). Many of these potential biases are present in much scientific research and are not unique to this body of work. As noted, where possible (and within available means) I attempted to mitigate these potential biases.

The second set of limitations related to the nature of the data. Most of the data was cross-sectional which meant I could not infer causality but merely examine associations. The feasibility trial had a small sample size limiting the power and

generalisability. Many of the factors examined in this thesis are likely related to each other in a bidirectional way with a resultant complex interplay of factors, e.g.:

1. EF deficits may increase the risk of acquiring HIV. HIV may increase the risk of EF deficits.
2. HIV may increase the risk of depression. Depression may increase the risk of acquiring HIV.
3. EF deficits may increase the risk of depression. Depression may increase EF deficits.

This complexity made it difficult to determine cause and effect or the initial directionality before the association became cyclical or bidirectional. I used linear analytical approaches to assess complex problems and relationships. These methods may be limited in their ability to capture or fully describe these complex phenomena. Meta-analysis of heterogeneous data (in terms of context, HIV-affected subpopulations, control groups) may have obscured some of the nuances and complexity within the data.

Finally, resource constraints limited the choice of measures and resulted in certain decisions being driven by pragmatism.

7.6. Contributions

This thesis has addressed various gaps in the literature. Existing knowledge suggested that EF was emerging as the cognitive domain most often affected in perinatally acquired HIV in the era of ART (Laughton et al., 2013; Phillips et al., 2016). The systematic review (Study 1) elucidated the specific pattern of EF deficits by subtype in perinatally acquired HIV for the first time.

Data on adolescents with behaviourally acquired HIV was still sparse but suggested similar set-shifting to controls (Baker et al., 2014; West, 2001). The nested case-control study (in Study 3) began to address the gaps on EF in adolescents with behaviourally acquired HIV using a comprehensive battery of both cool and hot EF tasks (OCS-EF) and only found poorer verbal working memory than in HIV-negative controls with no other EF deficits. This supported the systematic review finding suggesting that EF deficits are much more limited in adolescents with HIV acquired behaviourally later in the life course.

The existing literature indicates that adolescence is a period of heightened risk-taking because EF and behavioural regulation are still maturing while sensation seeking and reward sensitivity peak (Romer, Reyna, & Satterthwaite, 2017). Study 3 was one of the first to examine the cognitive contribution to HIV transmission risk in adolescent females in a high HIV prevalence, rural African setting and found that better EF, particularly verbal working memory and planning, was weakly associated with lower risky sexual and substance use behaviour. Interventions to improve EF might thus be another potential way to decrease HIV risk amongst adolescent girls in high prevalence contexts. This adds another potential strategy to the armamentarium when designing complex HIV prevention programmes.

Adolescents with HIV often have difficulties adhering to treatment and remaining in care, resulting in worse clinical outcomes (MacPherson et al., 2015; Zanoni et al., 2016). Baseline data from the AHEAD Study suggested that poorer working memory contributes to poorer adherence to treatment. Improving EF in HIV-positive adolescents thus seems like a potential way to decrease their HIV transmission risk behaviours and improve their adherence resulting in better individual- and population-level health outcomes.

The AHEAD Study adds evidence to the literature on cognitive rehabilitation and psychosocial interventions in HIV-positive adolescents. It also adds higher-quality evidence to the music literature on group drumming interventions for cognitive and socio-emotional outcomes. It suggests that group drumming might be a promising intervention to explore further in relation to adolescent mood and socio-emotional well-being more broadly.

7.7. Future directions

7.7.1. Research gaps and recommendations

There are various research gaps that remain or emerged as a result of this work. Adolescence is a key intervention period. The paucity of adolescent-disaggregated data or adolescent-only HIV literature was striking. Perhaps adolescents have not been prioritised because they are transitioning between, or straddling, paediatric and adult HIV care. There is thus an urgent need for more adolescent-focused HIV research, particularly in adolescents with behaviourally acquired HIV. HIV-positive adolescents have multiple and complex medical, cognitive and psychosocial needs. Therefore, we need more interdisciplinary research to develop complex interventions which target various needs simultaneously and can be delivered by non-specialists in LMICs (Chibanda, Benjamin, Weiss, & Abas, 2014). There is substantial value to be gained from using a systems-based approach (e.g. ToC or CICI) which acknowledges and embraces complexity when designing complex interventions, particularly those to effect behavioural change. New interventions should be evaluated using mixed methods and incorporate both cognitive tasks and behavioural report measures to assess the functional impact of any cognitive deficits. The use of innovative systems-based analytical techniques e.g. network analysis could also be explored in analysing the complex interactions and

bidirectional relationships present in HIV-related psychosocial and behavioural research (Choi, Batchelder, Ehlinger, Safren, & O'Cleirigh, 2017).

7.7.2. Recommendations for policy and practice

Various recommendations for policy and practice emerge from this work. Once evidence-based cognitive rehabilitation interventions have been developed and are available to offer patients, cognitive screening should be integrated into the care package of adolescents with perinatally acquired HIV. Easy-to-use, cognitive screening tools like OCS-EF should be optimised to be even briefer and provide immediate on-screen results so they are feasible to use in busy clinical settings. EF should be considered as another potential target when developing complex multilevel HIV prevention programmes for adolescent girls and young women in sub-Saharan Africa. Group music-making is a potentially powerful tool to engage adolescents and help to form a positive peer group. This should be considered when designing and implementing Adolescent and Youth Friendly Services in South Africa in line with the National Department of Health's National Adolescent and Youth Health Policy 2017 (Hodes et al., 2017). Group music-making could be incorporated into support groups for adolescents living with chronic diseases. This would require the Department of Health to provide human resources and funding to allow the implementation of such innovative methods to engage adolescents and ensure that their psychosocial needs are met.

7.8. Conclusion

This thesis aimed to examine whether executive function (EF) deficits are more common in adolescents with HIV, whether EF deficits in adolescents are associated with increased risk-taking behaviour predisposing to HIV transmission, and to develop and test a musical training intervention aiming to improve EF and

socio-emotional well-being in HIV-positive adolescents. Based on a systematic review and meta-analyses, a cross-sectional study, and a feasibility trial, it can be concluded that EF deficits are more common in adolescents with perinatally acquired HIV with the extent of deficits varying by EF subtype. These EF deficits are partly linked to HIV-related factors and partly to context-dependent psychosocial risk factors associated with living in an HIV-affected household. Further research is needed on EF in adolescents with behaviourally acquired HIV. Certain EF deficits are associated with increased risky sexual and substance use behaviour, and poorer adherence to treatment. These risky behaviours can result in poorer clinical outcomes for the individual and further HIV transmission, vertically to their children or horizontally to sexual partners within the community. EF deficits can also result in poorer academic, occupational and socioeconomic outcomes. EF deficits in HIV-positive adolescents are thus a potential target to improve clinical and functional outcomes in those living with HIV and to prevent further HIV transmission. Musical training in adolescents has been associated with better EF. Group musical training may have additional socioemotional benefits and may therefore be a useful intervention to target multiple needs simultaneously in HIV-positive adolescents. A short-term group drumming intervention was feasible and acceptable amongst HIV-positive adolescents in rural South Africa. It showed promising effects on socio-emotional well-being, including improving depressed mood; however, the 8-week intervention did not change EF or behavioural outcomes. Further studies are needed to develop suitable complex interventions that can be used in HIV-positive adolescents to target both EF deficits and broader socio-emotional issues contributing to poorer outcomes. Potential distal outcomes of improving EF and socio-emotional well-being in HIV-positive adolescents

include: improved adherence to treatment; reduced risky sexual and substance use behaviour; and improved academic, occupational and socio-economic outcomes, now and in the future. Adolescents are also the next generation of parents so improving their disease control and outcomes should increase their children's likelihood of HIV-free survival and better outcomes.

In summary, this thesis has addressed HIV and psychological disorders (depression and substance use disorders), some of the leading causes of death and disability in adolescents globally (Mokdad et al., 2016). It has attempted to respond to the call of the 'Our future: a *Lancet* commission on adolescent health and well-being' to address some of the treatable and preventable adolescent health problems through intersectoral multi-component interventions, potentially resulting in health, social and economic benefits for the adolescents now, in the future as adults, and for their children, the next generation (G. C. Patton et al., 2016).

References

Abrahams, T. P., & van Dooren, J. C. (2018). Musical Attention Control Training (MACT) in secure residential youth care: A randomised controlled pilot study. *Arts in Psychotherapy, 57*, 80-87. doi:10.1016/j.aip.2017.10.008

Agoston, A. M., & Rudolph, K. D. (2016). Interactive Contributions of Cumulative Peer Stress and Executive Function Deficits to Depression in Early Adolescence. *Journal of Early Adolescence, 36*(8), 1070-1094. doi:10.1177/0272431615593176

Ajilchi, B., & Nejati, V. (2017). Executive Functions in Students With Depression, Anxiety, and Stress Symptoms. *Basic and Clinical Neuroscience, 8*(3), 223-232. doi:10.18869/nirp.bcn.8.3.223

Al-Khindi, T., Zakzanis, K. K., & van Gorp, W. G. (2011). Does antiretroviral therapy improve HIV-associated cognitive impairment? A quantitative review of the literature. *Journal of the International Neuropsychological Society, 17*(6), 956-969. doi:10.1017/s1355617711000968

Alain, C., Khatamian, Y., He, Y., Lee, Y., Moreno, S., Leung, A. W. S., & Bialystok, E. (2018). Different neural activities support auditory working memory in musicians and bilinguals. *Ann N Y Acad Sci, 1423*(1), 435-446. doi:10.1111/nyas.13717

Albert, D., Chein, J., & Steinberg, L. (2013). The Teenage Brain: Peer Influences on Adolescent Decision Making. *Current Directions in Psychological Science, 22*(2), 114-120. doi:10.1177/0963721412471347

Ali, G., Ryan, G., & De Silva, M. J. (2016). Validated Screening Tools for Common Mental Disorders in Low and Middle Income Countries: A Systematic Review. *PLoS One, 11*(6), e0156939. doi:10.1371/journal.pone.0156939

Alvarez-Bueno, C., Pesce, C., Cavero-Redondo, I., Sanchez-Lopez, M., Martinez-Hortelano, J. A., & Martinez-Vizcaino, V. (2017). The Effect of Physical Activity Interventions on Children's Cognition and Metacognition: A Systematic Review and Meta-Analysis. *J Am Acad Child Adolesc Psychiatry, 56*(9), 729-738. doi:10.1016/j.jaac.2017.06.012

Amad, A., Seidman, J., Draper, S. B., Bruchhage, M. M. K., Lowry, R. G., Wheeler, J., . . . Smith, M. S. (2017). Motor Learning Induces Plasticity in the Resting Brain—Drumming Up a Connection. *Cerebral Cortex, 27*(3), 2010-2021. doi:10.1093/cercor/bhw048

Ananworanich, J., Melvin, D., Amador, J. T., Childs, T., Medin, G., Boscolo, V., . . . Gibb, D. M. (2016). Neurocognition and quality of life after reinitiating antiretroviral therapy in children randomized to planned treatment interruption. *Aids, 30*(7), 1075-1081. doi:10.1097/qad.0000000000001011

Anderson, V., Anderson, P., Grimwood, K., & Nolan, T. (2004). Cognitive and Executive Function 12 Years after Childhood Bacterial Meningitis: Effect of Acute Neurologic Complications and Age of Onset. *J Pediatr Psychol, 29*(2), 67-81. doi:10.1093/jpepsy/jsh011

Anderson, V., Spencer-Smith, M., Coleman, L., Anderson, P., Williams, J., Greenham, M., . . . Jacobs, R. (2010). Children's executive functions: Are they poorer after very early brain insult. *Neuropsychologia, 48*(7), 2041-2050. doi:10.1016/j.neuropsychologia.2010.03.025

Anshel, A., & Kipper, D. A. (1988). The Influence of Group Singing on Trust and Cooperation. *Journal of Music Therapy, 25*(3), 145-155. doi:10.1093/jmt/25.3.145

Arbuthnott, K., & Frank, J. (2000). Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. *J Clin Exp Neuropsychol, 22*(4), 518-528. doi:10.1076/1380-3395(200008)22:4;1-0;ft518

Arenas-Pinto, A., Castro, H., Melvin, D., Le Prevost, M., Foster, C., Sturgeon, K., . . . Judd, A. (2019). *Focused Cognitive Function Testing in Young People with Perinatal HIV in England*. Paper presented at the CROI, Seattle, Washington. https://www.croiconference.org/sessions/focused-cognitive-function-testing-young-people-perinatal-hiv-england

Arends, R. M., Nelwan, E. J., Soediro, R., van Crevel, R., Alisjahbana, B., Pohan, H. T., . . . Schellekens, A. F. A. (2019). Associations between impulsivity, risk behavior and HIV, HBV, HCV and syphilis seroprevalence among female prisoners in Indonesia: A cross-sectional study. *PLoS One, 14*(2), 13. doi:10.1371/journal.pone.0207970

Ascenso, S., Perkins, R., Atkins, L., Fancourt, D., & Williamon, A. (2018). Promoting well-being through group drumming with mental health service users and their carers. *Int J Qual Stud Health Well-being, 13*(1), 1484219. doi:10.1080/17482631.2018.1484219

Audet, C. M., Ngobeni, S., Graves, E., & Wagner, R. G. (2017). Mixed methods inquiry into traditional healers' treatment of mental, neurological and substance abuse disorders in rural South Africa. *PLoS One, 12*(12), e0188433. doi:10.1371/journal.pone.0188433

Babor, T. F., de la Fuente, J. R., Saunders, J. E., & Grant, M. (1992). *AUDIT: The Alcohol Use Disorders Identification Test. Guidelines for use in primary health care.* Retrieved from https://apps.who.int/iris/handle/10665/67205

Baddeley, A. (2003). Working memory: looking back and looking forward. *Nature Reviews Neuroscience, 4*(10), 829-839.

Baddeley, A. (2010). Working memory. *Current Biology, 20*(4), R136-R140. doi:10.1016/j.cub.2009.12.014

Baddeley, A. (2012). Working Memory: Theories, Models, and Controversies. *Annual review of psychology, 63*(1), 1-29. doi:10.1146/annurev-psych-120710-100422

Bagenda, D., Nassali, A., Kalyesubula, I., Sherman, B., Drotar, D., Boivin, M. J., & Olness, K. (2006). Health, neurologic, and cognitive status of HIV-infected, long-surviving, and antiretroviral-naive Ugandan children. *Pediatrics, 117*(3), 729-740. doi:10.1542/peds.2004-2699

Bailey, J., & Penhune, V. B. (2012). A sensitive period for musical training: contributions of age of onset and cognitive abilities. *Ann N Y Acad Sci, 1252*, 163-170. doi:10.1111/j.1749-6632.2011.06434.x

Baker, L. M., Paul, R. H., Heaps, J. H., Westerhaus, E., Chang, J. Y., Williams, S., . . . Ances, B. M. (2014). Impact of human immunodeficiency virus on neurocognition and risky behaviors in young adults. *J Neurovirol, 20*(5), 466-473. doi:10.1007/s13365-014-0264-4

Bamidis, P. D., Fissler, P., Papageorgiou, S. G., Zilidou, V., Konstantinidis, E. I., Billis, A. S., . . . Kolassa, I. (2015). Gains in cognition through combined cognitive and physical training: the role of training dosage and severity of

neurocognitive disorder. *Frontiers in Aging Neuroscience, 7*(152). doi:10.3389/fnagi.2015.00152

Bangirana, P., Boivin, M. J., Ruel, T., & Achan, J. (2015). *Long term effect of PI based ART versus NNRTI based ART on neuropsychological functioning in children*. Paper presented at the International Workshop on HIV Pediatrics, Vancouver, Canada. http://regist2.virology-education.com/abstractbook/2015_8.pdf

Bangirana, P., Giordani, B., John, C. C., Page, C., Opoka, R. O., & Boivin, M. J. (2009). Immediate neuropsychological and behavioral benefits of computerized cognitive rehabilitation in Ugandan pediatric cerebral malaria survivors. *Journal of Developmental and Behavioral Pediatrics, 30*(4), 310-318. doi:10.1097/DBP.0b013e3181b0f01b

Bangirana, P., Ruel, T., Boivin, M. J., Satish, P., Giron, L., Sikorskii, A., . . . Achan, J. (2016). *Subtype A is not associated with poorer neurocognitive outcomes than subtype D in HIV-infected children receiving antiretroviral therapy* Paper presented at the International Workshop on HIV Pediatrics, Durban, South Africa. http://www.infectiousdiseasesonline.com/wp-content/uploads/2016/07/8th-HIVPediatrics_abstractbook_web.pdf

Bass, J. K., Opoka, R., Familiar, I., Nakasujja, N., Sikorskii, A., Awadu, J., . . . Boivin, M. (2017). Randomized controlled trial of caregiver training for HIV-infected child neurodevelopment and caregiver well being. *Aids, 31*(13), 1877-1883. doi:10.1097/qad.0000000000001563

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1-3), 7-15.

Behrends, A., Müller, S., & Dziobek, I. (2012). Moving in and out of synchrony: A concept for a new intervention fostering empathy through interactional movement and dance. *The Arts in Psychotherapy, 39*(2), 107-116. doi:10.1016/j.aip.2012.02.003

Bender, R., Bunce, C., Clarke, M., Gates, S., Lange, S., Pace, N. L., & Thorlund, K. (2008). Attention should be given to multiplicity issues in systematic reviews. *J Clin Epidemiol, 61*(9), 857-865. doi:10.1016/j.jclinepi.2008.03.004

Benki-Nugent, S., Wamalwa, D., Laboso, T., Tamasha, N., Otieno, M., Bangirana, P., . . . John-Stewart, G. (2016). *HIV-infected children who initiated ART during infancy (early ART) have improved neurocognitive outcomes compared with late-treated children*. Paper presented at the International Workshop on HIV Pediatrics, Durban, South Africa. http://www.infectiousdiseasesonline.com/wp-content/uploads/2016/07/8th-HIVPediatrics_abstractbook_web.pdf

Bensimon, M., Amir, D., & Wolf, Y. (2008). Drumming through trauma: Music therapy with post-traumatic soldiers. *The Arts in Psychotherapy, 35*(1), 34-48. doi:10.1016/j.aip.2007.09.002

Bentler, P. M. (1990). Comparative fit indexes in structural models. *Psychological Bulletin, 107*(2), 238-246. doi:10.1037/0033-2909.107.2.238

Bergman Nutley, S., Darki, F., & Klingberg, T. (2014). Music practice is associated with development of working memory during childhood and adolescence. *Frontiers in Human Neuroscience, 7*. doi:10.3389/fnhum.2013.00926

Bernays, S., Jarrett, P., Kranzer, K., & Ferrand, R. A. (2014). Children growing up with HIV infection: the responsibility of success. *The Lancet, 383*(9925), 1355-1357. doi:10.1016/s0140-6736(13)62328-4

Best, J. R., Miller, P. H., & Naglieri, J. A. (2011). Relations between executive function and academic achievement from ages 5 to 17 in a large, representative national sample. *Learning and Individual Differences, 21*(4), 327-336. doi:10.1016/j.lindif.2011.01.007

Beusenberg, M., & Orley, J. (1994). *A user's guide to the Self Reporting Questionnaire (SRQ)*. Retrieved from http://apps.who.int/iris/bitstream/10665/61113/1/WHO_MNH_PSF_94.8.pdf

Bialystok, E., & Depape, A. M. (2009). Musical expertise, bilingualism, and executive functioning. *Journal of Experimental Psychology: Human Perception and Performance, 35*(2), 565-574. doi:10.1037/a0012735

Bidelman, G. M., Hutka, S., & Moreno, S. (2013). Tone language speakers and musicians share enhanced perceptual and cognitive abilities for musical pitch: evidence for bidirectionality between the domains of language and music. *PLoS One, 8*(4), e60676-e60676. doi:10.1371/journal.pone.0060676

Bishop, L., Bailes, F., & Dean, R. T. (2013). Musical Expertise and the Ability to Imagine Loudness. *PLoS One, 8*(2). doi:10.1371/journal.pone.0056052

Bisiacchi, P. S., Suppiej, A., & Laverda, A. (2000). Neuropsychological evaluation of neurologically asymptomatic HIV-infected children. *Brain Cogn, 43*(1-3), 49-52.

Bittman, B., Bruhn, K. T., Stevens, C., Westengard, J., & Umbach, P. O. (2003). Recreational Music-Making: A Cost-Effective Group Interdisciplinary Strategy for Reducing Burnout and Improving Mood States in Long-Term Care Workers. *Adv Mind Body Med, 19*(3-4), 4-15.

Bittman, B., Dickson, L., & Coddington, K. (2009). Creative musical expression as a catalyst for quality-of-life improvement in inner-city adolescents placed in a court-referred residential treatment program. *Adv Mind Body Med, 24*(1), 8-19.

Bittman, B. B., Snyder, C., Bruhn, K. T., Liebfreid, F., Stevens, C. K., Westengard, J., & Umbach, P. O. (2004). Recreational music-making: an integrative group intervention for reducing burnout and improving mood states in first year associate degree nursing students: insights and economic impact. *Int J Nurs Educ Scholarsh, 1*, Article12. doi:10.2202/1548-923x.1044

Blackett, P. S., & Payne, H. L. (2005). Health rhythms: A preliminary inquiry into group-drumming as experienced by participants on a structured day services programme for substance-misusers. *Drugs: Education, Prevention & Policy, 12*(6), 477-491. doi:10.1080/09687630500342881

Blakemore, S. J., & Choudhury, S. (2006). Development of the adolescent brain: implications for executive function and social cognition. *Journal of Child Psychology and Psychiatry, 47*(3-4), 296-312. doi:10.1111/j.1469-7610.2006.01611.x

Blanchette, N., Smith, M. L., King, S., Fernandes-Penney, A., & Read, S. (2002). Cognitive development in school-age children with vertically transmitted HIV infection. *Developmental Neuropsychology, 21*(3), 223-241. doi:10.1207/s15326942dn2103_1

Blokhuis, C., Peeters, C. F. W., Cohen, S., Scherpbier, H. J., Kuijpers, T. W., Reiss, P., . . . Pajkrt, D. (2019). Systemic and intrathecal immune activation in association with cerebral and cognitive outcomes in paediatric HIV. *Sci Rep, 9*(1), 8004. doi:10.1038/s41598-019-44198-z

Boebinger, D., Evans, S., Scott, S. K., Rosen, S., Lima, C. F., & Manly, T. (2015). Musicians and non-musicians are equally adept at perceiving masked speech. *Journal of the Acoustical Society of America, 137*(1), 378-387. doi:10.1121/1.4904537

Boh, B., Herholz, S. C., Lappe, C., & Pantev, C. (2011). Processing of Complex Auditory Patterns in Musicians and Nonmusicians. *PLoS One, 6*(7), 10. doi:10.1371/journal.pone.0021458

Boivin, M. J., Barlow-Mosha, L., Chernoff, M. C., Laughton, B., Zimmer, B., Joyce, C., . . . Team, I. P. S. (2018). Neuropsychological performance in African children with HIV enrolled in a multisite antiretroviral clinical trial. *Aids, 32*(2), 189-204. doi:10.1097/qad.0000000000001683

Boivin, M. J., Busman, R. A., Parikh, S. M., Bangirana, P., Page, C. F., Opoka, R. O., & Giordani, B. (2010). A Pilot Study of the Neuropsychological Benefits of Computerized Cognitive Rehabilitation in Ugandan Children With HIV. *Neuropsychology, 24*(5), 667-673. doi:10.1037/a0019312

Boivin, M. J., Chernoff, M., Laughton, B., Bwakura-Dangarembizi, M., Kamthunzi, P., Barlow-Mosha, L., . . . Palumbo, P. (2017). *Neuropsychological outcomes in a two year African-based pediatric observational study*. Paper presented at the CROI, Seattle, Washington, US. http://www.croiconference.org/sites/default/files/posters-2017/826_Boivin.pdf

Boivin, M. J., Chernoff, M., Laughton, B., Zimmer, B., Joyce, C., Barlow-Mosha, L., . . . Palumbo, P. (2018). *African Multi-Site 2-Year Study of Neurocognition in HIV Infected/Affected Children*. Paper presented at the CROI, Seattle, Washington. https://www.croiconference.org/sessions/african-multi-site-2-year-study-neurocognition-hiv-infectedaffected-children

Boivin, M. J., Green, S. D., Davies, A. G., Giordani, B., Mokili, J. K., & Cutting, W. A. (1995). A preliminary evaluation of the cognitive and motor effects of pediatric HIV infection in Zairian children. *Health Psychology, 14*(1), 13-21. doi:10.1037//0278-6133.14.1.13

Boivin, M. J., Nakasujja, N., Familiar-Lopez, I., Murray, S. M., Sikorskii, A., Awadu, J., . . . Bass, J. K. (2017). Effect of Caregiver Training on the Neurodevelopment of HIV-Exposed Uninfected Children and Caregiver Mental Health: A Ugandan Cluster-Randomized Controlled Trial. *Journal of Developmental and Behavioral Pediatrics, 38*(9), 753-764. doi:10.1097/DBP.0000000000000510

Boivin, M. J., Nakasujja, N., Sikorskii, A., Opoka, R. O., & Giordani, B. (2016). A Randomized Controlled Trial to Evaluate if Computerized Cognitive Rehabilitation Improves Neurocognition in Ugandan Children with HIV. *AIDS Res Hum Retroviruses, 32*(8), 743-755. doi:10.1089/aid.2016.0026

Boivin, M. J., Ruel, T. D., Boal, H. E., Bangirana, P., Cao, H., Eller, L. A., . . . Wong, J. K. (2010). HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children. *Aids, 24*(8), 1163-1170. doi:10.1097/qad.0b013e3283389dcc

Bornovalova, M. A., Gwadz, M. A., Kahler, C., Aklin, W. M., & Lejuez, C. W. (2008). Sensation seeking and risk-taking propensity as mediators in the relationship between childhood abuse and HIV-related risk behavior. *Child Abuse Negl, 32*(1), 99-109. doi:10.1016/j.chiabu.2007.04.009

Bos, K., Fox, N., Zeanah, C., & Nelson, C. (2009). Effects of early psychosocial deprivation on the development of memory and executive function. *Frontiers in Behavioral Neuroscience, 3*(16). doi:10.3389/neuro.08.016.2009

Botdorf, M., Rosenbaum, G. M., Patrianakos, J., Steinberg, L., & Chein, J. M. (2017). Adolescent risk-taking is predicted by individual differences in cognitive control over emotional, but not non-emotional, response conflict. *Cognition and Emotion, 31*(5), 972-979. doi:10.1080/02699931.2016.1168285

Bowmer, A., Mason, K., Knight, J., & Welch, G. (2018). Investigating the impact of a musical intervention on preschool children's executive function. *Front Psychol, 9*(DEC). doi:10.3389/fpsyg.2018.02389

Brahmbhatt, H., Boivin, M., Ssempijja, V., Kagaayi, J., Kigozi, G., Serwadda, D., . . . Gray, R. H. (2017). Impact of HIV and Atiretroviral Therapy on Neurocognitive Outcomes Among School-Aged Children. *Journal of Acquired Immune Deficiency Syndromes, 75*(1), 1-8. doi:10.1097/QAI.0000000000001305

Braun, V., Clarke, V., Hayfield, N., & Terry, G. (2018). Thematic Analysis. In P. Liamputtong (Ed.), *Handbook of Research Methods in Health Social Sciences* (pp. 1-18). Singapore: Springer Singapore.

Breslow, N. (1982). Design and analysis of case-control studies. *Annual Review of Public Health, 3*, 29-54. doi:10.1146/annurev.pu.03.050182.000333

Bruwer, B., Emsley, R., Kidd, M., Lochner, C., & Seedat, S. (2008). Psychometric properties of the Multidimensional Scale of Perceived Social Support in youth. *Compr Psychiatry, 49*(2), 195-201. doi:10.1016/j.comppsych.2007.09.002

Bugos, J. A., & DeMarie, D. (2017). The effects of a short-term music program on preschool children's executive functions. *Psychology of Music, 45*(6), 855-867. doi:10.1177/0305735617692666

Burdick, J. D., Roy, A. L., & Raver, C. C. (2013). Evaluating the Iowa Gambling Task as a Direct Assessment of Impulsivity with Low-Income Children. *Personality and Individual Differences, 55*(7), 771-776. doi:10.1016/j.paid.2013.06.009

Burkey, M. D., Murray, S. M., Bangirana, P., Familiar, I., Opoka, R. O., Nakasujja, N., . . . Bass, J. K. (2015). Executive function and attention-deficit/hyperactivity disorder in Ugandan children with perinatal HIV exposure. *Global Mental Health, 2*, e4. doi:10.1017/gmh.2015.2

Buss, C., Davis, E. P., Hobel, C. J., & Sandman, C. A. (2011). Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age. *Stress, 14*(6), 665-676. doi:10.3109/10253890.2011.623250

Calderone, D. J., Lakatos, P., Butler, P. D., & Castellanos, F. X. (2014). Entrainment of neural oscillations as a modifiable substrate of attention. *Trends Cogn Sci, 18*(6), 300-309. doi:10.1016/j.tics.2014.02.005

Campbell, W. K., Krusemark, E. A., Dyckman, K. A., Brunell, A. B., McDowell, J. E., Twenge, J. M., & Clementz, B. A. (2006). A magnetoencephalography

investigation of neural correlates for social exclusion and self-control. *Soc Neurosci, 1*(2), 124-134. doi:10.1080/17470910601035160
Casey, B. J., & Caudle, K. (2013). The Teenage Brain: Self Control. *Current Directions in Psychological Science, 22*(2), 82-87. doi:10.1177/0963721413480170
Casey, B. J., Getz, S., & Galvan, A. (2008). The adolescent brain. *Developmental review, 28*(1), 62-77. doi:10.1016/j.dr.2007.08.003
Cassotti, M., Aïte, A., Osmont, A., Houdé, O., & Borst, G. (2014). What have we learned about the processes involved in the Iowa Gambling Task from developmental studies? *Front Psychol, 5*, 915-915. doi:10.3389/fpsyg.2014.00915
Cauffman, E., Shulman, E. P., Steinberg, L., Claus, E., Banich, M. T., Graham, S., & Woolard, J. (2010). Age differences in affective decision making as indexed by performance on the Iowa Gambling Task. *Dev Psychol, 46*(1), 193. doi:10.1037/a0016128
Cerrillo-Urbina, A. J., Garcia-Hermoso, A., Sanchez-Lopez, M., Pardo-Guijarro, M. J., Santos Gomez, J. L., & Martinez-Vizcaino, V. (2015). The effects of physical exercise in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis of randomized control trials. *Child Care Health Dev, 41*(6), 779-788. doi:10.1111/cch.12255
Chacona, S. M. (2007). *Effect of world music drumming on auditory and visual attention skills of ADHD elementary students.* (68), Lynn University, Retrieved from https://spiral.lynn.edu/etds/26 Available from Ovid Technologies PsycINFO database. (7-A)
Chahroudi, A., Wagner, T. A., & Persaud, D. (2018). CNS Persistence of HIV-1 in Children: the Untapped Reservoir. *Curr HIV/AIDS Rep, 15*(5), 382-387. doi:10.1007/s11904-018-0412-1
Chang, L., Speck, O., Miller, E. N., Braun, J., Jovicich, J., Koch, C., . . . Ernst, T. (2001). Neural correlates of attention and working memory deficits in HIV patients. *Neurology, 57*(6), 1001-1007.
Chen, M., Hsu, J., Huang, K., Bai, Y., Ko, N., Su, T., . . . Chen, T. (2018). Sexually Transmitted Infection Among Adolescents and Young Adults With Attention-Deficit/Hyperactivity Disorder: A Nationwide Longitudinal Study. *Journal of the American Academy of Child & Adolescent Psychiatry, 57*(1), 48-53. doi:10.1016/j.jaac.2017.09.438
Cherian, V. I., Peltzer, K., & Cherian, L. (1998). The factor-structure of the Self Reporting Questionnaire (SRQ-20) in South Africa. *East Afr Med J, 75*(11), 654-656.
Chibanda, D., Benjamin, L., Weiss, H. A., & Abas, M. (2014). Mental, neurological, and substance use disorders in people living with HIV/AIDS in low- and middle-income countries. *Journal of Acquired Immune Deficiency Syndromes, 67 Suppl 1*, S54-67. doi:10.1097/qai.0000000000000258
Children's Act No. 38 of 2005, (2005).
Choi, K. W., Batchelder, A. W., Ehlinger, P. P., Safren, S. A., & O'Cleirigh, C. (2017). Applying network analysis to psychological comorbidity and health behavior: Depression, PTSD, and sexual risk in sexual minority men with trauma histories. *J Consult Clin Psychol, 85*(12), 1158-1170. doi:10.1037/ccp0000241

Ciccarelli, N., Fabbiani, M., Di Giambenedetto, S., Fanti, I., Baldonero, E., Bracciale, L., . . . Silveri, M. C. (2011). Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology, 76*(16), 1403-1409. doi:10.1212/WNL.0b013e31821670fb

Clayton, K. K., Swaminathan, J., Yazdanbakhsh, A., Zuk, J., Patel, A. D., & Kidd, G. (2016). Executive Function, Visual Attention and the Cocktail Party Problem in Musicians and Non-Musicians. *PLoS One, 11*(7), e0157638. doi:10.1371/journal.pone.0157638

Clayton, M. (2012). What is entrainment? Definition and applications in musical research. *Empirical musicology review, 7*(1-2), 49-56.

Clifford, D. B., & Ances, B. M. (2013). HIV-associated neurocognitive disorder. *The Lancet Infectious Diseases, 13*(11), 6-86. doi:10.1016/S1473-3099(13)70269-X

Cluver, L., Gardner, F., & Operario, D. (2009). Poverty and psychological health among AIDS-orphaned children in Cape Town, South Africa. *AIDS Care, 21*(6), 732-741. doi:10.1080/09540120802511885

Cluver, L., & Orkin, M. (2009). Cumulative risk and AIDS-orphanhood: interactions of stigma, bullying and poverty on child mental health in South Africa. *Social Science & Medicine, 69*(8), 1186-1193. doi:10.1016/j.socscimed.2009.07.033

Cluver, L. D., Gardner, F., & Operario, D. (2008). Effects of stigma on the mental health of adolescents orphaned by AIDS. *Journal of Adolescent Health, 42*(4), 410-417. doi:10.1016/j.jadohealth.2007.09.022

Cochrane Handbook for Systematic Reviews of Interventions. (2011). (J. P. Higgins & S. Green Eds. 5.1.0 ed.): The Cochrane Collaboration.

Cody, S. L., & Vance, D. E. (2016). The neurobiology of HIV and its impact on cognitive reserve: A review of cognitive interventions for an aging population. *Neurobiology of Disease, 92*, 144-156. doi:10.1016/j.nbd.2016.01.011

Cohen, E. E., Ejsmond-Frey, R., Knight, N., & Dunbar, R. I. (2010). Rowers' high: behavioural synchrony is correlated with elevated pain thresholds. *Biol Lett, 6*(1), 106-108. doi:10.1098/rsbl.2009.0670

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences, Second Edition*: Lawrence Erlbaum Associates.

Cohen, J. F., Gorski, M. T., Gruber, S. A., Kurdziel, L. B., & Rimm, E. B. (2016). The effect of healthy dietary consumption on executive cognitive functioning in children and adolescents: a systematic review. *British Journal of Nutrition, 116*(6), 989-1000. doi:10.1017/s0007114516002877

Cohen, S., & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychological Bulletin, 98*(2), 310-357.

Collishaw, S., Hammerton, G., Mahedy, L., Sellers, R., Owen, M. J., Craddock, N., . . . Thapar, A. (2016). Mental health resilience in the adolescent offspring of parents with depression: a prospective longitudinal study. *Lancet Psychiatry, 3*(1), 49-57. doi:10.1016/S2215-0366(15)00358-2

Cooper, E. R., Hanson, C., Diaz, C., Mendez, H., Abboud, R., Nugent, R., . . . Smeriglio, V. (1998). Encephalopathy and progression of human immunodeficiency virus disease in a cohort of children with perinatally acquired human immunodeficiency virus infection. Women and Infants Transmission Study Group. *J Pediatr, 132*(5), 808-812. doi:10.1016/s0022-3476(98)70308-7

Country Map of Africa Outline. (2019). Retrieved from https://www.worldatlas.com/webimage/countrys/af.htm
Cronbach, L. J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrika, 16*(3), 297-334. doi:10.1007/bf02310555
Crowell, C. S., Malee, K. M., Yogev, R., & Muller, W. J. (2014). Neurologic disease in HIV-infected children and the impact of combination antiretroviral therapy. *Reviews in Medical Virology, 24*(5), 316-331. doi:10.1002/rmv.1793
Cuevas, K., Deater-Deckard, K., Kim-Spoon, J., Watson, A. J., Morasch, K. C., & Bell, M. A. (2014). What's mom got to do with it? Contributions of maternal executive function and caregiving to the development of executive function across early childhood. *Dev Sci, 17*(2), 224-238. doi:doi:10.1111/desc.12073
D'Souza, A. A., Moradzadeh, L., & Wiseheart, M. (2018). Musical training, bilingualism, and executive function: working memory and inhibitory control. *Cognitive Research: Principles and Implications, 3*, 18. doi:10.1186/s41235-018-0095-6
D'Souza, A. A., & Wiseheart, M. (2018). Cognitive effects of music and dance training in children. *Archives of Scientific Psychology, 6*(1), 178-192. doi:10.1037/arc0000048
Da Silva, E. R., Dos Santos Baldin, M., & Dos Santos, F. H. (2017). Cognitive effects of numeracy musical training in Brazilian preschool children: A prospective pilot study. *Psychology and Neuroscience, 10*(3), 281-296. doi:10.1037/pne0000098
Dahl, V., Gisslen, M., Hagberg, L., Peterson, J., Shao, W., Spudich, S., . . . Palmer, S. (2013). An Example of Genetically Distinct HIV Type 1 Variants in Cerebrospinal Fluid and Plasma During Suppressive Therapy. *J Infect Dis, 209*(10), 1618-1622. doi:10.1093/infdis/jit805
Daniels, M. (2017). *Adolescents and HIV: Definitions and Disaggregation*. Retrieved from
Davidovich, S., Collishaw, S., Thapar, A. K., Harold, G., Thapar, A., & Rice, F. (2016). Do better executive functions buffer the effect of current parental depression on adolescent depressive symptoms? *J Affect Disord, 199*, 54-64. doi:10.1016/j.jad.2016.03.049
Davidson, L. L., Grigorenko, E. L., Boivin, M. J., Rapa, E., & Stein, A. (2015). A focus on adolescence to reduce neurological, mental health and substance-use disability. *Nature, 527*(7578), S161-166. doi:10.1038/nature16030
Davies, S. J., Lum, J. A., Skouteris, H., Byrne, L. K., & Hayden, M. J. (2018). Cognitive impairment during pregnancy: a meta-analysis. *Medical Journal of Australia, 208*(1), 35-40. doi:10.5694/mja17.00131
Davis-Craig, A. (2009). *Building Community: African Dancing and Drumming in the Little Village of Tallahassee, Florida.* (Doctor of Philosophy), Florida State University,
De Silva, M. J., Breuer, E., Lee, L., Asher, L., Chowdhary, N., Lund, C., & Patel, V. (2014). Theory of Change: a theory-driven approach to enhance the Medical Research Council's framework for complex interventions. *Trials, 15*(1), 267. doi:10.1186/1745-6215-15-267
Deater-Deckard, K. (2014). Family Matters:Intergenerational and Interpersonal Processes of Executive Function and Attentive Behavior. *Current*

Directions in Psychological Science, 23(3), 230-236. doi:10.1177/0963721414531597

Degé, F., Kubicek, C., & Schwarzer, G. (2011). Music Lessons and Intelligence: A Relation Mediated by Executive Functions. *Music Perception: An Interdisciplinary Journal, 29*(2), 195-201. doi:10.1525/mp.2011.29.2.195

Demeyere, N., Haupt, M., Strobel, L., Milosevich, E., Webb, S., Moore, M. J., . . . Duta, M. (2019). The OCS-Plus: validation of a tablet based short cognitive screening tool for mild cognitive impairment. *(manuscript in preparation)*.

DePrince, A. P., Weinzierl, K. M., & Combs, M. D. (2009). Executive function performance and trauma exposure in a community sample of children. *Child Abuse Negl, 33*(6), 353-361. doi:10.1016/j.chiabu.2008.08.002

Derefinko, K. J., Peters, J. R., Eisenlohr-Moul, T. A., Walsh, E. C., Adams, Z. W., & Lynam, D. R. (2014). Relations between trait impulsivity, behavioral impulsivity, physiological arousal, and risky sexual behavior among young men. *Arch Sex Behav, 43*(6), 1149-1158. doi:10.1007/s10508-014-0327-x

Desmond, K., Milburn, N., Richter, L., Tomlinson, M., Greco, E., van Heerden, A., . . . Rotheram-Borus, M. J. (2012). Alcohol consumption among HIV-positive pregnant women in KwaZulu-Natal, South Africa: prevalence and correlates. *Drug Alcohol Depend, 120*(1-3), 113-118. doi:10.1016/j.drugalcdep.2011.07.004

Diamond, A. (2013). Executive functions. *Annual review of psychology, 64*, 135-168. doi:10.1146/annurev-psych-113011-143750

Diamond, A., Barnett, W. S., Thomas, J., & Munro, S. (2007). Preschool program improves cognitive control. *Science, 318*(5855), 1387-1388. doi:10.1126/science.1151148

Diamond, A., & Lee, K. (2011). Interventions Shown to Aid Executive Function Development in Children 4 to 12 Years Old. *Science, 333*(6045), 959-964. doi:10.1126/science.1204529

Diamond, A., & Ling, D. S. (2016). Conclusions about interventions, programs, and approaches for improving executive functions that appear justified and those that, despite much hype, do not. *Dev Cogn Neurosci, 18*, 34-48. doi:10.1016/j.dcn.2015.11.005

Dickerson, D., Robichaud, F., Teruya, C., Nagaran, K., & Hser, Y. (2012). Utilizing drumming for American Indians/Alaska natives with substance use disorders: A focus group study. *Am J Drug Alcohol Abuse, 38*(5), 505-510. doi:10.3109/00952990.2012.699565

Ding, Y., Gray, K., Forrence, A., Wang, X., & Huang, J. (2018). A behavioral study on tonal working memory in musicians and non-musicians. *PLoS One, 13*(8). doi:10.1371/journal.pone.0201765

Dittinger, E., Valizadeh, S. A., Jancke, L., Besson, M., & Elmer, S. (2018). Increased functional connectivity in the ventral and dorsal streams during retrieval of novel words in professional musicians. *Human Brain Mapping, 39*(2), 722-734. doi:10.1002/hbm.23877

Doi, S. A., Barendregt, J. J., Khan, S., Thalib, L., & Williams, G. M. (2015a). Advances in the meta-analysis of heterogeneous clinical trials II: The quality effects model. *Contemporary Clinical Trials, 45*(Pt A), 123-129. doi:10.1016/j.cct.2015.05.010

Doi, S. A., Barendregt, J. J., Khan, S., Thalib, L., & Williams, G. M. (2015b). Simulation Comparison of the Quality Effects and Random Effects

Methods of Meta-analysis. *Epidemiology, 26*(4), e42-44. doi:10.1097/ede.0000000000000289
Doi, S. A., & Thalib, L. (2008). A quality-effects model for meta-analysis. *Epidemiology, 19*(1), 94-100. doi:10.1097/EDE.0b013e31815c24e7
Dos Reis, H. L. B., Araujo, K. D. S., Ribeiro, L. P., Da Rocha, D. R., Rosato, D. P., Passos, M. R. L., & Merçon De Vargas, P. R. (2015). Preterm birth and fetal growth restriction in HIV-infected Brazilian pregnant women. *Revista do Instituto de Medicina Tropical de Sao Paulo, 57*(2), 111-120. doi:10.1590/S0036-46652015000200003
Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health, 52*, 377-384. doi:10.1136/jech.52.6.377
du Plessis, S., Vink, M., Joska, J. A., Koutsilieri, E., Bagadia, A., Stein, D. J., & Emsley, R. (2015). HIV Infection Is Associated with Impaired Striatal Function during Inhibition with Normal Cortical Functioning on Functional MRI. *Journal of the International Neuropsychological Society, 21*(9), 722-731. doi:10.1017/s1355617715000971
Dunfee, R., Thomas, E. R., Gorry, P. R., Wang, J., Ancuta, P., & Gabuzda, D. (2006). Mechanisms of HIV-1 neurotropism. *Current HIV Research, 4*(3), 267-278. doi:10.2174/157016206777709500
Eckard, A. R., Rosebush, J. C., O'Riordan, M. A., Graves, C. C., Alexander, A., Grover, A. K., . . . McComsey, G. A. (2017). Neurocognitive dysfunction in HIV-infected youth: investigating the relationship with immune activation. *Antivir Ther, 22*(8), 669-680. doi:10.3851/imp3157
Edén, A., Fuchs, D., Hagberg, L., Nilsson, S., Spudich, S., Svennerholm, B., . . . Gisslén, M. (2010). HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. *J Infect Dis, 202*(12), 1819-1825. doi:10.1086/657342
Ellis, R. J., Moore, D. J., Childers, M. E., Letendre, S., McCutchan, J. A., Wolfson, T., . . . Group, f. t. H. (2002). Progression to Neuropsychological Impairment in Human Immunodeficiency Virus Infection Predicted by Elevated Cerebrospinal Fluid Levels of Human Immunodeficiency Virus RNA. *JAMA Neurology, 59*(6), 923-928. doi:10.1001/archneur.59.6.923
Elmer, S., Greber, M., Pushparaj, A., Kuhnis, J., & Jancke, L. (2017). Faster native vowel discrimination learning in musicians is mediated by an optimization of mnemonic functions. *Neuropsychologia, 104*, 64-75. doi:10.1016/j.neuropsychologia.2017.08.001
Ene, L., Marcotte, T. D., Umlauf, A., Grancea, C., Temereanca, A., Bharti, A., . . . Ruta, S. M. (2016). Latent toxoplasmosis is associated with neurocognitive impairment in young adults with and without chronic HIV infection. *J Neuroimmunol, 299*, 1-7. doi:10.1016/j.jneuroim.2016.08.003
Engle, P. L., & Black, M. M. (2008). The Effect of Poverty on Child Development and Educational Outcomes. *Ann N Y Acad Sci, 1136*(1), 243-256. doi:10.1196/annals.1425.023
Epstein, L. G., Sharer, L. R., Oleske, J. M., Connor, E. M., Goudsmit, J., Bagdon, L., . . . Koenigsberger, M. R. (1986). Neurologic manifestations of human immunodeficiency virus infection in children. *Pediatrics, 78*(4), 678-687.

Ernst, T., Chang, L., & Arnold, S. (2003). Increased glial metabolites predict increased working memory network activation in HIV brain injury. *Neuroimage, 19*(4), 1686-1693. doi:10.1016/s1053-8119(03)00232-5

Evan, M., Risher, K., Zungu, N., Shisana, O., Moyo, S., Celentano, D. D., . . . Rehle, T. M. (2016). Age-disparate sex and HIV risk for young women from 2002 to 2012 in South Africa. *J Int AIDS Soc, 19*(1), 21310-21310. doi:10.7448/IAS.19.1.21310

Ezeamama, A. E., Kizza, F. N., Zalwango, S. K., Nkwata, A. K., Zhang, M., Rivera, M. L., . . . Whalen, C. C. (2016). Perinatal HIV Status and Executive Function During School-Age and Adolescence: A Comparative Study of Long-Term Cognitive Capacity Among Children From a High HIV Prevalence Setting. *Medicine (Baltimore), 95*(17), e3438. doi:10.1097/md.0000000000003438

Familiar, I., Chernoff, M., Ruisenor-Escudero, H., Laughton, B., Joyce, C., Fairlie, L., . . . Boivin, M. (2018). *Caregiver depression and child neuropsychological outcomes in an observational study carried out in four sub-Saharan countries*. Paper presented at the Aids, Amsterdam, Netherlands. http://www.aids2018.org/Portals/4/File/AIDS2018_Abstract_book.pdf?ver=2018-08-06-160624-427

Familiar, I., Nakasujja, N., Bass, J., Sikorskii, A., Murray, S. M., Ruisenor-Escudero, H., . . . Boivin, M. J. (2016). Caregivers' depressive symptoms and parent-report of child executive function among young children in Uganda. *Learning and Individual Differences, 46*, 17-24. doi:10.1016/j.lindif.2015.01.012

Familiar, I., Ruisenor-Escudero, H., Giordani, B., Bangirana, P., Nakasujja, N., Opoka, R., & Boivin, M. (2015). Use of the Behavior Rating Inventory of Executive Function and Child Behavior Checklist in Ugandan children with HIV or a history of severe malaria. *Journal of Developmental and Behavioral Pediatrics, 36*(4), 277-284.

Fancourt, D., Perkins, R., Ascenso, S., Atkins, L., Kilfeather, S., Carvalho, L., . . . Williamon, A. (2016). Group drumming modulates cytokine response in mental health services users: A preliminary study. *Psychother Psychosom, 85*(1), 53-55. doi:10.1159/000431257

Fancourt, D., Perkins, R., Ascenso, S., Carvalho, L. A., Steptoe, A., & Williamon, A. (2016). Effects of group drumming interventions on anxiety, depression, social resilience and inflammatory immune response among mental health service users. *PLoS One, 11*(3), e0151136. doi:10.1371/journal.pone.0151136

Fasano, M. C., Semeraro, C., Cassibba, R., Kringelbach, M. L., Monacis, L., de Palo, V., . . . Brattico, E. (2019). Short-Term Orchestral Music Training Modulates Hyperactivity and Inhibitory Control in School-Age Children: A Longitudinal Behavioural Study. *Front Psychol, 10*, 750-750. doi:10.3389/fpsyg.2019.00750

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods, 41*(4), 1149-1160. doi:10.3758/brm.41.4.1149

Faulkner, S., Wood, L., Ivery, P., & Donovan, R. (2012). It Is Not Just Music and Rhythm . . . Evaluation of a Drumming-Based Intervention to Improve the

Social Wellbeing of Alienated Youth. *Children Australia, 37*(1), 31-39. doi:10.1017/cha.2012.5
Fauvel, B., Groussard, M., Mutlu, J., Arenaza-Urquijo, E. M., Eustache, F., Desgranges, B., & Platel, H. (2014). Musical practice and cognitive aging: two cross-sectional studies point to phonemic fluency as a potential candidate for a use-dependent adaptation. *Frontiers in Aging Neuroscience, 6*. doi:10.3389/fnagi.2014.00227
Flaugnacco, E., Lopez, L., Terribili, C., Montico, M., Zoia, S., & Schon, D. (2015). Music training increases phonological awareness and reading skills in developmental dyslexia: A randomized control trial. *PLoS One, 10*(9).
Flores, K. (2011). *African drumming as a medium to promote emotional and social well-being of children aged 7 to 12 in residential care* (PhD in Musicology), University of Pretoria,
Ford, C. B., Kim, H. Y., Brown, L. K., Aber, J. L., & Sheridan, M. A. (2019). A cognitive assessment tool designed for data collection in the field in low- and middle-income countries. *Research in Comparative and International Education, 14*(1), 141-157. doi:10.1177/1745499919829217
Foster, S. B., Lu, M., Glaze, D. G., Reuben, J. M., Harris, L. L., Cohen, E. N., . . . Shearer, W. T. (2012). Associations of cytokines, sleep patterns, and neurocognitive function in youth with HIV infection. *Clinical Immunology, 144*(1), 13-23. doi:10.1016/j.clim.2012.04.004
Foulkes, L., & Blakemore, S. J. (2016). Is there heightened sensitivity to social reward in adolescence? *Current Opinion in Neurobiology, 40*, 81-85. doi:10.1016/j.conb.2016.06.016
Franklin, M. S., Moore, K. S., Yip, C. Y., Jonides, J., Rattray, K., & Moher, J. (2008). The effects of musical training on verbal memory. *Psychology of Music, 36*(3), 353-365. doi:10.1177/0305735607086044
Friedman, N. P., Miyake, A., Robinson, J. L., & Hewitt, J. K. (2011). Developmental trajectories in toddlers' self-restraint predict individual differences in executive functions 14 years later: A behavioral genetic analysis. *Dev Psychol, 47*(5), 1410-1430. doi:10.1037/a0023750
Friedman, N. P., Miyake, A., Young, S. E., DeFries, J. C., Corley, R. P., & Hewitt, J. K. (2008). Individual differences in executive functions are almost entirely genetic in origin. *Journal of Experimental Psychology: General, 137*(2), 201-225. doi:10.1037/0096-3445.137.2.201
Furuya-Kanamori, L., Barendregt, J. J., & Doi, S. A. R. (2018). A new improved graphical and quantitative method for detecting bias in meta-analysis. *Int J Evid Based Healthc, 16*(4), 195-203. doi:10.1097/xeb.0000000000000141
Gansler, D. A., Jerram, M. W., Vannorsdall, T. D., & Schretlen, D. J. (2011). Does the Iowa Gambling Task Measure Executive Function? *Archives of Clinical Neuropsychology, 26*(8), 706-717. doi:10.1093/arclin/acr082
Garcia-Navarro, C., Gonzalez-Tome, M. I., Zamora, B., Navarro Gomez, M., Cortes, L., Escosa, M., . . . Lopez, C. (2013). *Attentional Deficits in a Paediatric HIV-cohort. NeuroCoRISpeS*. Paper presented at the European AIDS Conference, Brussels, Belgium. http://www.abstractserver.com/eacsabstractarchive/
Garvie, P. A., Brummel, S. S., Allison, S. M., Malee, K. M., Mellins, C. A., Wilkins, M. L., . . . Nichols, S. L. (2017). Roles of Medication Responsibility, Executive and Adaptive Functioning in Adherence for Children and

Adolescents With Perinatally Acquired HIV. *Pediatr Infect Dis J, 36*(8), 751-757. doi:10.1097/inf.0000000000001573
Gebauer, L., Kringelbach, M. L., & Vuust, P. (2012). Ever-changing cycles of musical pleasure: The role of dopamine and anticipation. *Psychomusicology: Music, Mind, and Brain, 22*(2), 152-167. doi:10.1037/a0031126
Gelding, R. W., Thompson, W. F., & Johnson, B. W. (2015). The pitch imagery arrow task: Effects of musical training, vividness, and mental control. *PLoS One, 10*(3). doi:10.1371/journal.pone.0121809
George, E. M., & Coch, D. (2011). Music training and working memory: an ERP study. *Neuropsychologia, 49*(5), 1083-1094. doi:10.1016/j.neuropsychologia.2011.02.001
Giordani, B., Novak, B., Sikorskii, A., Bangirana, P., Nakasujja, N., Winn, B. M., & Boivin, M. J. (2015). Designing and evaluating Brain Powered Games for cognitive training and rehabilitation in at-risk African children. *Global Mental Health, 2*. doi:10.1017/gmh.2015.5
Goldberg, D. P., Gater, R., Sartorius, N., Ustun, T. B., Piccinelli, M., Gureje, O., & Rutter, C. (1997). The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med, 27*(1), 191-197. doi:10.1017/s0033291796004242
Goldberg, D. P., & Hillier, V. F. (1979). A scaled version of the General Health Questionnaire. *Psychol Med, 9*(1), 139-145. doi:10.1017/S0033291700021644
Gomez-Olive, F. X., Angotti, N., Houle, B., Klipstein-Grobusch, K., Kabudula, C., Menken, J., . . . Clark, S. J. (2013). Prevalence of HIV among those 15 and older in rural South Africa. *AIDS Care, 25*(9), 1122-1128. doi:10.1080/09540121.2012.750710
Gregoire, L., Perruchet, P., & Poulin-Charronnat, B. (2015). How Does Stroop Interference Change With Practice? A Reappraisal From the Musical Stroop Paradigm. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 41*(2), 417-425. doi:10.1037/xlm0000044
Guhn, M., Emerson, S. D., & Gouzouasis, P. (2019). A population-level analysis of associations between school music participation and academic achievement. *Journal of Educational psychology*, No Pagination Specified-No Pagination Specified. doi:10.1037/edu0000376
Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa. (2006). Retrieved from Pretoria, South Africa:
Guo, X., Ohsawa, C., Suzuki, A., & Sekiyama, K. (2018). Improved digit span in children after a 6-week intervention of playing a musical instrument: An exploratory randomized controlled trial. *Front Psychol, 8*. doi:10.3389/fpsyg.2017.02303
Habibi, A., Damasio, A., Ilari, B., Elliott Sachs, M., & Damasio, H. (2018). Music training and child development: a review of recent findings from a longitudinal study. *Ann N Y Acad Sci, 1423*(1), 73-81. doi:10.1111/nyas.13606
Hackman, D. A., & Farah, M. J. (2009). Socioeconomic status and the developing brain. *Trends Cogn Sci, 13*(2), 65-73. doi:10.1016/j.tics.2008.11.003
Hannigan, P. D., & McBride, D. L. (2011). Drumming with intimate partner violence clients: Getting into the beat; Therapists' views on the use of

drumming in family violence treatment groups. *Canadian Art Therapy Association Journal, 24*(1), 2-9. doi:10.1080/08322473.2011.11434787

Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological Psychiatry, 63*(10), 927-934. doi:10.1016/j.biopsych.2008.03.015

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics, 42*(2), 377-381. doi:10.1016/j.jbi.2008.08.010

Hedayati, N., Schibli, K., & D'Angiulli, A. (2016). El Sistema-inspired ensemble music training is associated with changes in children's neurocognitive functional integration: preliminary ERP evidence. *Neurocase, 22*(6), 538-547. doi:10.1080/13554794.2016.1241885

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. San Diego, CA: Academic Press.

Hermetet-Lindsay, K. D., Correia, K. F., Williams, P. L., Smith, R., Malee, K. M., Mellins, C. A., . . . Pediatric, H. I. V. A. C. S. (2017). Contributions of Disease Severity, Psychosocial Factors, and Cognition to Behavioral Functioning in US Youth Perinatally Exposed to HIV. *AIDS Behav, 21*(9), 2703-2715. doi:10.1007/s10461-016-1508-5

Herrero, L., & Carriedo, N. (2018). Differences in updating processes between musicians and non-musicians from late childhood to adolescence. *Learning and Individual Differences, 61*, 188-195. doi:10.1016/j.lindif.2017.12.006

Hinkin, C. H., Castellon, S. A., Durvasula, R. S., Hardy, D. J., Lam, M. N., Mason, K. I., . . . Stefaniak, M. (2002). Medication adherence among HIV+ adults - Effects of cognitive dysfunction and regimen complexity. *Neurology, 59*(12), 1944-1950. doi:10.1212/01.wnl.0000038347.48137.67

Ho, P., Tsao, J. C., Bloch, L., & Zeltzer, L. K. (2011). The impact of group drumming on social-emotional behavior in low-income children. *Evidence-based Complementary and Alternative Medicine, 2011*, 250708. doi:10.1093/ecam/neq072

Hoare, J., Fouche, J. P., Spottiswoode, B., Donald, K., Philipps, N., Bezuidenhout, H., . . . Stein, D. (2012). A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naive "slow progressors". *J Neurovirol, 18*(3), 205-212. doi:10.1007/s13365-012-0099-9

Hoare, J., Heany, S. J., Fouche, J. P., Phillips, N., Joska, J. A., Myer, L., . . . Stein, D. J. (2019). Initiation of antiretroviral therapy after the critical neuronal developmental period of the second postnatal year affects white matter microstructure in adolescents living with HIV. *J Neurovirol*. doi:10.1007/s13365-018-0712-7

Hoare, J., Myer, L., Heany, S., Fouche, J. P., Phillips, N., Zar, H., & Stein, D. (2019). *Systemic inflammation and structural brain changes in perinatally HIV+ adolescents*. Paper presented at the CROI, Seattle, Washington. https://www.croiconference.org/sessions/systemic-inflammation-and-structural-brain-changes-perinatally-hiv-adolescents

Hoare, J., Phillips, N., Joska, J. A., Paul, R., Donald, K. A., Stein, D. J., & Thomas, K. G. (2016). Applying the HIV-associated neurocognitive disorder diagnostic criteria to HIV-infected youth. *Neurology, 87*(1), 86-93. doi:10.1212/wnl.0000000000002669

Hochhauser, C., Gaur, S., Marone, R., & Lewis, M. (2008). The impact of environmental risk factors on HIV-associated cognitive decline in children. *AIDS Care, 20*(6), 692-699. doi:10.1080/09540120701693982

Hodes, R., Cluver, L., Barron, P., Dlamini, N. R., Madisha, L., Mazibuko, N., . . . Schultz, L. (2017). *National Adolescent & Youth Health Policy 2017*. Pretoria Retrieved from http://www.health.gov.za/index.php/shortcodes/2015-03-29-10-42-47/2015-04-30-08-18-10/2015-04-30-08-25-54?download=2366:adolescent-and-youth-policy-4th-sept.

Hodes, R., Cluver, L., Toska, E., & Vale, B. (2018). Pesky metrics: the challenges of measuring ART adherence among HIV-positive adolescents in South Africa. *Critical Public Health*, 1-12. doi:10.1080/09581596.2018.1550253

Holding, P., Anum, A., van de Vijver, F. J. R., Vokhiwa, M., Bugase, N., Hossen, T., . . . Gomes, M. (2018). Can we measure cognitive constructs consistently within and across cultures? Evidence from a test battery in Bangladesh, Ghana, and Tanzania. *Applied Neuropsychology: Child, 7*(1), 1-13. doi:10.1080/21622965.2016.1206823

Holmes, J., Gathercole, S. E., & Dunning, D. L. (2009). Adaptive training leads to sustained enhancement of poor working memory in children. *Dev Sci, 12*(4), F9-15. doi:10.1111/j.1467-7687.2009.00848.x

Holochwost, S. J., Propper, C. B., Wolf, D. P., Willoughby, M. T., Fisher, K. R., Kolacz, J., . . . Jaffee, S. R. (2017). Music education, academic achievement, and executive functions. *Psychology of Aesthetics, Creativity, and the Arts, 11*(2), 147-166. doi:10.1037/aca0000112

Hooper, P., Jutai, J. W., Strong, G., & Russell-Minda, E. (2008). Age-related macular degeneration and low-vision rehabilitation: a systematic review. *Canadian Journal of Ophthalmology, 43*(2), 180-187. doi:10.3129/i08-001

Hosain, G. M. M., Berenson, A. B., Tennen, H., Bauer, L. O., & Wu, Z. H. (2012). Attention deficit hyperactivity symptoms and risky sexual behavior in young adult women. *Journal of Women's Health, 21*(4), 463-468. doi:10.1089/jwh.2011.2825

Hou, J., Chen, C., Wang, Y., Liu, Y., He, Q., Li, J., & Dong, Q. (2014). Superior pitch identification ability is associated with better executive functions. *Psychomusicology: Music, mind and brain, 24*(2), 136-146. doi:10.1037/a0036963

Hove, M. J., & Risen, J. L. (2009). It's All in the Timing: Interpersonal Synchrony Increases Affiliation. *Social Cognition, 27*(6), 949-960. doi:10.1521/soco.2009.27.6.949

Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal, 6*(1), 1-55. doi:10.1080/10705519909540118

Hu, L., Bentler, P. M., & Kano, Y. (1992). Can test statistics in covariance structure analysis be trusted? *Psychological Bulletin, 112*(2), 351-362. doi:10.1037/0033-2909.112.2.351

Hughes, C., Ensor, R., Wilson, A., & Graham, A. (2010). Tracking executive function across the transition to school: a latent variable approach. *Developmental Neuropsychology, 35*(1), 20-36. doi:10.1080/87565640903325691

Hughes, C., Roman, G., Hart, M. J., & Ensor, R. (2013). Does maternal depression predict young children's executive function? – a 4-year longitudinal study. *Journal of Child Psychology and Psychiatry, 54*(2), 169-177. doi:10.1111/jcpp.12014

Hughes, M. M., Linck, J. A., Bowles, A. R., Koeth, J. T., & Bunting, M. F. (2014). Alternatives to switch-cost scoring in the task-switching paradigm: Their reliability and increased validity. *Behav Res Methods, 46*(3), 702-721. doi:10.3758/s13428-013-0411-5

Humphreys, G. W., Duta, M. D., Montana, L., Demeyere, N., McCrory, C., Rohr, J., . . . Berkman, L. (2017). Cognitive Function in Low-Income and Low-Literacy Settings: Validation of the Tablet-Based Oxford Cognitive Screen in the Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI). *J Gerontol B Psychol Sci Soc Sci, 72*(1), 38-50. doi:10.1093/geronb/gbw139

ICMJE. (2017). Defining the Role of Authors and Contributors. Retrieved from http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) Current Step 4 version dated 9 November 2016. (2016). Retrieved from

Ireland, K., Parker, A., Foster, N., & Penhune, V. (2018). Rhythm and Melody tasks for school-aged children with and without musical training: Age-equivalent scores and reliability. *Front Psychol, 9*(APR). doi:10.3389/fpsyg.2018.00426

Jacobs, R., Harvey, A. S., & Anderson, V. (2007). Executive Function Following Focal Frontal Lobe Lesions: Impact of Timing of Lesion on Outcome. *Cortex, 43*(6), 792-805. doi:10.1016/S0010-9452(08)70507-0

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences, 105*(19), 6829-6833. doi:10.1073/pnas.0801268105

Jankiewicz, M., Holmes, M. J., Taylor, P. A., Cotton, M. F., Laughton, B., van der Kouwe, A. J. W., & Meintjes, E. M. (2017). White Matter Abnormalities in Children with HIV Infection and Exposure. *Frontiers in Neuroanatomy, 11*, 9. doi:10.3389/fnana.2017.00088

Janus, M., Lee, Y., Moreno, S., & Bialystok, E. (2016). Effects of short-term music and second-language training on executive control. *Journal of Experimental Child Psychology, 144*, 84-97. doi:10.1016/j.jecp.2015.11.009

Jaschke, A. C., Honing, H., & Scherder, E. J. A. (2018). Longitudinal Analysis of Music Education on Executive Functions in Primary School Children. *Frontiers in Neuroscience, 12*, 11. doi:10.3389/fnins.2018.00103

Jentzsch, I., Mkrtchian, A., & Kansal, N. (2014). Improved effectiveness of performance monitoring in amateur instrumental musicians. *Neuropsychologia, 52*, 117-124. doi:10.1016/j.neuropsychologia.2013.09.025

John, C. C., Bangirana, P., Byarugaba, J., Opoka, R. O., Idro, R., Jurek, A. M., . . . Boivin, M. J. (2008). Cerebral malaria in children is associated with long-

term cognitive impairment. *Pediatrics, 122*(1), e92-e99. doi:10.1542/peds.2007-3709
Jöreskog, K. G. (1999). *How Large Can a Standardizsed Coefficient be?* Retrieved from http://www.statmodel.com/download/Joreskog.pdf
Jöreskog, K. G., & Sörbom, D. (1993). *LISREL 8: Structural equation modeling with the SIMPLIS command language*. Hillsdale, NJ, US: Lawrence Erlbaum Associates, Inc.
Joret, M. E., Germeys, F., & Gidron, Y. (2017). Cognitive inhibitory control in children following early childhood music education. *Musicae Scientiae, 21*(3), 303-315. doi:10.1177/1029864916655477
Joseph, J., Cinque, P., Colosi, D., Dravid, A., Ene, L., Fox, H., . . . Spudich, S. (2016). Highlights of the Global HIV-1 CSF Escape Consortium Meeting, 9 June 2016, Bethesda, MD, USA. *Journal of virus eradication, 2*(4), 243-250.
Joubert, J., Bradshaw, D., Kabudula, C., Rao, C., Kahn, K., Mee, P., . . . Vos, T. (2014). Record-linkage comparison of verbal autopsy and routine civil registration death certification in rural north-east South Africa: 2006-09. *International Journal of Epidemiology, 43*(6), 1945-1958. doi:10.1093/ije/dyu156
Judd, A., Le Prevost, M., Melvin, D., Arenas-Pinto, A., Parrott, F., Winston, A., . . . Gibb, D. M. (2016). Cognitive Function in Young Persons with and Without Perinatal HIV in the AALPHI Cohort in England: Role of Non-HIV-Related Factors. *Clinical Infectious Diseases, 63*(10), 1380-1387. doi:10.1093/cid/ciw568
Judd, A., Nunn, A., Le Prevost, M., Sturgeon, K., Gibb, D. M., Arenas-Pinto, A., . . . Winston, A. (2015). Neurocognitive function in perinatally HIV-infected young people and HIV-negative siblings in England. *Hiv Medicine, 16*, 9. doi:10.1111/hiv.12264
Kabudula, C. W., Houle, B., Collinson, M. A., Kahn, K., Tollman, S., & Clark, S. (2016). Assessing Changes in Household Socioeconomic Status in Rural South Africa, 2001–2013: A Distributional Analysis Using Household Asset Indicators. *Social Indicators Research*, 1-27. doi:10.1007/s11205-016-1397-z
Kahn, K., Collinson, M. A., Gomez-Olive, F. X., Mokoena, O., Twine, R., Mee, P., . . . Tollman, S. M. (2012). Profile: Agincourt health and socio-demographic surveillance system. *International Journal of Epidemiology, 41*(4), 988-1001. doi:10.1093/ije/dys115
Kamat, R., Brown, G. G., Bolden, K., Fennema-Notestein, C., Archibald, S., Marcotte, T. D., . . . Group, T. (2014). Apathy is associated with white matter abnormalities in anterior, medial brain regions in persons with HIV infection. *J Clin Exp Neuropsychol, 36*(8), 854-866. doi:10.1080/13803395.2014.950636
Kamijo, K., Pontifex, M. B., O'Leary, K. C., Scudder, M. R., Wu, C., Castelli, D. M., & Hillman, C. H. (2011). The effects of an afterschool physical activity program on working memory in preadolescent children. *Dev Sci, 14*(5), 1046-1058. doi:10.1111/j.1467-7687.2011.01054.x
Kapetanovic, S., Griner, R., Zeldow, B., Nichols, S., Leister, E., Gelbard, H. A., . . . Williams, P. L. (2014). Biomarkers and neurodevelopment in perinatally HIV-infected or exposed youth: a structural equation model analysis. *Aids, 28*(3), 355-364. doi:10.1097/qad.0000000000000072

Kapetanovic, S., Leister, E., Nichols, S., Miller, T., Tassiopoulos, K., Hazra, R., . . . Williams, P. L. (2010). Relationships between markers of vascular dysfunction and neurodevelopmental outcomes in perinatally HIV-infected youth. *Aids, 24*(10), 1481-1491. doi:10.1097/QAD.0b013e32833a241b

Kaplan, C. D. (2000). *The short term effects of small group hand drumming on mood, group cohesiveness and rhythm perception.* (Doctoral dissertation), University of Connecticut, Retrieved from http://ovidsp.ovid.com/ Available from Ovid Technologies PsycINFO database. (11-B)

Kar, B. R., Rao, S. L., & Chandramouli, B. A. (2008). Cognitive development in children with chronic protein energy malnutrition. *Behavioral and Brain Functions, 4*, 31-31. doi:10.1186/1744-9081-4-31

Kaviani, H., Mirbaha, H., Pournaseh, M., & Sagan, O. (2014). Can music lessons increase the performance of preschool children in IQ tests? *Cogn Process, 15*(1), 77-84. doi:10.1007/s10339-013-0574-0

Kerr, A., & Zelazo, P. D. (2004). Development of "hot" executive function: the children's gambling task. *Brain Cogn, 55*(1), 148-157. doi:10.1016/s0278-2626(03)00275-6

Kerr, S. J., Puthanakit, T., Thongpaibul, K., Malee, K. M., Ly, P. S., Suwanlerk, T., . . . Mellins, C. A. (2018). *Increased risk of executive, working memory, and emotional-behavioral problems among virologically well-controlled perinatally HIV-infected adolescents in Thailand and Cambodia*. Paper presented at the AIDS Conference, Amsterdam, Netherlands. http://www.aids2018.org/Portals/4/File/AIDS2018_Abstract_book.pdf?ver=2018-08-06-160624-427

Kerr, S. J., Puthanakit, T., Vibol, U., Aurpibul, L., Vonthanak, S., Kosalaraksa, P., . . . Team, S. S. (2014). Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. *AIDS Care, 26*(11), 1327-1335. doi:10.1080/09540121.2014.920949

Khurana, A., Romer, D., Betancourt, L. M., Brodsky, N. L., Giannetta, J. M., & Hurt, H. (2012). Early adolescent sexual debut: the mediating role of working memory ability, sensation seeking, and impulsivity. *Dev Psychol, 48*(5), 1416-1428. doi:10.1037/a0027491

Khurana, A., Romer, D., Betancourt, L. M., Brodsky, N. L., Giannetta, J. M., & Hurt, H. (2015). Stronger Working Memory Reduces Sexual Risk Taking in Adolescents, Even After Controlling for Parental Influences. *Child Dev, 86*(4), 1125-1141. doi:10.1111/cdev.12383

Kidia, K., Ndhlovu, C., Jombo, S., Abas, M., & Makadzange, A. T. (2015). The mental health of HIV-positive adolescents. *Lancet Psychiatry, 2*(6), 487-488. doi:10.1016/S2215-0366(15)00101-7

Kilburn, K., Ranganathan, M., Stoner, M. C. D., Hughes, J. P., MacPhail, C., Agyei, Y., . . . Pettifor, A. (2018). Transactional sex and incident HIV infection in a cohort of young women from rural South Africa. *Aids, 32*(12), 1669-1677. doi:10.1097/qad.0000000000001866

Kilford, E. J., Garrett, E., & Blakemore, S. J. (2016). The development of social cognition in adolescence: An integrated perspective. *Neuroscience & Biobehavioral Reviews, 70*, 106-120. doi:10.1016/j.neubiorev.2016.08.016

Kim-Chang, J. J., Loop, M. S., Donovan, K., Hong, S., Fischer, B., Venturi, G., . . . Sleasman, J. W. (2019). *SCD14, SICAM-1, and SVCAM-1 correlate with neurocognitive function in youth with HIV*. Paper presented at the CROI,

Seattle, Washington. https://www.croiconference.org/sessions/scd14-sicam-1-and-svcam-1-correlate-neurocognitive-function-youth-hiv
Kim, M. H., Mazenga, A. C., Yu, X., Devandra, A., Nguyen, C., Ahmed, S., . . . Sharp, C. (2015). Factors associated with depression among adolescents living with HIV in Malawi. *BMC Psychiatry, 15*(1), 264. doi:10.1186/s12888-015-0649-9
Kingdon, D., Cardoso, C., & McGrath, J. J. (2016). Research Review: Executive function deficits in fetal alcohol spectrum disorders and attention-deficit/hyperactivity disorder – a meta-analysis. *Journal of Child Psychology and Psychiatry, 57*(2), 116-131. doi:doi:10.1111/jcpp.12451
Kinghorn, A., Shanaube, K., Toska, E., Cluver, L., & Bekker, L. G. (2018). Defining adolescence: priorities from a global health perspective. *The Lancet Child & Adolescent Health, 2*(5), e10. doi:10.1016/S2352-4642(18)30096-8
Kirschner, S., & Tomasello, M. (2010). Joint music making promotes prosocial behavior in 4-year-old children. *Evolution and Human Behavior, 31*(5), 354-364. doi:10.1016/j.evolhumbehav.2010.04.004
Kline, R. B. (2016). *Principles and practice of structural equation modeling, 4th ed*. New York, NY, US: Guilford Press.
Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlstrom, K., . . . Westerberg, H. (2005). Computerized training of working memory in children with ADHD--a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry, 44*(2), 177-186. doi:10.1097/00004583-200502000-00010
Knoll, L. J., Magis-Weinberg, L., Speekenbrink, M., & Blakemore, S. J. (2015). Social Influence on Risk Perception During Adolescence. *Psychol Sci, 26*(5), 583-592. doi:10.1177/0956797615569578
Koban, L., Ramamoorthy, A., & Konvalinka, I. (2019). Why do we fall into sync with others? Interpersonal synchronization and the brain's optimization principle. *Soc Neurosci, 14*(1), 1-9. doi:10.1080/17470919.2017.1400463
Koekkoek, S., de Sonneville, L. M., Wolfs, T. F., Licht, R., & Geelen, S. P. (2008). Neurocognitive function profile in HIV-infected school-age children. *European Journal of Paediatric Neurology, 12*(4), 290-297. doi:10.1016/j.ejpn.2007.09.002
Koike, S., Hardy, R., & Richards, M. (2015). Adolescent self-control behavior predicts body weight through the life course: a prospective birth cohort study. *International Journal Of Obesity, 40*, 71. doi:10.1038/ijo.2015.213
Kokal, I., Engel, A., Kirschner, S., & Keysers, C. (2011). Synchronized drumming enhances activity in the caudate and facilitates prosocial commitment--if the rhythm comes easily. *PLoS One, 6*(11), e27272. doi:10.1371/journal.pone.0027272
Koss, M., Burden, M. J., Jonides, J., Nelson, C. A., Kaciroti, N., Jimenez, E., & Lozoff, B. (2010). Iron deficiency in infancy and neurocognitive functioning at 19 years: evidence of long-term deficits in executive function and recognition memory AU - Lukowski, Angela F. *Nutritional Neuroscience, 13*(2), 54-70. doi:10.1179/147683010X12611460763689
Kuhn, D. (2006). Do Cognitive Changes Accompany Developments in the Adolescent Brain? *Perspectives on Psychological Science, 1*(1), 59-67. doi:10.1111/j.1745-6924.2006.t01-2-.x

Lakatos, P., Karmos, G., Mehta, A. D., Ulbert, I., & Schroeder, C. E. (2008). Entrainment of Neuronal Oscillations as a Mechanism of Attentional Selection. *Science, 320*(5872), 110-113. doi:10.1126/science.1154735
Lakes, K. D., & Hoyt, W. T. (2004). Promoting self-regulation through school-based martial arts training. *J Appl Dev Psychol, 25*(3), 283-302. doi:10.1016/j.appdev.2004.04.002
Latzman, R. D., & Markon, K. E. (2010). The factor structure and age-related factorial invariance of the Delis-Kaplan Executive Function System (D-KEFS). *Assessment, 17*(2), 172-184. doi:10.1177/1073191109356254
Laughton, B., Cornell, M., Boivin, M., & Van Rie, A. (2013). Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. *J Int AIDS Soc, 16*, 18603. doi:10.7448/ias.16.1.18603
Lechenadec, J., Benmebarek, Y., Meyer, L., Warszawski, J., Douard, D., Monpoux, F., . . . Blanche, S. (2007). Long-Term Nonprogression of HIV Infection in Children: Evaluation of the ANRS Prospective French Pediatric Cohort. *Clinical Infectious Diseases, 45*(6), 785-794. doi:10.1086/521165
Lee, K., Bull, R., & Ho, R. M. (2013). Developmental changes in executive functioning. *Child Dev, 84*(6), 1933-1953. doi:10.1111/cdev.12096
Lee, Y. S., Lu, M. J., & Ko, H. P. (2007). Effects of skill training on working memory capacity. *Learning and Instruction, 17*(3), 336-344. doi:10.1016/j.learninstruc.2007.02.010
Lejuez, C. W., Aklin, W., Daughters, S., Zvolensky, M., Kahler, C., & Gwadz, M. (2007). Reliability and validity of the youth version of the Balloon Analogue Risk Task (BART-Y) in the assessment of risk-taking behavior among inner-city adolescents. *Journal of Clinical Child and Adolescent Psychology, 36*(1), 106-111. doi:10.1080/15374410709336573
Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., . . . Brown, R. A. (2002). Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology: Applied, 8*(2), 75-84.
Letendre, S., Marquie-Beck, J., Capparelli, E., Best, B., Clifford, D., Collier, A. C., . . . Ellis, R. J. (2008). Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol, 65*(1), 65-70. doi:10.1001/archneurol.2007.31
Lewis-de los Angeles, C. P., Alpert, K. I., Williams, P. L., Malee, K., Huo, Y., Csernansky, J. G., . . . Study, f. t. P. H. A. C. (2016). Deformed Subcortical Structures Are Related to Past HIV Disease Severity in Youth With Perinatally Acquired HIV Infection. *J Pediatric Infect Dis Soc, 5*(suppl_1), S6-S14. doi:10.1093/jpids/piw051
Lewis-de los Angeles, C. P., Williams, P. L., Huo, Y., Wang, S. D., Uban, K. A., Herting, M. M., . . . Wang, L. (2017). Lower total and regional grey matter brain volumes in youth with perinatally-acquired HIV infection: Associations with HIV disease severity, substance use, and cognition. *Brain Behav Immun, 62*, 100-109. doi:10.1016/j.bbi.2017.01.004
Li, J. J., Chung, T. A., Vanyukov, M. M., Scott Wood, D., Ferrell, R., & Clark, D. B. (2015). A Hierarchical Factor Model of Executive Functions in Adolescents: Evidence of Gene-Environment Interplay. *Journal of the International Neuropsychological Society, 21*(1), 62-73. doi:10.1017/s1355617714001039

Lima, C. F., & Castro, S. L. (2011). Speaking to the trained ear: musical expertise enhances the recognition of emotions in speech prosody. *Emotion, 11*(5), 1021-1031. doi:10.1037/a0024521

Lindenberger, U., Li, S., Gruber, W., & Müller, V. (2009). Brains swinging in concert: cortical phase synchronization while playing guitar. *BMC Neurosci, 10*(1), 22. doi:10.1186/1471-2202-10-22

Linnavalli, T., Putkinen, V., Lipsanen, J., Huotilainen, M., & Tervaniemi, M. (2018). Music playschool enhances children's linguistic skills. *Sci Rep, 8*(1). doi:10.1038/s41598-018-27126-5

Llorente, A. M., Brouwers, P., Leighty, R., Malee, K., Smith, R., Harris, L., . . . Chase, C. (2014). An analysis of select emerging executive skills in perinatally HIV-1-infected children. *Applied Neuropsychology: Child, 3*(1), 10-25. doi:10.1080/21622965.2012.686853

Loman, M. M., & Gunnar, M. R. (2010). Early experience and the development of stress reactivity and regulation in children. *Neuroscience & Biobehavioral Reviews, 34*(6), 867-876. doi:10.1016/j.neubiorev.2009.05.007

Longhofer, J., & Floersch, J. (1993). African drumming and psychiatric rehabilitation. *Psychosocial Rehabilitation Journal, 16*(4), 3-10. doi:10.1037/h0095656

Loo, K. K., Rizzo, S., Chen, Q. L., Weiss, R. E., Sugar, C. A., Ettyang, G., . . . Neumann, C. G. (2017). Effects of biscuit-type feeding supplementation on the neurocognitive outcomes of HIV-affected school-age children: a randomized, double-blind, controlled intervention trial in Kenya. *Family Medicine and Community Health, 5*(4), 245-258. doi:10.15212/fmch.2017.0130

Lu, C., & Greenwald, M. (2016). Reading and working memory in adults with or without formal musical training: Musical and lexical tone. *Psychology of Music, 44*(3), 369-387.

Luna, B. (2009). Developmental Changes in Cognitive Control through Adolescence. In B. Patricia (Ed.), *Advances in Child Development and Behavior* (Vol. Volume 37, pp. 233-278): JAI.

Ma, D. S., Correll, J., & Wittenbrink, B. (2015). The Chicago face database: A free stimulus set of faces and norming data. *Behav Res Methods, 47*(4), 1122-1135. doi:10.3758/s13428-014-0532-5

Maartens, G., Celum, C., & Lewin, S. R. (2014). HIV infection: epidemiology, pathogenesis, treatment, and prevention. *The Lancet, 384*(9939), 258-271. doi:10.1016/S0140-6736(14)60164-1

Mackinlay, E. (2014). An ABC of drumming: Children's narratives about beat, rhythm and groove in a primary classroom. *British Journal of Music Education, 31*(2), 209-230. doi:10.1017/S0265051714000114

Macmillan, N. A., & Creelman, C. D. (1990). Response bias: Characteristics of detection theory, threshold theory, and "nonparametric" indexes. *Psychological Bulletin, 107*(3), 401-413. doi:10.1037/0033-2909.107.3.401

Macmillan, N. A., & Kaplan, H. L. (1985). Detection theory analysis of group data: estimating sensitivity from average hit and false-alarm rates. *Psychological Bulletin, 98*(1), 185-199.

MacPherson, P., Munthali, C., Ferguson, J., Armstrong, A., Kranzer, K., Ferrand, R. A., & Ross, D. A. (2015). Service delivery interventions to improve adolescents' linkage, retention and adherence to antiretroviral therapy and

HIV care. *Tropical Medicine & International Health, 20*(8), 1015-1032. doi:10.1111/tmi.12517

Maganlal, U. (2013). *Executive function performance in HIV positive adolescents on anti-retroviral treatment in Johannesburg, South Africa.* (M.A. Masters), University of the Witwatersrand, Retrieved from http://wiredspace.wits.ac.za/bitstream/handle/10539/13960/U%20Maganlal%20-%20Executive%20Function%20in%20HIV%20Positive%20Adolescents%20Final%20Sep%202013.pdf?sequence=3 Available from OCLC WorldCat database.

Malee, K. M., Chernoff, M. C., Sirois, P. A., Williams, P. L., Garvie, P. A., Kammerer, B. L., . . . Nichols, S. L. (2017). Impact of Perinatally Acquired HIV Disease Upon Longitudinal Changes in Memory and Executive Functioning. *Journal of Acquired Immune Deficiency Syndromes, 75*(4), 455-464. doi:10.1097/qai.0000000000001441

Marsh, K. L., Richardson, M. J., & Schmidt, R. C. (2009). Social connection through joint action and interpersonal coordination. *Topics in Cognitive Science, 1*(2), 320-339. doi:10.1111/j.1756-8765.2009.01022.x

Marston, C., & King, E. (2006). Factors that shape young people's sexual behaviour: a systematic review. *The Lancet, 368*(9547), 1581-1586. doi:10.1016/S0140-6736(06)69662-1

Martin, S. C., Wolters, P. L., Toledo-Tamula, M. A., Zeichner, S. L., Hazra, R., & Civitello, L. (2006). Cognitive Functioning in School-Aged Children With Vertically Acquired HIV Infection Being Treated With Highly Active Antiretroviral Therapy (HAART). *Developmental Neuropsychology, 30*(2), 633-657. doi:10.1207/s15326942dn3002_1

Mavhu, W., Berwick, J., Chirawu, P., Makamba, M., Copas, A., Dirawo, J., . . . Cowan, F. M. (2013). Enhancing psychosocial support for HIV positive adolescents in Harare, Zimbabwe. *PLoS One, 8*(7), e70254-e70254. doi:10.1371/journal.pone.0070254

Mburu, G., Ram, M., Oxenham, D., Haamujompa, C., Iorpenda, K., & Ferguson, L. (2014). Responding to adolescents living with HIV in Zambia: A social–ecological approach. *Children and Youth Services Review, 45*, 9-17. doi:10.1016/j.childyouth.2014.03.033

McHugh, G., Rylance, J., Mujuru, H., Nathoo, K., Chonzi, P., Dauya, E., . . . Ferrand, R. A. (2016). Chronic Morbidity Among Older Children and Adolescents at Diagnosis of HIV Infection. *Journal of Acquired Immune Deficiency Syndromes, 73*(3), 275-281. doi:10.1097/qai.0000000000001073

Mee, P., Kahn, K., Kabudula, C. W., Wagner, R. G., Gómez-Olivé, F. X., Madhavan, S., . . . Byass, P. (2016). The development of a localised HIV epidemic and the associated excess mortality burden in a rural area of South Africa. *Global health, epidemiology and genomics, 1*, e7-e7. doi:10.1017/gheg.2016.3

Mellins, C. A., Elkington, K. S., Bauermeister, J. A., Brackis-Cott, E., Dolezal, C., McKay, M., . . . Abrams, E. J. (2009). Sexual and drug use behavior in perinatally HIV-infected youth: mental health and family influences. *J Am Acad Child Adolesc Psychiatry, 48*(8), 810-819. doi:10.1097/CHI.0b013e3181a81346

Mellins, C. A., & Malee, K. M. (2013). Understanding the mental health of youth living with perinatal HIV infection: lessons learned and current challenges. *J Int AIDS Soc, 16*(18593). doi:10.7448/IAS.16.1.18593

Mellins, C. A., Tassiopoulos, K., Malee, K., Moscicki, A. B., Patton, D., Smith, R., . . . Seage, G. R. (2011). Behavioral health risks in perinatally HIV-exposed youth: Co-occurrence of sexual and drug use behavior, mental health problems, and nonadherence to antiretroviral treatment. *AIDS Patient Care STDS, 25*(7), 413-422. doi:10.1089/apc.2011.0025

Melrose, R. J., Tinaz, S., Castelo, J. M., Courtney, M. G., & Stern, C. E. (2008). Compromised fronto-striatal functioning in HIV: an fMRI investigation of semantic event sequencing. *Behav Brain Res, 188*(2), 337-347. doi:10.1016/j.bbr.2007.11.021

Merker, B. H., Madison, G. S., & Eckerdal, P. (2009). On the role and origin of isochrony in human rhythmic entrainment. *Cortex, 45*(1), 4-17. doi:10.1016/j.cortex.2008.06.011

Metzler-Baddeley, C., Cantera, J., Coulthard, E., Rosser, A., Jones, D. K., & Baddeley, R. J. (2014). Improved Executive Function and Callosal White Matter Microstructure after Rhythm Exercise in Huntington's Disease. *J Huntingtons Dis, 3*(3), 273-283. doi:10.3233/jhd-140113

Miller, M., Nevado-Montenegro, A. J., & Hinshaw, S. P. (2012). Childhood executive function continues to predict outcomes in young adult females with and without childhood-diagnosed ADHD. *J Abnorm Child Psychol, 40*(5), 657-668. doi:10.1007/s10802-011-9599-y

Milligan, R. (2016). *A comparison of working memory profiles in HIV-infected and HIV-exposed uninfected children.* (PhD Doctoral thesis), University of the Witwatersrand, Available from OCLC WorldCat database.

Milligan, R., & Cockcroft, K. (2017). Working Memory Profiles in HIV-Exposed, Uninfected and HIV-Infected Children: A Comparison with Neurotypical Controls. *Frontiers in Human Neuroscience, 11*, 13. doi:10.3389/fnhum.2017.00348

Miyake, A., & Friedman, N. P. (2012). The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions. *Current Directions in Psychological Science, 21*(1), 8-14. doi:10.1177/0963721411429458

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cognitive Psychology, 41*(1), 49-100. doi:10.1006/cogp.1999.0734

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., . . . Caspi, A. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences, 108*(7), 2693-2698. doi:10.1073/pnas.1010076108

Mokdad, A. H., Forouzanfar, M. H., Daoud, F., Mokdad, A. A., El Bcheraoui, C., Moradi-Lakeh, M., . . . Murray, C. J. L. (2016). Global burden of diseases, injuries, and risk factors for young people's health during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet, 387*(10036), 2383-2401. doi:10.1016/S0140-6736(16)00648-6

Monsell, S. (2003). Task switching. *Trends Cogn Sci, 7*(3), 134-140. doi:10.1016/S1364-6613(03)00028-7

Montello, L., & Coons, E. E. (1998). Effects of active versus passive group music therapy on preadolescents with emotional, learning, and behavioral disorders. *Journal of Music Therapy, 35*(1), 49-67. doi:10.1093/jmt/35.1.49
Moreno, S., Bialystok, E., Barac, R., Schellenberg, E. G., Cepeda, N. J., & Chau, T. (2011). Short-term music training enhances verbal intelligence and executive function. *Psychol Sci, 22*(11), 1425-1433. doi:10.1177/0956797611416999
Moreno, S., Wodniecka, Z., Tays, W., Alain, C., & Bialystok, E. (2014). Inhibitory control in bilinguals and musicians: event related potential (ERP) evidence for experience-specific effects. *PLoS One, 9*(4), e94169. doi:10.1371/journal.pone.0094169
MRC/Wits-Agincourt Unit: Rural Public Health and Health Transitions Research Unit. (2019). Retrieved from https://www.agincourt.co.za/
Muenchhoff, M., Prendergast, A. J., & Goulder, P. J. R. (2014). Immunity to HIV in Early Life. *Frontiers in Immunology, 5*(391). doi:10.3389/fimmu.2014.00391
Murphy, D. A., Durako, S. J., Moscicki, A. B., Vermund, S. H., Ma, Y., Schwarz, D. F., & Muenz, L. R. (2001). No change in health risk behaviors over time among HIV infected adolescents in care: role of psychological distress. *The Journal of Adolescent Health, 29*(3 Suppl), 57-63.
Murphy, D. A., Wilson, C. M., Durako, S. J., Muenz, L. R., & Belzer, M. (2001). Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care, 13*(1), 27-40. doi:10.1080/09540120020018161
Nabunya, P., & Ssewamala, F. M. (2014). The Effects of Parental Loss on the Psychosocial Wellbeing of AIDS-Orphaned Children Living in AIDS-Impacted Communities: Does Gender Matter? *Children and Youth Services Review, 43*, 131-137. doi:10.1016/j.childyouth.2014.05.011
Nachman, S., Chernoff, M., Williams, P., Hodge, J., Heston, J., & Gadow, K. D. (2012). Human immunodeficiency virus disease severity, psychiatric symptoms, and functional outcomes in perinatally infected youth. *Archives of Pediatrics & Adolescent Medicine, 166*(6), 528-535. doi:10.1001/archpediatrics.2011.1785
Nagarajan, R., Sarma, M. K., Thomas, M. A., Chang, L., Natha, U., Wright, M., . . . Keller, M. A. (2012). Neuropsychological function and cerebral metabolites in HIV-infected youth. *Journal of Neuroimmune Pharmacology, 7*(4), 981-990. doi:10.1007/s11481-012-9407-7
Ndhlovu, L. C., Umaki, T., Chew, G. M., Chow, D. C., Agsalda, M., Kallianpur, K. J., . . . Shikuma, C. M. (2014). Treatment intensification with maraviroc (CCR5 antagonist) leads to declines in CD16-expressing monocytes in cART-suppressed chronic HIV-infected subjects and is associated with improvements in neurocognitive test performance: implications for HIV-associated neurocognitive disease (HAND). *J Neurovirol, 20*(6), 571-582. doi:10.1007/s13365-014-0279-x
Newman, B. M., Lohman, B. J., & Newman, P. R. (2007). Peer group membership and a sense of belonging: their relationship to adolescent behavior problems. *Adolescence, 42*(166), 241-263.
Newman, G. F., Maggott, C., & Alexander, D. G. (2015). Group drumming as a burnout prevention initiative among staff members at a child and

adolescent mental health care facility. *South African Journal of Psychology, 45*(4), 439-451. doi:10.1177/0081246315581346
Nichols, S. L., Bethel, J., Garvie, P. A., Patton, D. E., Thornton, S., Kapogiannis, B. G., . . . Woods, S. P. (2013). Neurocognitive functioning in antiretroviral therapy-naive youth with behaviorally acquired human immunodeficiency virus. *Journal of Adolescent Health, 53*(6), 763-771. doi:10.1016/j.jadohealth.2013.07.006
Nichols, S. L., Bethel, J., Kapogiannis, B. G., Li, T., Woods, S. P., Patton, E. D., . . . Garvie, P. A. (2016). Antiretroviral treatment initiation does not differentially alter neurocognitive functioning over time in youth with behaviorally acquired HIV. *J Neurovirol, 22*(2), 218-230. doi:10.1007/s13365-015-0389-0
Nichols, S. L., Brummel, S. S., Smith, R. A., Garvie, P. A., Hunter, S. J., Malee, K. M., . . . Mellins, C. A. (2015). Executive Functioning in Children and Adolescents With Perinatal HIV Infection. *Pediatr Infect Dis J, 34*(9), 969-975. doi:10.1097/inf.0000000000000809
Nichols, S. L., Chernoff, M. C., Malee, K. M., Sirois, P. A., Woods, S. P., Williams, P. L., . . . Kammerer, B. (2016). Executive Functioning in Children and Adolescents With Perinatal HIV Infection and Perinatal HIV Exposure. *J Pediatric Infect Dis Soc, 5*(suppl 1), S15-s23. doi:10.1093/jpids/piw049
Nicubunu. (2009). Card backs: grid blue. Retrieved from https://openclipart.org/detail/23034/card-backs-grid-blue
Nwosu, E. C., Robertson, F. C., Holmes, M. J., Cotton, M. F., Dobbels, E., Little, F., . . . Meintjes, E. M. (2018). Altered brain morphometry in 7-year old HIV-infected children on early ART. *Metab Brain Dis, 33*(2), 523-535. doi:10.1007/s11011-017-0162-6
O'Leary, M. J., & Barber, P. J. (1993). Interference effects in the Stroop and Simon paradigms. *Journal of Experimental Psychology: Human Perception and Performance, 19*(4), 830-844. doi:10.1037/0096-1523.19.4.830
Oberle, E., Schonert-Reichl, K. A., & Zumbo, B. D. (2011). Life Satisfaction in Early Adolescence: Personal, Neighborhood, School, Family, and Peer Influences. *J Youth Adolesc, 40*(7), 889-901. doi:10.1007/s10964-010-9599-1
Oechslin, M. S., Van De Ville, D., Lazeyras, F., Hauert, C. A., & James, C. E. (2013). Degree of musical expertise modulates higher order brain functioning. *Cerebral Cortex, 23*(9), 2213-2224. doi:10.1093/cercor/bhs206
Ofori-Mante, J. A., Kaul, A., Rigaud, M., Fidelia, A., Rochford, G., Krasinski, K., . . . Borkowsky, W. (2007). Natural history of HIV infected pediatric long-term or slow progressor population after the first decade of life. *Pediatr Infect Dis J, 26*(3), 217-220.
Okada, B. M., & Slevc, L. R. (2018). Individual differences in musical training and executive functions: A latent variable approach. *Mem Cognit, 46*(7), 1076-1092. doi:10.3758/s13421-018-0822-8
Ortega, M., Brier, M. R., & Ances, B. M. (2015). Effects of HIV and combination antiretroviral therapy on cortico-striatal functional connectivity. *Aids, 29*(6), 703-712. doi:10.1097/QAD.0000000000000611

Overy, K., & Molnar-Szakacs, I. (2009). Being Together in Time. *Music Perception, 26*(5), 489-504. doi:10.1525/mp.2009.26.5.489
Pallesen, K. J., Brattico, E., Bailey, C. J., Korvenoja, A., Koivisto, J., Gjedde, A., & Carlson, S. (2010). Cognitive control in auditory working memory is enhanced in musicians. *PLoS One, 5*(6), e11120-e11120. doi:10.1371/journal.pone.0011120
Pantelyat, A., Syres, C., Reichwein, S., & Willis, A. (2016). DRUM-PD: The use of a drum circle to improve the symptoms and signs of Parkinson's disease (PD). *Mov Disord Clin Pract, 3*(3), 243-249. doi:10.1002/mdc3.12269
Parbery-Clark, A., Skoe, E., Lam, C., & Kraus, N. (2009). Musician enhancement for speech-in-noise. *Ear Hear, 30*(6), 653-661. doi:10.1097/AUD.0b013e3181b412e9
Patel, P. B., Apornpong, T., Kerr, S. J., Puthanakit, T., Thongpibul, K., Kosalaraksa, P., . . . Group, O. b. o. t. P. R. S. (2018). Group Based Trajectory Analysis of Cognitive Outcomes in Children with Perinatal HIV. *BioRxiv*. doi:10.1101/398339
Patton, G. C., Olsson, C. A., Skirbekk, V., Saffery, R., Wlodek, M. E., Azzopardi, P. S., . . . Sawyer, S. M. (2018). Adolescence and the next generation. *Nature, 554*, 458. doi:10.1038/nature25759
Patton, G. C., Sawyer, S. M., Santelli, J. S., Ross, D. A., Afifi, R., Allen, N. B., . . . Viner, R. M. (2016). Our future: a Lancet commission on adolescent health and wellbeing. *The Lancet, 387*(10036), 2423-2478. doi:10.1016/S0140-6736(16)00579-1
Patton, M. Q. (1999). Enhancing the quality and credibility of qualitative analysis. *Health services research, 34*(5 Pt 2), 1189-1208.
Pearson, R. M., Bornstein, M. H., Cordero, M., Scerif, G., Mahedy, L., Evans, J., . . . Stein, A. (2016). Maternal perinatal mental health and offspring academic achievement at age 16: the mediating role of childhood executive function. *Journal of Child Psychology and Psychiatry, 57*(4), 491-501. doi:10.1111/jcpp.12483
Peltzer, K., Rodriguez, V. J., & Jones, D. (2016). Prevalence of prenatal depression and associated factors among HIV-positive women in primary care in Mpumalanga province, South Africa. *SAHARA : Journal of Social Aspects of HIV / AIDS Research Alliance, 13*(1), 60-67. doi:10.1080/17290376.2016.1189847
Peluso, M. J., Ferretti, F., Peterson, J., Lee, E., Fuchs, D., Boschini, A., . . . Spudich, S. (2012). Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load. *Aids, 26*(14), 1765-1774. doi:10.1097/QAD.0b013e328355e6b2
Perkins, R., Ascenso, S., Atkins, L., Fancourt, D., & Williamon, A. (2016). Making music for mental health: how group drumming mediates recovery. *Psychol Well Being, 6*(1), 11. doi:10.1186/s13612-016-0048-0
Petersen, O. P. (2012). *Rhythm as an intervention for health and mental health difficulties: A comprehensive literature review.* (Doctor of Psychology Doctoral), Alliant International University, Los Angeles, Los Angeles. Available from Ovid Technologies PsycINFO database. (2-B(E))
Pettifor, A., MacPhail, C., Hughes, J. P., Selin, A., Wang, J., Gómez-Olivé, F. X., . . . Kahn, K. (2016). The effect of a conditional cash transfer on HIV

incidence in young women in rural South Africa (HPTN 068): a phase 3, randomised controlled trial. *The Lancet Global Health, 4*(12), e978-e988. doi:10.1016/S2214-109X(16)30253-4

Pettifor, A., MacPhail, C., Selin, A., Gómez-Olivé, F. X., Rosenberg, M., Wagner, R. G., . . . Kahn, K. (2016). HPTN 068: A Randomized Control Trial of a Conditional Cash Transfer to Reduce HIV Infection in Young Women in South Africa—Study Design and Baseline Results. *AIDS Behav, 20*(9), 1863-1882. doi:10.1007/s10461-015-1270-0

Pfadenhauer, L. M., Gerhardus, A., Mozygemba, K., Lysdahl, K. B., Booth, A., Hofmann, B., . . . Rehfuess, E. (2017). Making sense of complexity in context and implementation: the Context and Implementation of Complex Interventions (CICI) framework. *Implementation Science, 12*(1), 21. doi:10.1186/s13012-017-0552-5

Phillips, N., Amos, T., Kuo, C., Hoare, J., Ipser, J., Thomas, K. G. F., & Stein, D. J. (2016). HIV-Associated Cognitive Impairment in Perinatally Infected Children: A Meta-analysis. *Pediatrics, 138*(5). doi:10.1542/peds.2016-0893

Poon, K. (2017). Hot and Cool Executive Functions in Adolescence: Development and Contributions to Important Developmental Outcomes. *Front Psychol, 8*, 2311-2311. doi:10.3389/fpsyg.2017.02311

Portowitz, A., Peppler, K. A., & Downton, M. (2014). In Harmony: A technology-based music education model to enhance musical understanding and general learning skills. *International Journal of Music Education, 32*(2), 242-260. doi:10.1177/0255761413517056

Posedel, J., Emery, L., Souza, B., & Fountain, C. (2012). Pitch perception, working memory, and second-language phonological production. *Psychology of Music, 40*(4), 508-517. doi:10.1177/0305735611415145

Prencipe, A., Kesek, A., Cohen, J., Lamm, C., Lewis, M. D., & Zelazo, P. D. (2011). Development of hot and cool executive function during the transition to adolescence. *Journal of Experimental Child Psychology, 108*(3), 621-637. doi:10.1016/j.jecp.2010.09.008

Protection of Personal Information Act, 4 Stat. (2013 11 April 2014).

Puthanakit, T., Ananworanich, J., Vonthanak, S., Kosalaraksa, P., Hansudewechakul, R., Lugt, J., . . . Wongsawat, J. (2013). Cognitive function and neurodevelopmental outcomes in HIV-infected Children older than 1 year of age randomized to early versus deferred antiretroviral therapy: the PREDICT neurodevelopmental study. *Pediatr Infect Dis J, 32*. doi:10.1097/INF.0b013e31827fb19d

Putkinen, V., Tervaniemi, M., Saarikivi, K., & Huotilainen, M. (2015). Promises of formal and informal musical activities in advancing neurocognitive development throughout childhood. *Ann N Y Acad Sci, 1337*, 153-162. doi:10.1111/nyas.12656

Ramachandra, V., Meighan, C., & Gradzki, J. (2012). The impact of musical training on the phonological memory and the central executive: A brief report. *North American Journal of Psychology, 14*(3), 541-548. doi:10.1371/journal.pone.0011120

Ramaiya, M. K., Sullivan, K. A., O' Donnell, K., Cunningham, C. K., Shayo, A. M., Mmbaga, B. T., & Dow, D. E. (2016). A Qualitative Exploration of the Mental Health and Psychosocial Contexts of HIV-Positive Adolescents in

Tanzania. *PLoS One, 11*(11), e0165936. doi:10.1371/journal.pone.0165936
Ribeiro, F. S., & Dos Santos, F. H. (2012). Musical training and working memory span in beginners, veterans and with no musical knowledge children. *Psicologia: Reflexao e Critica, 25*(3), 559-567. doi:10.1590/S0102-79722012000300016
Robbins, R., Bucek, A., Raymond, J., Nguyen, N., Dolezal, C., Abrams, E., . . . Mellins, C. A. (2018). *Neurocognitive outcomes among perinatally-HIV infected young adults*. Paper presented at the Aids, Amsterdam, Netherlands. http://www.aids2018.org/Portals/4/File/AIDS2018_Abstract_book.pdf?ver=2018-08-06-160624-427
Robbins, R. N., Zimmerman, R., Korich, R., Raymond, J., Dolezal, C., Choi, C. J., . . . Mellins, C. A. (2019). Longitudinal trajectories of neurocognitive test performance among individuals with perinatal HIV-infection and -exposure: adolescence through young adulthood. *AIDS Care*, 1-9. doi:10.1080/09540121.2019.1626343
Rochat, T. J., Houle, B., Stein, A., Coovadia, H., Coutsoudis, A., Desmond, C., . . . Bland, R. M. (2016). Exclusive Breastfeeding and Cognition, Executive Function, and Behavioural Disorders in Primary School-Aged Children in Rural South Africa: A Cohort Analysis. *PLoS Medicine, 13*(6), e1002044. doi:10.1371/journal.pmed.1002044
Rochat, T. J., Houle, B., Stein, A., Pearson, R. M., Newell, M. L., & Bland, R. M. (2017). Cohort Profile: The Siyakhula Cohort, rural South Africa. *International Journal of Epidemiology, 46*(6), 1755-1756n. doi:10.1093/ije/dyx148
Rochette, F., Moussard, A., & Bigand, E. (2014). Music lessons improve auditory perceptual and cognitive performance in deaf children. *Frontiers in Human Neuroscience, 8*. doi:10.3389/fnhum.2014.00488
Romer, D., Reyna, V. F., & Satterthwaite, T. D. (2017). Beyond stereotypes of adolescent risk taking: Placing the adolescent brain in developmental context. *Dev Cogn Neurosci, 27*, 19-34. doi:10.1016/j.dcn.2017.07.007
Rosenberg, M., Pettifor, A., Duta, M., Demeyere, N., Wagner, R. G., Selin, A., . . . Kahn, K. (2018). Executive function associated with sexual risk in young South African women: Findings from the HPTN 068 cohort. *PLoS One, 13*(4), 14. doi:10.1371/journal.pone.0195217
Ross, J. M., Coxe, S., Schuster, R. M., Rojas, A., & Gonzalez, R. (2015). The moderating effects of cannabis use and decision making on the relationship between conduct disorder and risky sexual behavior. *J Clin Exp Neuropsychol, 37*(3), 303-315. doi:10.1080/13803395.2015.1010489
Ross, J. M., Duperrouzel, J., Vega, M., & Gonzalez, R. (2016). The Neuropsychology of Risky Sexual Behavior. *Journal of the International Neuropsychological Society, 22*(6), 586-594. doi:10.1017/S1355617716000400
Rotheram-Borus, M. J., Tomlinson, M., le Roux, I., Weichle, T., Stewart, J., Gordon, S., & Lin, C. (2018). *Outcomes of South African mothers living with HIV (MLH) and their children compared to neighborhood peer mothers without HIV (MWOH) and their children over five years*. Paper presented at the Aids, Amsterdam, Netherlands.

http://www.aids2018.org/Portals/4/File/AIDS2018_Abstract_book.pdf?ver=2018-08-06-160624-427
Rotheram-Borus, M. J., Tomlinson, M., Scheffler, A., Harris, D. M., & Nelson, S. (2017). Adjustment of a Population of South African Children of Mothers Living With/and Without HIV Through Three Years Post-Birth. *AIDS Behav, 21*(6), 1601-1610. doi:10.1007/s10461-016-1436-4
Rowe, K., Duta, M., Demeyere, N., Wagner, R. G., Pettifor, A., Kahn, K., . . . Stein, A. (2019). Validation of OCS-EF, a tablet-based executive function assessment tool for use in low- and middle-income countries, amongst late adolescent females in the HPTN 068 cohort. *Manuscript in preparation*.
Rubin, L. H., & Maki, P. M. (2019). HIV, Depression, and Cognitive Impairment in the Era of Effective Antiretroviral Therapy. *Curr HIV/AIDS Rep, 16*(1), 82-95. doi:10.1007/s11904-019-00421-0
Ruel, T. D., Boivin, M. J., Boal, H. E., Bangirana, P., Charlebois, E., Havlir, D. V., . . . Wong, J. K. (2012). Neurocognitive and Motor Deficits in HIV-Infected Ugandan Children With High CD4 Cell Counts. *Clinical Infectious Diseases, 54*(7), 1001-1009. doi:10.1093/cid/cir1037
Ruisenor-Escudero, H., Familiar, I., Nakasujja, N., Bangirana, P., Opoka, R., Giordani, B., & Boivin, M. (2015). Immunological correlates of behavioral problems in school-aged children living with HIV in Kayunga, Uganda. *Global Mental Health, 2*, e9. doi:10.1017/gmh.2015.7
Saarikivi, K., Putkinen, V., Tervaniemi, M., & Huotilainen, M. (2016). Cognitive flexibility modulates maturation and music-training-related changes in neural sound discrimination. *The European Journal Of Neuroscience, 44*(2), 1815-1825. doi:10.1111/ejn.13176
Sachs, M., Kaplan, J., Der Sarkissian, A., & Habibi, A. (2017). Increased engagement of the cognitive control network associated with music training in children during an fMRI Stroop task. *PLoS One, 12*(10), e0187254-e0187254. doi:10.1371/journal.pone.0187254
Salama, C., Morris, M., Armistead, L., Koenig, L. J., Demas, P., Ferdon, C., & Bachanas, P. (2013). Depressive and conduct disorder symptoms in youth living with HIV: the independent and interactive roles of coping and neuropsychological functioning. *AIDS Care, 25*(2), 160-168. doi:10.1080/09540121.2012.687815
Sanchez-Cubillo, I., Perianez, J. A., Adrover-Roig, D., Rodriguez-Sanchez, J. M., Rios-Lago, M., Tirapu, J., & Barcelo, F. (2009). Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society, 15*(3), 438-450. doi:10.1017/s1355617709090626
Satorra, A., & Bentler, P. M. (1994). Corrections to test statistics and standard errors in covariance structure analysis. In *Latent variables analysis: Applications for developmental research.* (pp. 399-419). Thousand Oaks, CA, US: Sage Publications, Inc.
Satorra, A., & Bentler, P. M. (2001). A scaled difference chi-square test statistic for moment structure analysis. *Psychometrika, 66*(4), 507-514. doi:10.1007/bf02296192

Satorra, A., & Bentler, P. M. (2010). Ensuring Positiveness of the Scaled Difference Chi-square Test Statistic. *Psychometrika, 75*(2), 243-248. doi:10.1007/s11336-009-9135-y

Sawyer, S. M., Azzopardi, P. S., Wickremarathne, D., & Patton, G. C. (2018). The age of adolescence. *The Lancet Child & Adolescent Health, 2*(3), 223-228. doi:10.1016/S2352-4642(18)30022-1

Saylor, D., Dickens, A. M., Sacktor, N., Haughey, N., Slusher, B., Pletnikov, M., . . . McArthur, J. C. (2016). HIV-associated neurocognitive disorder — pathogenesis and prospects for treatment. *Nature Reviews Neurology, 12*, 234. doi:10.1038/nrneurol.2016.27

Schaefer, R., Gregson, S., Eaton, J. W., Mugurungi, O., Rhead, R., Takaruza, A., . . . Nyamukapa, C. (2017). Age-disparate relationships and HIV incidence in adolescent girls and young women: evidence from Zimbabwe. *Aids, 31*(10), 1461-1470. doi:10.1097/QAD.0000000000001506

Schellenberg, E. (2011). Examining the association between music lessons and intelligence. *British Journal of Psychology, 102*(3), 283-302.

Schiavone, S., Colaianna, M., & Curtis, L. (2015). Impact of early life stress on the pathogenesis of mental disorders: relation to brain oxidative stress. *Current Pharmaceutical Design, 21*(11), 1404-1412. doi:10.2174/1381612821666150105143358

Schlam, T. R., Wilson, N. L., Shoda, Y., Mischel, W., & Ayduk, O. (2013). Preschoolers' Delay of Gratification Predicts their Body Mass 30 Years Later. *J Pediatr, 162*(1), 90-93. doi:10.1016/j.jpeds.2012.06.049

Schroeder, S. R., Marian, V., Shook, A., & Bartolotti, J. (2016). Bilingualism and Musicianship Enhance Cognitive Control. *Neural Plast, 2016*, 4058620. doi:10.1155/2016/4058620

Schulz, K. P., Fan, J., Magidina, O., Marks, D. J., Hahn, B., & Halperin, J. M. (2007). Does the emotional go/no-go task really measure behavioral inhibition? Convergence with measures on a non-emotional analog. *Archives of Clinical Neuropsychology, 22*(2), 151-160. doi:10.1016/j.acn.2006.12.001

Schumacker, R. E., & Lomax, R. G. (2004). *A beginner's guide to structural equation modeling (Second Edition)*. Mahway, New Jersey: Lawrence Erlbaum Associates.

Semkovska, M., Quinlivan, L., O'Grady, T., Johnson, R., Collins, A., O'Connor, J., . . . Gload, T. (2019). Cognitive function following a major depressive episode: a systematic review and meta-analysis. *The Lancet Psychiatry*. doi:10.1016/S2215-0366(19)30291-3

Seppanen, M., Pesonen, A. K., & Tervaniemi, M. (2012). Music training enhances the rapid plasticity of P3a/P3b event-related brain potentials for unattended and attended target sounds. *Attention Perception & Psychophysics, 74*(3), 600-612. doi:10.3758/s13414-011-0257-9

Sherr, L., Hensels, I. S., Tomlinson, M., Skeen, S., & Macedo, A. (2018). Cognitive and physical development in HIV-positive children in South Africa and Malawi: A community-based follow-up comparison study. *Child Care Health Dev, 44*(1), 89-98. doi:10.1111/cch.12533

Sherr, L., Macedo, A., Tomlinson, M., Skeen, S., & Cluver, L. D. (2017). Could cash and good parenting affect child cognitive development? A cross-sectional study in South Africa and Malawi. *BMC Pediatrics, 17*(1). doi:10.1186/s12887-017-0883-z

Shing, Y. L., Lindenberger, U., Diamond, A., Li, S., & Davidson, M. C. (2010). Memory maintenance and inhibitory control differentiate from early childhood to adolescence. *Developmental Neuropsychology, 35*(6), 679-697. doi:10.1080/87565641.2010.508546

Shisana, O., Rehle, T., Simbayi, L. C., Zuma, K., Jooste, S., Zungu, N., . . . Onoya, D. (2014). *South African National HIV Prevalence, Incidence and Behaviour Survey, 2012* (H. Press Ed.). Cape Town: Human Sciences Research Council.

Shulman, E. P., Smith, A. R., Silva, K., Icenogle, G., Duell, N., Chein, J., & Steinberg, L. (2016). The dual systems model: Review, reappraisal, and reaffirmation. *Dev Cogn Neurosci, 17*, 103-117. doi:10.1016/j.dcn.2015.12.010

Silverman, M. J., & Marcionetti, M. J. (2004). Immediate effects of a single music therapy intervention with persons who are severely mentally ill. *The Arts in Psychotherapy, 31*(5), 291-301. doi:10.1016/j.aip.2004.06.008

Simon, J. R., & Rudell, A. P. (1967). Auditory S-R compatibility: The effect of an irrelevant cue on information processing. *Journal of Applied Psychology, 51*(3), 300-304. doi:10.1037/h0020586

Singh, D., Joska, J. A., Goodkin, K., Lopez, E., Myer, L., Paul, R. H., . . . Sunpath, H. (2010). Normative scores for a brief neuropsychological battery for the detection of HIV-associated neurocognitive disorder (HAND) among South Africans. *BMC Res Notes, 3*(1), 28. doi:10.1186/1756-0500-3-28

Singh, K. K., Barroga, C. F., Hughes, M. D., Chen, J., Raskino, C., McKinney, R. E., & Spector, S. A. (2003). Genetic influence of CCR5, CCR2, and SDF1 variants on human immunodeficiency virus 1 (HIV-1)-related disease progression and neurological impairment, in children with symptomatic HIV-1 infection. *J Infect Dis, 188*(10), 1461-1472. doi:10.1086/379038

Sirois, P. A., Chernoff, M. C., Malee, K. M., Garvie, P. A., Harris, L. L., Williams, P. L., . . . Nichols, S. L. (2016). Associations of Memory and Executive Functioning With Academic and Adaptive Functioning Among Youth With Perinatal HIV Exposure and/or Infection. *J Pediatric Infect Dis Soc, 5*(Suppl 1), S24-S32. doi:10.1093/jpids/piw046

Skeef, E. (1999). African Drumming: a perfect tool for a more open and inclusive approach to intercultural education and development. *European Journal of Intercultural studies, 10*(3), 329-338. doi:10.1080/0952391990100317

Skuy, M., Schutte, E., Fridjhon, P., & O'Carroll, S. (2001). Suitability of published neuropsychological test norms for urban African secondary school students in South Africa. *Personality and Individual Differences, 30*(8), 1413-1425. doi:10.1016/S0191-8869(00)00123-9

Slater, J., Ashley, R., Tierney, A., & Kraus, N. (2018). Got Rhythm? Better Inhibitory Control Is Linked with More Consistent Drumming and Enhanced Neural Tracking of the Musical Beat in Adult Percussionists and Nonpercussionists. *Journal Of Cognitive Neuroscience, 30*(1), 14-24. doi:10.1162/jocn_a_01189

Slater, J., Azem, A., Nicol, T., Swedenborg, B., & Kraus, N. (2017). Variations on the theme of musical expertise: cognitive and sensory processing in percussionists, vocalists and non-musicians. *European Journal of Neuroscience, 45*(7), 952-963. doi:10.1111/ejn.13535

Slevc, L. R., Davey, N. S., Buschkuehl, M., & Jaeggi, S. M. (2016). Tuning the mind: Exploring the connections between musical ability and executive functions. *Cognition, 152*, 199-211. doi:10.1016/j.cognition.2016.03.017

Smalley, S. L., Kitil, M. J., Galla, B. M., Kaiser-Greenland, S., Locke, J., Ishijima, E., & Kasari, C. (2010). Effects of Mindful Awareness Practices on Executive Functions in Elementary School Children AU - Flook, Lisa. *Journal of Applied School Psychology, 26*(1), 70-95. doi:10.1080/15377900903379125

Smayda, K. E., Worthy, D. A., & Chandrasekaran, B. (2018). Better late than never (or early): Music training in late childhood is associated with enhanced decision-making. *Psychology of Music, 46*(5), 734-748. doi:10.1177/0305735617723721

Smith, C., Viljoen, J. T., & McGeachie, L. (2014). African drumming: a holistic approach to reducing stress and improving health? *Journal of Cardiovascular Medicine, 15*(6), 441-446. doi:10.2459/jcm.0000000000000046

Smith, R., Chernoff, M., Williams, P. L., Malee, K. M., Sirois, P. A., Kammerer, B., . . . Usitalo, A. (2012). Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. *Pediatr Infect Dis J, 31*. doi:10.1097/INF.0b013e318253844b

Smurzynski, M., Wu, K., Letendre, S., Robertson, K., Bosch, R. J., Clifford, D. B., . . . Ellis, R. (2011). Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. *Aids, 25*(3), 357-365. doi:10.1097/QAD.0b013e32834171f8

Snow, S., & D'Amico, M. (2010). The drum circle project: A qualitative study with at-risk youth in a school setting. *Canadian Journal of Music Therapy, 16*(1), 12-39.

Sobierajewicz, J., Naskręcki, R., Jaśkowski, W., & Van der Lubbe, R. H. J. (2018). Do musicians learn a fine sequential hand motor skill differently than non-musicians? *PLoS One, 13*(11). doi:10.1371/journal.pone.0207449

Sommerfeldt, S. L., Cullen, K. R., Han, G., Fryza, B. J., Houri, A. K., & Klimes-Dougan, B. (2016). Executive Attention Impairment in Adolescents With Major Depressive Disorder. *Journal of Clinical Child & Adolescent Psychology, 45*(1), 69-83. doi:10.1080/15374416.2015.1072823

Sowell, E. R., Trauner, D. A., Gamst, A., & Jernigan, T. L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Developmental Medicine and Child Neurology, 44*(1), 4-16.

Spies, G., Ahmed-Leitao, F., Fennema-Notestine, C., Cherner, M., & Seedat, S. (2016). Effects of HIV and childhood trauma on brain morphometry and neurocognitive function. *J Neurovirol, 22*(2), 149-158. doi:10.1007/s13365-015-0379-2

Spinella, M. (2007). The role of prefrontal systems in sexual behavior. *International Journal of Neuroscience, 117*(3), 369-385. doi:10.1080/00207450600588980

Spudich, S., Gisslen, M., Hagberg, L., Lee, E., Liegler, T., Brew, B., . . . Price, R. W. (2011). Central nervous system immune activation characterizes primary human immunodeficiency virus 1 infection even in participants

with minimal cerebrospinal fluid viral burden. *J Infect Dis, 204*(5), 753-760. doi:10.1093/infdis/jir387
Stanislaw, H., & Todorov, N. (1999). Calculation of signal detection theory measures. *Behavior Research Methods, Instruments, & Computers, 31*(1), 137-149. doi:10.3758/bf03207704
Steiger, J. H., & Lind, C. (1980). *Statistically-Based Tests for the Number of Common Factors*. Paper presented at the The Annual Meeting of the Psychometric Society, Iowa City, Iowa.
Steinberg, L. (2005). Cognitive and affective development in adolescence. *Trends Cogn Sci, 9*(2), 69-74. doi:10.1016/j.tics.2004.12.005
Steinberg, L. (2008). A social neuroscience perspective on adolescent risk-taking. *Developmental review, 28*(1), 78-106. doi:10.1016/j.dr.2007.08.002
Steinberg, L., Icenogle, G., Shulman, E. P., Breiner, K., Chein, J., Bacchini, D., . . . Takash, H. M. S. (2017). Around the world, adolescence is a time of heightened sensation seeking and immature self-regulation. *Dev Sci*, e12532. doi:10.1111/desc.12532
Stevens, C. (2003). *Art and Heart of Drum Circles*. New York: Hal Leonard Corporation.
Stoebenau, K., Heise, L., Wamoyi, J., & Bobrova, N. (2016). Revisiting the understanding of "transactional sex" in sub-Saharan Africa: A review and synthesis of the literature. *Social Science & Medicine, 168*, 186-197. doi:10.1016/j.socscimed.2016.09.023
Stone, N. N. (2005). Hand-drumming to build community: the story of the Whittier Drum Project. *New Dir Youth Dev*(106), 73-83, 76.
Strait, D. L., Kraus, N., Parbery-Clark, A., & Ashley, R. (2010). Musical experience shapes top-down auditory mechanisms: evidence from masking and auditory attention performance. *Hear Res, 261*(1-2), 22-29. doi:10.1016/j.heares.2009.12.021
Strait, D. L., O'Connell, S., Parbery-Clark, A., & Kraus, N. (2014). Musicians' enhanced neural differentiation of speech sounds arises early in life: developmental evidence from ages 3 to 30. *Cerebral Cortex, 24*(9), 2512-2521. doi:10.1093/cercor/bht103
Strait, D. L., Parbery-Clark, A., Hittner, E., & Kraus, N. (2012). Musical training during early childhood enhances the neural encoding of speech in noise. *Brain Lang, 123*(3), 191-201. doi:10.1016/j.bandl.2012.09.001
Sturdevant, C. B., Dow, A., Jabara, C. B., Joseph, S. B., Schnell, G., Takamune, N., . . . Swanstrom, R. (2012). Central Nervous System Compartmentalization of HIV-1 Subtype C Variants Early and Late in Infection in Young Children. *PLOS Pathogens, 8*(12), e1003094. doi:10.1371/journal.ppat.1003094
Suarez, L., Elangovan, S., & Au, A. (2016). Cross-sectional study on the relationship between music training and working memory in adults. *Australian Journal of Psychology, 68*(1), 38-46. doi:10.1111/ajpy.12087
Tamnes, C. K., Herting, M. M., Goddings, A., Meuwese, R., Blakemore, S. J., Dahl, R. E., . . . Mills, K. L. (2017). Development of the Cerebral Cortex across Adolescence: A Multisample Study of Inter-Related Longitudinal Changes in Cortical Volume, Surface Area, and Thickness. *The Journal of Neuroscience, 37*(12), 3402-3412. doi:10.1523/jneurosci.3302-16.2017
Tau, G. Z., & Peterson, B. S. (2010). Normal development of brain circuits. *Neuropsychopharmacology, 35*(1), 147-168. doi:10.1038/npp.2009.115

Tavakol, M., & Dennick, R. (2011). Making sense of Cronbach's alpha. *International journal of medical education, 2*, 53-55. doi:10.5116/ijme.4dfb.8dfd

Taylor, H. G., & Clark, C. A. (2016). Executive function in children born preterm: Risk factors and implications for outcome. *Semin Perinatol, 40*(8), 520-529. doi:10.1053/j.semperi.2016.09.004

Tecumseh Fitch, W. (2012). The biology and evolution of rhythm: unravelling a paradox. In P. Rebuschat, M. Rohrmeier, J. A. Hawkins, & I. Cross (Eds.), *Language and Music as Cognitive Systems*. Oxford: Oxford University Press.

Thomas, J. B., Brier, M. R., Snyder, A. Z., Vaida, F. F., & Ances, B. M. (2013). Pathways to neurodegeneration: effects of HIV and aging on resting-state functional connectivity. *Neurology, 80*(13), 1186-1193. doi:10.1212/WNL.0b013e318288792b

Thorell, L. B., Lindqvist, S., Bergman Nutley, S., Bohlin, G., & Klingberg, T. (2009). Training and transfer effects of executive functions in preschool children. *Dev Sci, 12*(1), 106-113. doi:10.1111/j.1467-7687.2008.00745.x

Thriemer, K., Ley, B., Ame, S. M., Puri, M. K., Hashim, R., Chang, N. Y., . . . Ali, M. (2012). Replacing paper data collection forms with electronic data entry in the field: findings from a study of community-acquired bloodstream infections in Pemba, Zanzibar. *BMC Research Notes, 5*(1), 113. doi:10.1186/1756-0500-5-113

Tideman, E., Maršál, K., & Ley, D. (2007). Cognitive function in young adults following intrauterine growth restriction with abnormal fetal aortic blood flow. *Ultrasound in Obstetrics & Gynecology, 29*(6), 614-618. doi:10.1002/uog.4042

Tomasi, D., Chang, L., Caparelli, E. D., Telang, F., & Ernst, T. (2006). The human immunodeficiency virus reduces network capacity: Acoustic noise effect. *Ann Neurol, 59*(2), 419-423. doi:10.1002/aila.20766

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., . . . Nelson, C. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res, 168*(3), 242-249. doi:10.1016/j.psychres.2008.05.006

Treisman, G. J., & Kaplin, A. I. (2002). Neurologic and psychiatric complications of antiretroviral agents. *Aids, 16*(9), 1201-1215.

Tyor, W., Fritz-French, C., & Nath, A. (2013). Effect of HIV clade differences on the onset and severity of HIV-associated neurocognitive disorders. *J Neurovirol, 19*(6), 515-522. doi:10.1007/s13365-013-0206-6

Uban, K. A., Herting, M. M., Williams, P. L., Ajmera, T., Gautam, P., Huo, Y., . . . Sowell, E. R. (2015). White matter microstructure among youth with perinatally acquired HIV is associated with disease severity. *Aids, 29*(9), 1035-1044. doi:10.1097/qad.0000000000000648

UNAIDS. (2016). *Get on the Fast-Track: The life-cycle approach to HIV. Finding solutions for everyone at every stage of life*. Retrieved from https://www.unaids.org/sites/default/files/media_asset/Get-on-the-Fast-Track_en.pdf

UNAIDS. (2018a). UNAIDS Data 2018. Retrieved from https://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf

UNAIDS. (2018b). Undetectable = Untransmittable: Public Health and HIV Viral Load Suppression [Press release]. Retrieved from https://www.unaids.org/sites/default/files/media_asset/undetectable-untransmittable_en.pdf
UNICEF. (2018). *HIV epidemiology among children and adolescents*. Retrieved from https://data.unicef.org/topic/hivaids/global-regional-trends/
Valdesolo, P., & Desteno, D. (2011). Synchrony and the social tuning of compassion. *Emotion, 11*(2), 262-266. doi:10.1037/a0021302
Van Dalen, Y. W., Blokhuis, C., Cohen, S., Ter Stege, J. A., Teunissen, C. E., Kuhle, J., . . . Pajkrt, D. (2016). Neurometabolite alterations associated with cognitive performance in perinatally HIV-infected children. *Medicine (Baltimore), 95*(12). doi:10.1097/MD.0000000000003093
Van den Hof, M., Ter Haar, A. M., Scherpbier, H. J., van der Lee, J. H., Reiss, P., Wit, F. W. N. M., . . . Pajkrt, D. (2019). Neurocognitive development in perinatally HIV-infected adolescents on long-term treatment compared to healthy matched controls: a longitudinal study. *Clinical Infectious Diseases*. doi:10.1093/cid/ciz386
van der Westhuizen, C., Wyatt, G., Williams, J. K., Stein, D. J., & Sorsdahl, K. (2016). Validation of the Self Reporting Questionnaire 20-Item (SRQ-20) for Use in a Low- and Middle-Income Country Emergency Centre Setting. *Int J Ment Health Addict, 14*(1), 37-48. doi:10.1007/s11469-015-9566-x
van Ee, R., van Boxtel, J. J. A., Parker, A. L., & Alais, D. (2009). Multisensory Congruency as a Mechanism for Attentional Control over Perceptual Selection. *The Journal of Neuroscience, 29*(37), 11641-11649. doi:10.1523/jneurosci.0873-09.2009
van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., & Ebstein, R. P. (2011). Methylation Matters in Child Development: Toward Developmental Behavioral Epigenetics. *Child Dev Perspect, 5*(4), 305-310. doi:10.1111/j.1750-8606.2011.00202.x
Vance, D. E. (2010). Implications of positive and negative neuroplasticity on cognition in HIV. *Medical Science Monitor, 16*(4), HY3-HY5.
Vassena, E., Kochman, K., Latomme, J., & Verguts, T. (2016). Unimodal and cross-modal prediction is enhanced in musicians. *Sci Rep, 6*. doi:10.1038/srep25225
Venkit, V. R., Godse, A. A., & Godse, A. S. (2013). Exploring the potentials of group drumming as a group therapy for young female commercial sex workers in Mumbai, India. *Arts & Health: An International Journal of Research, Policy and Practice, 5*(2), 132-141. doi:10.1080/17533015.2012.698629
Vuust, P., & Kringelbach, M. L. (2010). The Pleasure of Making Sense of Music. *Interdisciplinary Science Reviews, 35*(2), 166-182. doi:10.1179/030801810X12723585301192
Wachi, M., Koyama, M., Utsuyama, M., Bittman, B. B., Kitagawa, M., & Hirokawa, K. (2007). Recreational music-making modulates natural killer cell activity, cytokines, and mood states in corporate employees. *Medical Science Monitor, 13*(2), Cr57-70.
Walker, K. A., & Brown, G. G. (2018). HIV-associated executive dysfunction in the era of modern antiretroviral therapy: A systematic review and meta-analysis. *J Clin Exp Neuropsychol, 40*(4), 357-376. doi:10.1080/13803395.2017.1349879

Walker, S. Y., Pierre, R. B., Christie, C. D., & Chang, S. M. (2013). Neurocognitive function in HIV-positive children in a developing country. *International Journal of Infectious Diseases, 17*(10), e862-867. doi:10.1016/j.ijid.2013.02.014

Watanabe, K., Ogino, T., Nakano, K., Hattori, J., Kado, Y., Sanada, S., & Ohtsuka, Y. (2005). The Rey-Osterrieth Complex Figure as a measure of executive function in childhood. *Brain Dev, 27*(8), 564-569. doi:10.1016/j.braindev.2005.02.007

Watson, J., Washington, G., & Stepteau-Watson, D. (2015). Umoja: A culturally specific approach to mentoring young African American males. *Child & Adolescent Social Work Journal, 32*(1), 1-10. doi:10.1007/s10560-014-0367-z

Watts-English, T., Fortson, B. L., Gibler, N., Hooper, S. R., & De Bellis, M. D. (2006). The Psychobiology of Maltreatment in Childhood. *Journal of Social Issues, 62*(4), 717-736. doi:10.1111/j.1540-4560.2006.00484.x

Webb, L., Perry-Parrish, C., Ellen, J., & Sibinga, E. (2017). Mindfulness instruction for HIV-infected youth: a randomized controlled trial. *AIDS Care*, 1-8. doi:10.1080/09540121.2017.1394434

Weber, V., Radeloff, D., Reimers, B., Salzmann-Manrique, E., Bader, P., Schwabe, D., & Konigs, C. (2017). Neurocognitive development in HIV-positive children is correlated with plasma viral loads in early childhood. *Medicine (Baltimore), 96*(23), 6. doi:10.1097/md.0000000000006867

Wechsberg, W. M., Luseno, W., Riehman, K., Karg, R., Browne, F., & Parry, C. (2008). Substance use and sexual risk within the context of gender inequality in South Africa. *Subst Use Misuse, 43*(8-9), 1186-1201. doi:10.1080/10826080801918247

Weiss, A. H., Biron, T., Lieder, I., Granot, R. Y., & Ahissar, M. (2014). Spatial vision is superior in musicians when memory plays a role. *J Vis, 14*(9). doi:10.1167/14.9.18

West, A. (2001). *Comparison of neuropsychological performances of asymptomatic HIV positive and HIV negative adolescents and young adults (immune deficiency).* (PhD in Psychology), Palo Alto University, ProQuest database.

WHO. (2016). *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. Second Edition.* Retrieved from Geneva, Switzerland: https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf;jsessionid=7FE564240EA92A61D460765A035FA2FF?sequence=1

Wiebe, S. A., Espy, K. A., & Charak, D. (2007). Using confirmatory factor analysis to understand executive control in preschool children: I. Latent structure. *Dev Psychol, 44*(2), 575-587. doi:10.1037/0012-1649.44.2.575

Wiebe, S. A., Espy, K. A., & Charak, D. (2008). Using confirmatory factor analysis to understand executive control in preschool children: I. Latent structure. *Dev Psychol, 44*(2), 575-587. doi:10.1037/0012-1649.44.2.575

Wilkinson, A., Pettifor, A., Rosenberg, M., Halpern, C. T., Thirumurthy, H., Collinson, M. A., & Kahn, K. (2017). The employment environment for youth in rural South Africa: A mixed-methods study. *Development Southern Africa, 34*(1), 17-32. doi:10.1080/0376835X.2016.1259986

Wilkinson, A. L., Fleming, P. J., Halpern, C. T., Herring, A. H., & Harris, K. M. (2018). Adherence to gender-typical behavior and high frequency substance use from adolescence into young adulthood. *Psychology of Men and Masculinity, 19*(1), 145-155. doi:10.1037/men0000088

Willen, E. J., Cuadra, A., Arheart, K. L., Post, M. J. D., & Govind, V. (2017). Young adults perinatally infected with HIV perform more poorly on measures of executive functioning and motor speed than ethnically matched healthy controls. *AIDS Care, 29*(3), 387-393. doi:10.1080/09540121.2016.1234677

Wilson, M. J., & Vassileva, J. (2016). Neurocognitive and psychiatric dimensions of hot, but not cool, impulsivity predict HIV sexual risk behaviors among drug users in protracted abstinence. *Am J Drug Alcohol Abuse, 42*(2), 231-241. doi:10.3109/00952990.2015.1121269

Wiltermuth, S. S., & Heath, C. (2009). Synchrony and cooperation. *Psychol Sci, 20*(1), 1-5. doi:10.1111/j.1467-9280.2008.02253.x

Winkelman, M. (2003). Complementary therapy for addiction: "drumming out drugs". *Am J Public Health, 93*(4), 647-651. doi:10.2105/ajph.93.4.647

Wood, L., Ivery, P., Donovan, R., & Lambin, E. (2013). “To the beat of a different drum”: improving the social and mental wellbeing of at-risk young people through drumming. *Journal of Public Mental Health, 12*(2), 70-79. doi:10.1108/JPMH-09-2012-0002

World Development Report 2007: Development and the Next Generation. (2007). Retrieved from Washington DC:

World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. (2013). Retrieved from Fortaleza, Brazil:

Wyatt, J. (2000). *Drumming for violence prevention: The effects of group music therapy on self-esteem and peer relationships in high school students.* (Masters in Music Therapy), Michigan State University,

Young, C., & Mayson, T. (2010). The Alcohol Use Disorders Identification Scale (AUDIT) normative scores for a multiracial sample of Rhodes University residence students. *Journal of Child & Adolescent Mental Health, 22*(1), 15-23. doi:10.2989/17280583.2010.493659

Yu, X., Gao, L., Wang, H., Yin, Z., Fang, J., Chen, J., . . . Gui, X. (2019). Neuroanatomical Changes Underlying Vertical HIV Infection in Adolescents. *Frontiers in Immunology, 10*(814). doi:10.3389/fimmu.2019.00814

Yuhi, T., Kyuta, H., Mori, H. A., Murakami, C., Furuhara, K., Okuno, M., . . . Higashida, H. (2017). Salivary Oxytocin Concentration Changes during a Group Drumming Intervention for Maltreated School Children. *Brain Sciences, 7*(11). doi:10.3390/brainsci7110152

Zanoni, B. C., Archary, M., Buchan, S., Katz, I. T., & Haberer, J. E. (2016). Systematic review and meta-analysis of the adolescent HIV continuum of care in South Africa: the Cresting Wave. *BMJ Global Health, 1*(3), e000004. doi:10.1136/bmjgh-2015-000004

Zelazo, P. D., & Carlson, S. M. (2012). Hot and Cool Executive Function in Childhood and Adolescence: Development and Plasticity. *Child Development Perspectives, 6*(4), 354-360. doi:10.1111/j.1750-8606.2012.00246.x

Zelazo, P. D., & Müller, U. (2002). Executive Function in Typical and Atypical Development. In U. Goswami (Ed.), *Blackwell Handbook of Childhood Cognitive Development* (pp. 445-469): Blackwell Publishers Ltd.
Zimet, G. D., Dahlem, N. W., Zimet, S. G., & Farley, G. K. (1988). The Multidimensional Scale of Perceived Social Support. *J Pers Assess, 52*(1), 30-41. doi:10.1207/s15327752jpa5201_2
Zuk, J., Benjamin, C., Kenyon, A., & Gaab, N. (2014). Behavioral and neural correlates of executive functioning in musicians and non-musicians. *PLoS One, 9*(6), e99868. doi:10.1371/journal.pone.0099868

Appendices

Appendix 1: Study 1 methods

Table I. Search strategy for PubMed

Population	Concept
1. HIV	23. executive function*
2. HIV/AIDS	24. dysexecutive syndrome
3. human immunodeficiency virus	25. frontal lobe function
4. HIV+	26. executive cognitive function
5. HIV-infected	27. prefrontal function
6. HIV infection	28. executive dyscontrol
7. HIV-positive	29. executive dysfunction
8. 1 or 2 or 3 or 4 or 5 or 6 or 7	30. frontal systems behaviours
9. animals.sh. not	31. executive skills
10. vertically transmitted	32. inhibitory control
11. vertical transmission	33. task switching
12. perinatally acquired	34. set shifting
13. perinatal infection	35. cognitive flexibility
14. mother-to-child transmission	36. working memory
15. paediatric AIDS	37. ADHD
16. pediatric AIDS	38. attention deficit
17. HIV-exposed	39. attention deficit hyperactivity disorder
18. HIV-exposed uninfected	40. impulsivity
19. children	41. neurodevelopment
20. adolescents	42. cognitive development
21. youth	43. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
22. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	44. 8 and 9 and 22 and 43

Key: * truncation symbol

Table II. Downs and Black Quality Assessment Checklist

Criterion number	Description of criterion (with additional explanation as required, determined by consensus of raters)	Possible answers
1	Is the hypothesis / aim / objective of the study clearly described? Must be explicit.	Yes/No
2	Are the main outcomes to be measured clearly described in the Introduction or Methods sections? If the main outcomes are first mentioned in the Results section, the question should be answered No. All primary outcomes should be described for Yes.	Yes/No
3	Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	Yes/No
4	Are the interventions of interest clearly described? Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes/No
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided.	Yes/No
6	Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.	Yes/No
7	Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data, the standard error, standard deviation or confidence intervals should be reported.	Yes/No
8	Have all important adverse events that may be a consequence of the intervention been reported? This should be answered Yes if the study demonstrates that there was a comprehensive attempt to measure adverse events.	Yes/No
9	Have the characteristics of patients lost to follow-up been described? If not explicit = No. Retrospective: if not described = UTD; if not explicit re: numbers agreeing to participate = No.	Yes/No/ UTD

10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes/No
Criterion number	**Description of criterion (with additional explanation as required, determined by consensus of raters)**	**Possible answers**
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected.	Yes/No/ UTD
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated.	Yes/No/ UTD
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes/No/ UTD
14	Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered Yes. Retrospective, single group = No; UTD if > 1 group and blinding not explicitly stated.	Yes/No/ UTD
15	Was an attempt made to blind those measuring the main outcomes of the intervention? Must be explicit.	Yes/No/ UTD
16	If any of the results of the study were based on “data dredging”, was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. Retrospective = No. Prospective = Yes.	Yes/No/ UTD
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? Where follow-up was the same for all study patients the answer should be Yes. Studies where differences in follow-up are ignored should be answered No. Acceptable range: 1 year follow up = 1 month each way; 2 years follow up = 2 months; 3 years follow up = 3 months; 10 years follow up = 10 months.	Yes/No/ UTD
18	Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be	Yes/No/ UTD

	appropriate to the data. If no tests done, but would have been appropriate to do = No.	
Criterion number	**Description of criterion (with additional explanation as required, determined by consensus of raters)**	**Possible answers**
19	Was compliance with the intervention/s reliable? Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered No.	Yes/No/ UTD
20	Were the main outcome measures used accurate (valid and reliable)? Where outcome measures are clearly described, which refer to other work or that demonstrate the outcome measures are accurate = Yes. All primary outcomes valid and reliable for Yes.	Yes/No/ UTD
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Patients for all comparison groups should be selected from the same hospital. The question should be answered UTD for cohort and case control studies where there is no information concerning the source of patients.	Yes/No/ UTD
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time? For a study which does not specify the time period over which patients were recruited, the question should be answered as UTD.	Yes/No/ UTD
23	Were study subjects randomised to intervention groups? Studies which state that subjects were randomised should be answered Yes except where method of randomisation would not ensure random allocation.	Yes/No/ UTD
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered No.	Yes/No/ UTD
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? In nonrandomised studies, if the effect of the main confounders was not investigated or no adjustment was made in the final analyses the question should be answered as No. If no significant difference between groups shown, then Yes.	Yes/No/ UTD
26	Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported = UTD.	Yes/No/ UTD

Criterion number	Description of criterion (with additional explanation as required, determined by consensus of raters)	Possible answers
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance was <5%? Sample sizes have been calculated to detect a difference of x% and y%.	Yes/No/ UTD

Key: UTD = unable to determine

Table III. Application of Downs and Black Quality Assessment Checklist criteria according to study type

	Study type			
Criteria	Observational studies with more than 1 group	Observational studies with 1 group only	Controlled interventional studies	Non-controlled interventional studies
Include	1, 2, 3, 5, 6, 7, 10, 11, 12, 13, 15, 16, 18, 20, 21, 22, 25, 27 (Total 18)	1, 2, 3, 6, 7, 10, 11, 12, 13, 16, 18, 20, 25, 27 (Total 14)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 (Total 26)	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 19, 20, 25, 26, 27 (Total 20)
Include only if longitudinal follow-up data	9, 17, 26 (Total 21)	9, 17, 26 (Total 17)	-	-
Exclude	4, 8, 14, 19, 23, 24	4, 5, 8, 14, 19, 21, 22, 23, 24	14	5, 14, 15, 21, 22, 23, 24

Table IV. Key data extracted into study database tables

Study type	Data extracted
Any	First author; year published; journal or conference; countries of data collection; study design; temporal nature of data (e.g. two-year follow-up data); age range of participants; total sample size; target subpopulation (e.g. perinatally acquired HIV) and size; comparator group/s subpopulation (e.g. perinatally HIV-exposed uninfected) and size; method of group selection; number of groups; behavioural report outcomes including measure, mean, standard deviation and effect size; cognitive task outcomes for core and complex executive functions including measure, mean, standard deviation and effect size; associated individual factors (e.g. sex); associated caregiver factors (e.g. caregiver level of education); associated disease-related factors (e.g. current viral load); associated outcomes (e.g. treatment adherence).
Experimental or quasi-experimental	Type of control arm (active, receiving an alternative intervention, or passive, receiving nothing) and size; intervention type; size of intervention arm; dosage and timing of intervention (e.g. duration, number and length of sessions).

Table V. Formulae used for conversions prior to meta-analysis

Estimates reported	**Conversion**	**Method source**
Standard error of mean	$SD = SE \times \sqrt{N}$	Cochrane Handbook 5.1
95% confidence interval	$SD = \sqrt{N} \times (upper\ limit - lower\ limit)/3.92$	Cochrane Handbook 5.1
Means of two subgroups	$Pooled\ mean = \frac{N1M_1+N_2M_2}{N_1+N_2}$	Cochrane Handbook 5.1
Standard deviations of two subgroups	$Pooled\ SD = \sqrt{\frac{(N_1-1){SD_1}^2 + (N2-1){SD_2}^2 + \frac{N_1N_2}{N_1+N_2}\left({M_1}^2 + {M_2}^2 - 2M_1M_2\right)}{N_1+N_2-1}}$	Cochrane Handbook 5.1

Key: SD = standard deviation; SE = standard error of the mean; N = number of participants; M = mean

Appendix 2: Study 1 included studies

Table A. Characteristics of included observational studies: perinatally acquired HIV and perinatally HIV-exposed uninfected participants

First author & year (quality assessment score)[a]	Country (cohort/ study name)	Study design[b]	Sampling frame[c]	Response rate and retention rate[c]	Target population (sample size)[c]	Comparator (sample size)[c]	HIV disease stage and/or CD4 count/%[d]	% HIV+ on ART[e]	Cognitive task measures[f]	Cognitive task findings (effect size estimate)[g]	Behavioural report measures[h]	Behavioural findings (effect size estimate)[h]
Robbins 2019 (81%) Robbins 2018 (14%)	US (CASAH)	PC (C)	Health facility-based	71% retention	PHIV 15-29 years (n=146 at 1st cognitive visit)	PHEU (n=96)	NR	100%	TMT, DS	Cross-sectional: WM: PHIV<PHEU at 2 of 3 visits. TS: PHIV<PHEU at 1 of 3 visits. Longitudinal: WM, TS: PHIV=PHEU	NA	NA
Hoare 2019 (86%) Hoare 2019 (29%) †Phillips 2018 (62%)	South Africa (CTAAC neuro substudy)	PC (C)	PHIV: health facility based. PHU: Youth centres.	NR	PHIV 9-12 years (n=203)	PHU (n=44)	CD4 count: mean 953 (SD 496)	100%	WISC-IV DSB CTT NEPSY-II inhibition Semantic fluency	Baseline: WM: PHIV<PHU (M) TS: PHIV<PHU (S)	NA	NA
Blokhuis 2019 (61%) Van den Hof 2019 (81%) Van Dalen 2016 (67%) †Cohen 2015 (69%)	Nether-lands (NOVICE)	PC (C)	PHIV: health facility based. PHU: community-based	60-62% retention	PHIV 8-18 years (n=26) at baseline; 12-23 years at follow-up (n=21)	PHU (n=36) at baseline; PHU (n=23) at follow-up	27% CDC C at baseline	85% at baseline ; 95% at follow-up	WISC/WAIS -III DS TMT-B	Baseline: TS: PHIV<PHU (S). WM: PHIV<PHU (L) Follow-up: TS: PHIV<PHU (L). WM: PHIV=PHU.	NA	NA
†Debeaudrap 2018 (57%)	Cameroon (Pediacam ANRS-12140)	Nested CS(C) in PC (C)	Health facility-based	61% retention at neuro substudy	PHIV 4-9 years (n=126)	PHEU (n=101); PHU (n=110)	Mean CD4% 44 (SD 12)	100%	KABC-II: DS, HM (all). KABC-II: PR, SC (6-8 years)	WM: PHIV<PHU (L), PHIV<PHEU (M), PHEU=PHU. PL: PHIV<PHU (L), PHIV<PHEU (S), PHEU=PHU	NA	NA
†Bisiacchi 2018 (67%)	Italy	CS (C)	Health facility-based	NR	PHIV 8-15 years (n=16)	PHU 9-17 years (n=28)	NR	100%	BVN: Corsi blocks, DSB, Tower of London, TMT, VF	Verbal WM, TS: PHIV<PHU (L) Visuospatial WM, PL: PHIV=PHU	NA	NA
†Boivin 2018 (81%) Boivin 2018 (43%) 2018 (33%) Boivin 2017 (33%)	South Africa, Zimbabwe, Malawi, Uganda (P1104S)	PC (C)	Health facility-based	Response >95% in HIV+ group; retention NR.	PHIV 5-11 years (n=246 at baseline)	PHEU (n=183); PHU (n=182)	WHO stage: 15% I 24% II 56% III 5% IV	100%	KABC-II: DS, HM, PR, SC. TOVA	Baseline: WM: PHIV<PHU (M). PHIV<PHEU (M). PHEU=PHU. PL: PHIV<PHU (M). PHIV<PHEU (S). PHEU=PHU.	BRIEF PR	Baseline: GEC, BRI, MI: PHIV=PHEU=PHU. 1-year follow-up: PHIV<PHEU. PHIV<PHU. 2-year follow-up: PHIV>PHEU, PHU

										IC: PHIV=PHEU=PHU. 1-year & 2-year follow-ups: Similar findings		
First author & year (quality assessment score)[a]	**Country (cohort/ study name)**	**Study design[b]**	**Sampling frame[c]**	**Response rate and retention rate[c]**	**Target population (sample size)[c]**	**Comparator (sample size)[c]**	**HIV disease stage and/or CD4 count/%[d]**	**% HIV+ on ART[e]**	**Cognitive task measures[f]**	**Cognitive task findings (effect size estimate)[g]**	**Behavioural report measures[h]**	**Behavioural findings (effect size estimate)[h]**
†Sherr 2018 (76%) Sherr 2017 (67%)	South Africa, Malawi	CS (C)	CBO-based: stratified random sample	Response 99%; retention 86%.	PHIV 5-15 years (n=135 at baseline)	Mixed PHEU/PHU (n=854 at baseline)	NR	93%	DS	Baseline: PHIV< PHEU/PHU (M). Follow-up: PHIV< PHEU/PHU (S).	NA	NA
†Yadav 2018 (39%) Yadav 2017 (47%)	India	CS (C)	NR	Response NR.	PHIV mean age 9.3, SD 2.5 years (n=49)	PHU mean age 8.7, SD 2.7 years (n=23)	CD4 count: mean 483 (SD 240)	100%	Mazes	PL: PHIV=PHU	NA	NA
†Milligan 2017 (78%) †Milligan 2016 (78%)	South Africa	CS (C)	Health facility-based	NR	PHIV 6-8 years (n=95) (NEPSY-II subsample: PHIV n=29)	PHEU (n=88); PHU (n=92) (NEPSY-II subsample: PHEU n=29; PHU n=29)	Stable CD4 count.	100%	AWMA (Verbal WM: listening, counting & backward DS; Visuospatial WM: odd one out, Mister X, spatial recall) NEPSY-II auditory attention & response set, design fluency, inhibition	Verbal WM: PHIV<PHU (L). PHIV<PHEU (M). PHEU<PHU (L). Spatial WM: PHIV<PHU (L). PHIV<PHEU (M). PHEU<PHU (M). IC: PHIV=PHEU. PHIV<PHU (L). PHEU<PHU (L).	NA	NA
Brahmbhatt 2017 (62%)	Uganda (Rakai cohort)	PC (C)	2 previous study cohorts & health facility-based	NR	PHIV 7-14 years (n=140)	PHEU (n=26); PHU (204)	NR	41%	KABC-II	WM: PHIV=PHU. PL: PHIV=PHU.	NA	NA
Lewis-de los Angeles 2017 (52%) Garvie 2017 (75%) Malee 2017 (71%) †Nichols 2016 (69%)	US, Puerto Rico (some sub-studies only US) (PHACS AMP)	PC (C)	Health facility-based	82% of full cohort: valid baseline data	PHIV 7-16 years (n=358 at baseline); PHIV 9-18 years (n=173) in EF sub-study	PHEU (n=200 at baseline); PHU (n=314; only for neuroimaging sub-study; none for	Baseline: 25% CDC C	93% (EF sub-study)	WISC/WAIS-IV CCTT -Memory & EF substudy: 4 subtests of DKEFS: VF, Design	Baseline: WM: CDC C=non-C=PHEU. TS: CDC C≤PHEU. CDC C≤non-C. IC: CDC C<PHEU. CDC C≤non-C. PL: PHIV (no encephalopathy)	BRIEF PR BRIEF SR (≥11 years)	Baseline: PR BRI: PHIV (no encephalopathy)< PHEU. PHIV (encephalopathy)<PHEU. SR BRI, PR MI, SR MI: PHIV (no encephalopathy) = PHIV

Sirois 2016 (72%) †Nichols 2015 (62%) Uban 2015 (50%) †Smith 2012 (61%) Kapetanovic 2010 (64%)					starting at 2 years; PHIV 11-20 years (n=144) at EF sub-study follow-up at 4 years	some sub-studies)			Fluency, CWIT, Twenty Questions	=PHIV (encephalopathy=PHEU. Change at follow-up: CDC C=non-C=PHEU. All improved.		(encephalopathy)=PHEU. PR GEC: PHIV (no encephalo-pathy) > PHEU. PHIV (encephalo-pathy)=PHEU SR GEC: PHIV (no encephalo-pathy) = PHIV (encephalo-pathy) = PHEU.
First author & year (quality assessment score)[a]	**Country (cohort/ study name)**	**Study design[b]**	**Sampling frame[c]**	**Response rate and retention rate[c]**	**Target population (sample size)[c]**	**Comparator (sample size)[c]**	**HIV disease stage and/or CD4 count/%[d]**	**% HIV+ on ART[e]**	**Cognitive task measures[f]**	**Cognitive task findings (effect size estimate)[g]**	**Behavioural report measures[h]**	**Behavioural findings (effect size estimate)[h]**
Weber 2017 (71%)	Germany	RC	Health facility-based	NR	PHIV 6-16 years (n=14)	None	Median CD4 count 1751	100%	WISC-IV WMI	WM: PHIV>norms (S)	NA	NA
†Willen 2017 (75%)	US	CS (C)	PHIV: health facility-based PHU: community-based	PHIV 41% & PHU 87% response.	PHIV 18-24 years (n=29)	PHU (n=13)	28% history of encephalo-pathy; mean CD4 count 408 (SD 288)	76%	WAIS-III DS & LNS WMS-IV SS DKEFS TMT (Trails 1-5) & VF Test (Conditions 1 & 2)	Verbal WM: PHIV<PHU (L). Spatial WM: PHIV<PHU (L). Simple sequencing: PHIV<PHU (M). Complex sequencing: PHIV<PHU (L). VF: PHIV<PHU (L).	NA	NA
Rotheram-Borus 2018 (43%) †Rotheram-Borus 2017 (74%)	South Africa	PC (C)	Population-based	98% response; 85% retention at 3 years	PHEU 3 years (Baseline: n=177; follow-up: n=131)	PHU (Baseline: n=398; follow-up: n=316)	NA	NA	Executive score (3 tasks: 'Some-thing's the same', 'silly sounds', operational span)	3 & 5 years old: PHEU=PHU	SDQ	Hyperactivity/ inattention subscale not reported
Arenas-Pinto 2019 (61%) †Judd 2016 (71%)	UK (AALPHI)	PC (C)	Health facility-based & CBO-based	NR	PHIV 12-21 years (n=296)	Mixed 13-23 years PHEU/PHU siblings (n=97)	26% CDC C; median CD4 599 (IQR 407-790)	86%	Baseline: Colour Trails 2 CogState Groton maze learning test, one back Follow-up: NIH Toolbox Flanker, dimensional	Baseline: WM: PHIV<PHEU/PHU (S), CDC=non-C. TS: PHIV<PHEU/PHU (S), CDC C<non-C Follow-up: IC: PHIV-C=non-C=PHEU/PHU, TS: PHIV-C=non-C=PHEU/PHU	NA	NA

									change card sort			
First author & year (quality assessment score)[a]	**Country (cohort/ study name)**	**Study design[b]**	**Sampling frame[c]**	**Response rate and retention rate[c]**	**Target population (sample size)[c]**	**Comparator (sample size)[c]**	**HIV disease stage and/or CD4 count/%[d]**	**% HIV+ on ART[e]**	**Cognitive task measures[f]**	**Cognitive task findings (effect size estimate)[g]**	**Behavioural report measures[h]**	**Behavioural findings (effect size estimate)[h]**
†Ene 2016 (61%)	Romania	CS (C)	PHIV: facility-based. PHEU/PHU: community based.	NR	PHIV mean age 24.0, SD 1.5 years (n=194)	Mixed PHEU/PHU (n=51)	Median CD4 count 479	92%	WM (PASAT 50 item, WMS-III Spatial Span). EF (Halstead Category Test, WCST, TMT Part B, Colour Trails II, Stroop incongruent) VF (letter, animal and action fluency).	WM: HIV+ < HIV-. EF: HIV+ < HIV-. VF: HIV+ = HIV-.	Frontal System Behaviour Scale (self-report)	Executive dysfunction: HIV+ < HIV- (S).
Bangirana 2016 (29%)	Uganda (PRO-MOTE substudy)	CS	Subsample from an ART RCT (likely health facility-based)	NR	PHIV IQR age 6.3-8.4 years (n=105) (subtype A n=78, subtype D n=27)	None	Median CD4 count 868 (IQR 416-1204)	100% (52% PI-based; 48% NNRTI-based)	KABC-II TOVA	Subtype A = Subtype D	NA	NA
†Ezeamama 2016 (75%)	Uganda	CS (C)	Health facility-based	NR	PHIV 6-18 years (n=58)	PHEU (n=55); PHU (n=53)	Median CD4 count 772 (Range 63–2521)	78% (40% NVP-based; 28% EFV-based; 10% other)	NA	NA	BRIEF-PR BRIEF-SR (11-18 years)	PR GEC: PHIV<PHEU (L) PHIV<PHU (L) PHEU<PHU (S) SR GEC: PHIV<PHEU (M) PHIV<PHU (M) PHEU=PHU
†Hoare 2016 (64%)	South Africa	CS (C)	PHIV: health facility based. PHU: school-based	NR	PHIV 6-16 years (n=86)	PHU (n=34)	27% slow progressors; 21% HIV encephalo-pathy	73%	Color Trails 2; NEPSY-II inhibition, switching; WISC-IV DS; VF	IC: PHIV<PHU (S). TS: PHIV<PHU (S). WM: PHIV=PHU. VF: PHIV≤PHU	CBCL	CBCL attention problems scale NR

First author & year (quality assessment score)[a]	Country (cohort/ study name)	Study design[b]	Sampling frame[c]	Response rate and retention rate[c]	Target population (sample size)[c]	Comparator (sample size)[c]	HIV disease stage and/or CD4 count/%[d]	% HIV+ on ART[e]	Cognitive task measures[f]	Cognitive task findings (effect size estimate)[g]	Behavioural report measures[h]	Behavioural findings (effect size estimate)[h]
†James 2016 (39%)	India	CS (C)	PHIV: care facility based. PHU: school-based	NR	PHIV 6-12 years (n=70)	PHU (n=70)	NR	NR (likely 100%)	WISC-III FDI: Arithmetic, DS	WM: PHIV<PHU (L)	NA	NA
†Rochat 2016 (67%)	South Africa	PC (C)	Population-based	99% response; 70% retention	PHEU 8-11 years (n=332)	PHU (n=574)	NA	NA	KABC-II NEPSY-II EF tests (animal sorting, auditory attention & response set)	WM: PHEU=PHU. IC: PHEU=PHU. TS: PHEU=PHU. PL: PHEU=PHU.	CBCL attention problems	PHEU=PHU
Familiar 2016 (75%)	Uganda (MISC)	CS (C) (RCT base-line: see Bass 2017)	Health facility-based & research facility-based	NR	PHIV 2-5 years (n=118)	PHEU (n=164)	NR	NR	NA	NA	Pre-school BRIEF	IC, FL, MI, GEC: PHIV=PHEU.
Benki-Nugent 2016 (19%)	Kenya	PC (C)	NR	NR	PHIV early-treated median 6.9 years (n=54); PHIV late treated median 13.4 years (n=24)	PHU median 6.7 years (n=63); PHEU median 7.4 years (n=43)	NR	?100%	KABC-II TOVA	WM: PHIV late-treated<PHU. PHIV late-treated < early-treated.	NA	NA
Burkey 2015 (71%)	Uganda	CS(C)	Community-based	NR	PHIV 3-12 years (n=19) (based on proxy variables)	PHEU (n=213)	NR	53% of presumed HIV+	KABC-II number recall & planning TOVA	WM, IC, PL: ADHD=no ADHD.	BRIEF	IC, WM, PL: ADHD = no ADHD MI, GEC: ADHD<no ADHD (L).
†Ashby 2015 (53%)	UK	CS (C)	Health facility-based & CBO-based	NR	PHIV 16-25 years (n=33)	Mixed PHEU/PHU siblings (n=14)	Mean CD4 count 444	79%	CogState EF	EF: PHIV=PHEU/PHU	NA	NA
Bangirana 2015 (28%)	Uganda	RC	NR	NR	PHIV 5-10 years (n=132) PI versus	None	NR	100% in past; current ART NR	KABC-II TOVA	IC: NNRTI<PI WM, PL: PI=NNRTI	NA	NA

					NRRTI-based ART								
First author & year (quality assessment score)[a]	**Country (cohort/ study name)**	**Study design[b]**	**Sampling frame[c]**	**Response rate and retention rate[c]**	**Target population (sample size)[c]**	**Comparator (sample size)[c]**	**HIV disease stage and/or CD4 count/%[d]**	**% HIV+ on ART[e]**	**Cognitive task measures[f]**	**Cognitive task findings (effect size estimate)[g]**	**Behavioural report measures[h]**	**Behavioural findings (effect size estimate)[h]**
Familiar 2015 (61%)	Uganda	CS (C)	Health facility-based	NR	PHIV 5-12 years (n=144)	PHU with a history of severe malaria (n=106)	NR	44%	NA	NA	BRIEF	BRI, GEC: Malaria<PHIV (L). MI: Malaria<PHIV (M)
†Linn 2015 (53%)	Myanmar	PC (C)	Care facility-based	Response NR; retention 71%	PHIV orphans 6-16 years (n=28)	PHU orphans (n=31)	Mean CD4 count 827 (IQR 545-1063)	100%	DS backwards Design fluency VF	TS, PL: PHIV<PHU Verbal WM: PHIV=PHU	NA	NA
Patel 2018 (38%) Kerr 2018 (29%) Jahanshad 2015 (56%) Kerr 2014 (52%) †Puthanakit 2013 (79%)	Cambodia, Thailand (PREDICT)	PC (C) post-RCT	PHIV: Health facility-based PHEU/PHU: siblings of PHIV participants	Response PHIV 93–97% for substudy, PHEU & PHU NR; retention PHIV 99%, PHEU & PHU 100%	PHIV 2-15 years (n=284) at start of neuro sub-study Median age at follow-up: 14 years	PHEU (n=166), PHU (n=167). 5-15 years PHEU (n=30) & PHU (n=33) in imaging sub-study	Median CD4%: early 33%; deferred 24%	100% early arm; 48% deferred arm	WISC-III FDI Children's Color Trails Stanford-Binet II memory tasks (DS, sentence memory, object memory)	Baseline: TS, PL: HIV+ early = HIV+ deferred = PHEU = PHU. WM: Early = deferred. PHEU=PHU. Verbal WM: PHIV<PHEU (M). PHIV<PHU (M). Spatial WM: PHIV<PHEU (S). PHIV<PHU (S). Follow-up: TS, WM, PL: PHIV<PHU. PHEU=PHU.	CBCL attention problems	Baseline: PHEU=PHU
†Haase 2014 (67%)	Brazil	CS (C)	PHIV: Health facility based. PHU: School-based.	NR	PHIV 5-17 years (n=41)	PHU (n=82)	71% CDC C (n=29) 29% non-C (n=12)	100%	DS backwards Day-night Stroop Abstract Stroop Tower of Hanoi task	IC: PHIV/C<PHU (S-M). PHIV/C=non-C. Non-C=PHU. WM: PHIV/C<PHU (L). PHIV/C<non-C (M). Non-C=PHU. PL: PHIV/C<PHU (M). PHIV/C=non-C. Non-C=PHU.	NA	NA
†Llorente 2014 (67%)	US, Puerto Rico (WITS)	PC (C)	Health facility-based	NR	PHIV 3-8 years (n=96) at baseline; PHIV 8-12 years (n=76) in 2nd substudy	PHEU (n=211) at baseline; PHEU (n=85) in 2nd substudy	29% CDC C (n=22) 71% non-C (n=54)	89%	NEPSY subtests (Tower, Auditory Attention/ Set, Visual Attention) TMT-B Woodcock-Johnson Revised	10 years old: TS, IC, PL: PHIV/C=non-C= PHEU.	BRIEF PR	PHIV/C=non-C=PHEU.

									analysis-synthesis subtest			
First author & year (quality assessment score)[a]	**Country (cohort/ study name)**	**Study design[b]**	**Sampling frame[c]**	**Response rate and retention rate[c]**	**Target population (sample size)[c]**	**Comparator (sample size)[c]**	**HIV disease stage and/or CD4 count/%[d]**	**% HIV+ on ART[e]**	**Cognitive task measures[f]**	**Cognitive task findings (effect size estimate)[g]**	**Behavioural report measures[h]**	**Behavioural findings (effect size estimate)[h]**
†Ravindran 2014 (42%)	India	CS (C)	Care facility-based	67% eligible & participated	PHIV institutionalised 8-12 years (n=20)	PHU institutionalised (n=20)	NR	100%	DS TMT-B	WM, TS: PHIV<PHU (L)	NA	NA
García-Navarro 2013 (36%)	Spain (Co-RISpeS)	PC	Health facility-based	13% of original cohort assessed in substudy	PHIV 5-21 years (n=51 in Neuro sub-study at baseline); 11-19 years (n=95) in 2nd sub-study	None	29% CDC C (12% encephalopathy)	NR. Median years on ART 11.6 (Range 0-18.6)	WISC-IV DS Luria DNA battery ENFEN Digit-symbol test TMT VF	% impaired: WM 38% IC 14% TS 15% VF 13-50%	NA	NA
Walker 2013 (56%)	Jamaica	CS	Health facility-based	NR	PHIV median age 8.7 years, IQR 7.6–10.8 (n=30)	None	50% CDC C (encephalopathy) 50% non-C (no encephalopathy)	NR. Median years on ART: CDC C 5.5 (IQR 4.8-7.5). Non-C: 2.3 (IQR 0-5.3)	Corsi blocks	WM: encephalopathic<non-encephalopathic	NA	NA
Maganlal 2013 (50%)	South Africa	CS (C)	Health facility-based	NR	PHIV 13-16 years (n=29)	PHU (n=66)	CD4 count: 31%<200 28% 200-349 14% 350-499 28% ≥500	100%	DSB DKEFS CWIT TMT-B WISC-R mazes WCST	WM: PHIV<PHU (M) IC: PHIV<PHU (S) TS: PHIV≤PHU (S) PL: PHIV=PHU	NA	NA
†Gadow 2012 (71%) Nachman 2012 (71%)	US, Puerto Rico (IMPAACT P1055)	PC (C)	Health facility-based	92% retention	PHIV 6-17 years (n=319) at baseline (n=196 12-18 years in substance substudy); n=296 at 2-year follow-up	PHEU (n=174); PHU living in HIV-affected household (n=82). PHEU+PHU (n=229) at 2-year follow-up	22% CDC C; 76% baseline CD4%>25%	83%	WISC-IV LNS	PHIV=PHEU/PHU	CASI-4R/YSR-4/CSR-4 ADHD symptoms	PHIV=PHEU/PHU

First author & year (quality assessment score)[a]	Country (cohort/ study name)	Study design[b]	Sampling frame[c]	Response rate and retention rate[c]	Target population (sample size)[c]	Comparator (sample size)[c]	HIV disease stage and/or CD4 count/%[d]	% HIV+ on ART[e]	Cognitive task measures[f]	Cognitive task findings (effect size estimate)[g]	Behavioural report measures[h]	Behavioural findings (effect size estimate)[h]
†Ruel 2012 (64%)	Uganda	CS (C)	PHIV: facility based. PHU: community based.	NR	PHIV 6-12 years (n=93)	PHU (n=106)	WHO stage: 73% I-II 27% III Slow progressors: CD4 counts>350, median CD4 count 655	0%	KABC-II SPI (word order, number recall, hand movements) & planning index (PR, SC) TOVA visual & auditory	WM, PL: PHIV<PHU (S) IC: PHIV=PHU	NA	NA
†Foster 2012 (60%)	US	PC (C)	PHIV: health facility based. PHU: relatives & friends of PHIV participants.	Response NR; 88-89% retention	PHIV 8-17 years (n=38)	PHEU (n=11); PHU (n=22); unknown (n=2)	Mean CD4% 28.7 (SD 12.1)	NR	CCPT-II Children's PASAT B-E	IC: PHIV=PHEU/PHU WM: PHIV<PHEU/PHU (M)	BRIEF PR BRIEF SR	PHIV=PHEU/PHU
†Hoare 2012 (56%)	South Africa	CS (C)	Health facility-based	NR	PHIV 8-12 years (n=12)	PHU (n=12)	All slow progressors: mean CD4 count 585	0%	WISC-IV DSB CTT NEPSY-II inhibition Semantic fluency	TS: PHIV<PHU (L) WM, IC: PHIV=PHU	NA	NA
†Nagarajan 2012 (61%)	US	CS (C)	PHIV: health facility-based PHEU/PHU: health facility & relatives & friends of PHIV participants	NR	PHIV 13-25 years (n=16)	Mixed PHEU/PHU (n=14)	Mean CD4 count 536 (SD 340)	100%	Executive/ problem-solving score using DKEFS subtests (TMT subtest C4, Tower Test, CWIT inhibition & switching trials)	PHIV=PHEU/PHU	NA	NA

First author & year (quality assessment score)[a]	Country (cohort/ study name)	Study design[b]	Sampling frame[c]	Response rate and retention rate[c]	Target population (sample size)[c]	Comparator (sample size)[c]	HIV disease stage and/or CD4 count/%[d]	% HIV+ on ART[e]	Cognitive task measures[f]	Cognitive task findings (effect size estimate)[g]	Behavioural report measures[h]	Behavioural findings (effect size estimate)[h]
†De Pereira 2012 (31%)	Brazil	CS (C)	PHIV: health facility based. PHU: school-based	NR	PHIV 7-16 years (n=34)	PHU (n=34)	NR	NR	WISC-III DSB	PHIV<PHU (L)	NA	NA
Boivin 2010 (72%)	Uganda	CS	Health facility-based (from ongoing PC)	NR	PHIV 6-12 years (n=102)	None	9% WHO 1 29% WHO 2 14% WHO 3 1% WHO 4 47% NR	0%	KABC-II SPI (word order, number recall, hand movements) & planning index (PR, SC) TOVA visual & auditory	Viral subtypes A vs D: WM: A<D (S) IC, PL: A=D	NA	NA
Koekkoek 2008 (79%)	Nether-lands	CS	Health facility-based	NR	PHIV 6-13 years (n=22)	None	Median CD4% 30 (Range 12-42)	82%	ANT (set shifting, pattern recognition, spatial span, verbal fluency)	WM: PHIV<norms (M) TS: PHIV≤norms (S-M) VF: PHIV<norms (M)	NA	NA
Martin 2006 (61%)	US	CS	Health facility-based	100% response	PHIV 6-16 years (n=41)	None	Mean CD4% 22 (SD 12)	100%	WISC-III FDI (arithmetic, DSB)	WM: PHIV<norms (M) Abnormal CTB<normal CTB (L)	NA	NA
†Bagenda 2006 (71%)(Bagenda et al., 2006)	Uganda	PC (C)	Health facility-based	Response NR; 95% retention	PHIV 6-12 years (n=28)	PHEU (n=42); PHU (n=37)	29% CDC C Slow progressors	0%	KABC SPI (DS, word order, HM)	WM: PHIV≤PHEU (S-M) PHIV=PHU	NA	NA
†Blanchette 2002 (56%)	Canada	CS (C)	PHIV: health facility-based Controls: siblings of PHIV participants	NR	PHIV 6-14 years (n=14)	Mixed PHEU/PHU (n=11)	50% CDC A 29% CDC B 21% CDC C	86%	WISC-III arithmetic, DS FAS VF Animal/food VF	WM, VF: PHIV=PHEU/PHU	NA	NA

First author & year (quality assessment score)[a]	Country (cohort/ study name)	Study design[b]	Sampling frame[c]	Response rate and retention rate[c]	Target population (sample size)[c]	Comparator (sample size)[c]	HIV disease stage and/or CD4 count/%[d]	% HIV+ on ART[e]	Cognitive task measures[f]	Cognitive task findings (effect size estimate)[g]	Behavioural report measures[h]	Behavioural findings (effect size estimate)[h]
Bisiacchi 2000 (33%)	Italy	CS (C)	Health facility-based	NR	PHIV 6-15 years (n=29)	PHEU (n=13)	17% CDC A 52% CDC B 31% CDC C	NR	TMT-B DS Verbal fluency Phonemic fluency Elithorn's maze test Tower of London	EF: PHIV<PHEU WM: NR separately	NA	NA
†Boivin 1995 (61%)	DRC	CS (C)	PHIV & PHEU: health facility-based PHU: Community-based	15-58% response in PHIV/ PHEU (from an original cohort)	PHIV >2 years (preschool age) (n=11)	PHEU (n=15); PHU (n=15)	WHO: No major signs & no more than 3 minor signs of AIDS	0%	KABC SPI (DS, word order, HM)	WM: PHIV<PHU (L) PHIV≤PHEU PHEU≤PHU	NA	NA

Key:

[a] † = included in meta-analysis; % = higher means better quality with lower risk of bias

[b] CS = cross-sectional study; C = controls; PC = prospective cohort study; RCT = randomised controlled trial; RC = retrospective cohort study

[c] CBO = community-based organisation; NR = not reported; PHIV = perinatally acquired HIV; PHU = perinatally unexposed uninfected; PHEU = perinatally HIV-exposed uninfected; EF = executive function; IQR = interquartile range

[d] WHO = World Health Organization; SD = standard deviation; CDC = Centres for Disease Control and Prevention HIV stage; NA = not applicable

[e] ART = antiretroviral therapy; PI = protease inhibitor; NNRTI = non-nucleoside reverse-transcriptase inhibitor; NVP = nevirapine; EFV = efavirenz

[f] TMT = trail-making task; DS = digit span; KABC = Kaufman Assessment Battery for Children; WM = working memory; HM = hand movements; PL = planning; PR = pattern reasoning; SC = story completion; BVN = 'Batteria di Valutazione Neuropsicologica per l'Età Evolutiva' (Neuropsychological Assessment Battery for Children; TOVA = Test of Variables of Attention, a continuous performance task; Automated Working Memory Assessment (AWMA); TOVA = Test of Variables of Attention; WISC = Wechsler Intelligence Scale for Children; WISC-R = Wechsler Intelligence Scale for Children-Revised; WAIS = Wechsler Adult Intelligence Scale; CCTT = Children's Colour Trails Test; EF = executive function; DKEFS = Delis-Kaplan Executive Function System; VF = verbal fluency; CWIT = Colour-Word Interference Test, a Stroop task; WMI = working memory index; LNS = letter number sequencing; WMS = Wechsler Memory Scale; SS = symbol span; PASAT = Paced Auditory Serial Addition Test; WCST = Wisconsin Card Sorting Test; NEPSY = A Developmental Neuropsychological Assessment; FDI = Freedom from distractibility index; TMT-B = trail-making task part B; Luria-DNA = Luria Diagnostic Neuropsychological Evaluation of Adults; ENFEN = Neuropsychological Evaluation of Executive Function in Children; DSB = digit span backwards; SPI = sequential processing index; CCPT = Conner's Continuous Performance Task; CTT = Colour Trails Test; WASI = Wechsler Abbreviated Scale of Intelligence; ANT = Amsterdam Neuropsychological Tasks

[g] Effect size estimate: small S d = 0.2-0.49, medium M d = 0.5-0.79, large L d ≥ 0.8; direction of effect: < worse, > better, ≤ worse than or the same as, = the same as; WM = working memory; PL = planning; IC = inhibitory control; TS = task switching; CTB = computed tomography brain scan

[h] BRIEF = Behavioural Rating Inventory of Executive Function; PR = parent report; SR = self-report; SDQ = Strengths and Difficulties Questionnaire; CBCL = Child Behaviour Checklist; GEC = global executive composite; BRI = behavioural regulation index; MI = metacognitive index; FL = cognitive flexibility; CASI-4R = Child and Adolescent Symptom Inventory-4R; YSR-4 = youth self-report-4; CSR-4 = child self-report-4

Table B. Characteristics of included observational studies: behaviourally acquired HIV

First author & year (quality assessment score)[a]	Country (cohort/ study name)	Study design[b]	Sampling frame	Response rate and retention rate[c]	Target population (sample size)[c]	Comparator/s (sample size)[c]	HIV disease stage and/or CD4 count[d]	% HIV+ on ART[e]	Cognitive task measures[f]	Cognitive task findings (effect size estimate)[g]	Behavioural report measures[h]	Behavioural findings (effect size estimate)[g]
Kim-Chang 2019 (50%) Nichols 2016 (67%) Nichols 2013 (71%)	US, Puerto Rico (ATN 071) Biomarker substudy drawn from ATN 071 & ATN 101	PC	Health facility-based	Response NR. Retention 62%.	BHIV 18-24 years (n=220) at baseline; 4 follow-up visits (n=137 at final visit) Biomarker substudy: BHIV 18-28 years (n=128)	None	88% CDC A 11% CDC B 1% CDC C Median CD4 398	0% at baseline. 3 subgroups initiated ART at different times.	Executive scale (TMT-B, Stroop interference test, COWA). Attention/ working memory scale (DS, LNS)	Baseline (% impaired): TS: HIV+ < norms. IC: HIV+ = norms. WM: HIV+ = norms. Follow-up: Trajectories not affected by ART timing.	BRIEF-Adult (baseline)	Baseline (% impaired): MI, BRI, GEC: HIV+< norms
†Baker 2014 (58%)	US	CS (C)	Health facility-based	NR	BHIV 18-24 years (n=23)	HIV- (n=21)	Mean CD4 count 562 (SD 265, range 93-1137)	65%	WAIS-III LNS TMT-B Verb fluency task FAS VF	TS, WM: BHIV=HIV- VF: BHIV<=HIV-(L/S)	NA	NA
Salama 2013 (68%)	US	CS	Health facility-based	Response NR; 94% retention	BHIV 14-23 years (n=59 evaluated)	None	CD4 count: 5% <200 61% 200-500 34% >500	32%	WCST	BHIV=norms	NA	NA
†West 2001 (61%)	US	CS (C)	Health facility-based	NR	BHIV 16-26 years (n=32)	HIV- (n=26)	78% CDC A 13% CDC B 9% CDC C Mean CD4 count 590 (SD 250)	6%	TMT-B WCST Stroop FAS VF	BHIV<=HIV-(S)	NA	NA

Key:
[a] % = higher means better quality with lower risk of bias; † = included in meta-analysis
[b] CS = cross-sectional study; C = controls; PC = prospective cohort study
[c] NR = not reported; BHIV = behaviourally acquired HIV; HIV- = HIV-negative
[d] CDC = Centres for Disease Control and Prevention HIV stage
[e] ART = antiretroviral therapy;
[f] TMT-B = trail-making task part B; COWA = Controlled Oral Word Association Test, a verbal fluency task; DS = digit span; LNS – letter number sequencing; WAIS = Wechsler Adult Intelligence Scale; VF = verbal fluency; WCST = Wisconsin Card Sorting Test
[g] Effect size estimate: small S d = 0.2-0.49, medium M d = 0.5-0.79, large L d ≥ 0.8; direction of effect: < worse, > better, ≤ worse than or the same as, = the same as
[h] BRIEF = Behavioural Report Inventory of Executive Functioning; BRI = behavioural regulation index; MI = metacognitive index; GEC = global executive composite

Table C. Characteristics of included experimental and quasi-experimental studies

First author & year (quality assessment score)[a]	Country (cohort/ study name)	Study design (control type)[b]	Intervention type and timing[b]	Control group type and timing	Sampling frame	Response or retention rate[c]	Target population (sample size)[c]	HIV disease stage and % on ART[d]	Cognitive task measures[e]	Cognitive task findings (effect size estimate)[f]	Behavioural report measures[g]	Behavioural report findings (effect size estimate)[h]
†Boivin 2019 (81%)	Malawi & Uganda (PROMISE-BF)	PC post-RCT (4 assessments 1, 2, 4 & 5 years)	HIV+ mothers randomised to triple ART or AZT alone in pregnancy; randomised postpartum to triple ART or infant NVP during breastfeeding	PHU matched for age, sex, socioeconomic status enrolled at clinics	Health facility-based	64% of 4-year visit completed 5-year visit	48-month visit: PHEU 4 years (n=321); PHU 4 years (n=261)	Children HIV-. 4 PHEU subgroups: Triple ART + infant NVP, triple ART throughout, AZT + infant NVP, antenatal AZT + postnatal triple ART	KABC-II SPI	PHEU=PHU at 4 & 5 years	NA	NA
Loo 2017 (73%)	Kenya	Three-arm RCT	Nutrition intervention: caregivers & children fed 1 of 3 isocaloric biscuits (beef, soy, or wheat) 5 days/week x 18 months	Active: wheat biscuit	Health facility-based	73% retention	PHIV (n=1) & PHEU (n=48) 4-8 years	1 PHIV participant started ART during intervention	DSB	Beef=soy= wheat (all improved significantly over time)	NA	NA
Webb 2017 (63%)	US	Pilot RCT	Mindfulness-based stress reduction therapy (MBSR) programme; 9 sessions; ~ 8 weeks	Active: 'Healthy Topics' (HT) health education programme; nine sessions; ~ 8 weeks	Health facility-based	Response NR; retention 72% post-programme & 55% at 3-month follow-up	HIV+ (source NR) 14-22 years (n=72); intervention (n=38); control (n=34)	100% CD4 count>200; 100% on ART	Non-emotional Stroop Emotional Stroop	Post-programme & 3-month follow-up: MBSR=HT (except negative emotion Stroop MBSR>HT (L) post-programme)	NA	NA

First author & year (quality assessment score)[a]	Country (cohort/ study name)	Study design (control type)[b]	Intervention type and timing[b]	Control group type and timing	Sampling frame	Response or retention rate[c]	Target population (sample size)[c]	HIV disease stage and % on ART	Cognitive task measures[d]	Cognitive task findings (effect size estimate)[e]	Behavioural report measures[e]	Behavioural report findings (effect size estimate)[e]
Bass 2017 (75%) Boivin 2017 (92%)	Uganda (MISC)	Cluster RCT	Mediational intervention for sensitising caregivers (MISC) programme biweekly x 1 year; plus nutritional supplement biweekly x 1 year	UCOBAC nutrition & hygiene curriculum; plus nutritional supplement biweekly x 1 year	Health facility-based	PHIV: 98% response; retention: 95% children & 92% CGs at 6 months; 91% children & CGs at 1 year; 90% children & 85% CGs at 2 years	HIV-exposed children: PHIV 2-5 years (n=118); PHEU 2-3 years (n=221)	Stage NR. ART: 67% MISC, 58% UCOBAC	NA	NA	BRIEF-PR	1 year: MISC < UCOBAC 2 years: PHIV: MISC = UCOBAC. PHEU: MISC < UCOBAC
Ananworanich 2016 (42%)	France, Ireland, Italy, Poland, Spain, Switzerland, UK (PENTA 11)	PC starting 1 year post-RCT	Planned treatment interruption (PTI) for 72 weeks	Continuous treatment (CT) for 72 weeks	NR (presumably facility-based)	87% response; retention NR.	PHIV median age 12.6 years, IQR 9.6–15.2 (n=88): PTI (n=47); CT (n=41)	PC baseline CDC C: PTI 19%; CT 39%. ART: PTI 91%; CT 100%.	WISC/WAIS-IV digit span	Year 1 & 2: PTI=CT	NA	NA
Boivin 2016 (77%) Ruiseñor-Escudero 2015 (79%)	Uganda	RCT	Captain's Log Computerised Cognitive Rehabilitation Training (CCRT): 9 games targeting working memory, attention & visual–spatial analysis. Titration of difficulty. 24 hour-long sessions: 3/week.	2 control groups. Active controls: limited CCRT without titration. Passive controls: no CCRT.	NR	84% response; 99% retention at immediate post-programme and 3-month post-programme assessments	PHIV 6-12 years (n=159): full CCRT (n=53); limited CCRT (n=52); passive controls (n=54)	All WHO Stage I or II. ART: Full CCRT 49%; limited CCRT 72%; control 53%	TOVA KABC-II SPI, planning CogState one-back test, maze learning	IC, verbal WM: CCRT groups = control Spatial WM & PL: Full CCRT>limited CCRT> control. PL: CCRT> control	BRIEF	Change score: full CCRT = limited CCRT = control

First author & year (quality assessment score)[a]	Country (cohort/ study name)	Study design (control type)[b]	Intervention type and timing[b]	Control group type and timing	Sampling frame	Response or retention rate[c]	Target population (sample size)[c]	HIV disease stage and % on ART	Cognitive task measures[d]	Cognitive task findings (effect size estimate)[e]	Behavioural report measures[e]	Behavioural report findings (effect size estimate)[e]
Giordani 2015 (52%)	Uganda	Uncontrolled pre-post study	'Brain Powered Games' CCRT. 24 sessions over 2 months; 45–60 mins per session.	No control group. Same group measured twice pre-intervention → own controls	NR (participants were controls from previous CCRT study)	NR	PHIV 6-12 years (n=33)	58% had CD4%>35%. 58% on ART.	TOVA CogState one-back, Groton maze learning test	IC, verbal WM: control = pre = post Spatial WM & PL: control< pre (S) pre < post (L)	NA	NA
Puthanakit 2013 (79%)	Cambodia, Thailand (PREDICT)	Prospective cohort post-RCT	Early ART: ART started at Week 0.	Deferred ART until CD4<15% or AIDS-defining illness (CDC C)	Health facility-based	93-97% response; 99% retention	PHIV 2-15 years (n=284) at start of neuro sub-study: early ART (n=139); deferred ART (n=145)	No CDC C. Week 144: median CD4%: early 33%, deferred 24%; ART: 100% early, 48% deferred.	Children's Colour Trails Stanford-Binet II memory tasks (DS, sentence memory, object memory)	TS, verbal & spatial WM: early = deferred	CBCL	CBCL attention problems subscale NR
Boivin 2010 (67%)	Uganda	Pilot RCT	Captain's Log CCRT: 15 exercises with titration of difficulty. 45 minutes per session. Twice weekly x 5 weeks.	Passive: no intervention.	Non-profit organisation-based	Response NR. 97% retention.	PHIV 6-16 years (n=60)	Mean CD4%: control 34%, CCRT 35%. ART: 36% controls, 41% CCRT	CogState one-back & Groton maze learning test	Verbal WM: CCRT = control Spatial WM & PL: CCRT > control	NA	NA

Key:

[a] % = higher means better quality with lower risk of bias

[b] RCT = randomised controlled trial; PC = prospective cohort; ART = antiretroviral therapy; CCRT = Computerised Cognitive Rehabilitation Training

[c] NR = not reported; PHIV = perinatally acquired HIV; PHEU = perinatally HIV-exposed unexposed; PHU = perinatally HIV-unexposed uninfected

[d] AZT = zidovudine; NVP = nevirapine; ART = antiretroviral therapy; UCOBAC = Uganda Community Based Association for Women and Children Welfare; CG = caregiver

[e] NA = not applicable; WISC = Wechsler Intelligence Scale for Children; WAIS = Wechsler Adult Intelligence Scale; TOVA = Test of Variables of Attention, a continuous performance task; KABC = Kaufman Assessment Battery for Children; SPI = sequential processing index

[f] Effect size estimate: small S d = 0.2-0.49, medium M = 0.5-0.79, large L ≥0.8; direction of effect: < worse, > better, ≤ worse than or the same as, = the same as; IC = inhibitory control; WM = working memory; PL = planning; TS = task switching; BRIEF = Behavioural Rating Inventory of Executive Function; PR = parent report; CBCL = Child Behaviour Checklist

Appendix 3: OCS-EF task descriptions

Trails

Procedure

The participant was asked to use the stylus to draw lines to connect shapes presented on the tablet. The task consisted of two baseline conditions and a switching condition (see Figure 36 for configurations). Prior to each test run (baseline and switching), participants were given a demonstration by the examiner and performed two practice runs to ensure they were familiar with using the stylus and understood the task instructions. They were then instructed to complete each test run as quickly and accurately as possible. For each condition, participants were presented with a set of light grey squares and dark grey circles of varying sizes, positioned in a semi-random arrangement. The test rounds for the two baseline conditions required the participant to (i) connect circles in increasing order of size in the presence of square distractors, and (ii) connect squares in decreasing order of size in the presence of circle distractors. The test run for the shape switching condition required the participant to connect the shapes alternating between circles and squares, with circles going in ascending order of size and squares in descending order of size, starting with the largest square and the smallest circle.

Scores

Participants scored 1 point for each correct connection, with a maximum score of 7 for each baseline condition and 14 for the switching condition.

Iowa Gambling Task

The image of the blue card back for the Iowa Gambling Task was sourced from Open Clip Art (Nicubunu, 2009).

Procedure

Participants were presented with two decks of cards facing down and instructed to score as many points as they could by the end of the task. There were 50 trials, 5 mini-blocks of 10 trials each, presented in a fixed order. In each trial, participants picked a card from the top of one of the decks. Each card had a specific reward and a specific penalty. Deck 1 was advantageous overall (net gain) with a reward of 100 points per card and 0 or -100 penalties per card. Deck 2 was disadvantageous overall (net loss) with a reward of 200 points per card and potentially higher penalties of 0, -400, -500 or -600 points. After each trial, the updated score was calculated (adding the card reward and subtracting the card penalty) and displayed on the screen. The participant should learn which deck is more advantageous to maximise long-term gain.

Scores

Participants scored a certain number of points during each trial, starting with 0. The advantageous deck had a total reward of 5000 points and a total penalty of 2500 points. The disadvantageous deck had a total reward of 10000 points and a total penalty of 12500 points. The maximum possible score was 5900 points and the minimum possible score was -5900 points.

Emotional go/no-go task

Procedure

Participants were presented with a series of visual stimuli: faces belonging to three different women displaying one of three different emotional expressions (happy, neutral or fearful). The task consisted of a practice block (6 trials) and four test blocks (36 trials each). For each trial a face was displayed centrally on the screen for 500ms, followed by a blank screen for 1500ms. Participants were asked to keep their stylus just below the screen and use it to tap the screen when target faces appeared (go trials) while refraining from tapping for any other type of face (no-go trials). The response could be given either during the face presentation, or during the blank screen period. If a response was given during the first 200ms of the presentation of the next face, the response was considered a late response to the preceding face. Each block was subdivided into 3 mini-blocks of 12 trials each. The ratio of go to no-go trials within each block was 2:1 to create a prepotent tendency to respond and the need to inhibit this automatic response on no-go trials. The neutral faces were the targets in every block. In blocks 1 and 4, distractors were fearful faces (fearful blocks). In blocks 2 and 3, the distractors were happy faces (happy blocks). A correct hit (tapping a target face) was followed by a low-pitched auditory tone.

The order of the faces, based on pseudo-randomisation criteria, was fixed for all participants. A block always began with a go trial. Each specific face did not appear more than twice in a mini-block. Tapping a target within the 200-2000ms time frame was a correct hit (true positive). Non-response to a target was an omission error (false negative). Inhibiting a response correctly by not touching a non-target was a

correct inhibition (true negative). The failure to inhibit in which the participant touched the screen during a no-go trial was a commission error (false positive).

Scores

Participants scored 1 for each correct response. There was a maximum score of 96 for go-trials (go accuracy) and 48 for no-go trials (no-go accuracy). Commission errors and omission errors were derived from these. The following reaction times were recorded: early response (within 200ms); proper response (200-2000ms); repeated response (a second tap between 200 and 2000ms); late response (a response within 200ms of the next stimulus presentation).

Rule-finding task

Procedure

The participant was presented with a grid of three columns with alternating geometric shapes (squares-triangles-squares), eight shapes per column. Most shapes were light grey but one item per row was dark grey. A red dot moved around the grid from one shape to another following one of five predefined rules. The participant was asked to predict where the dot would move next based on previous moves (the most recent preceding position was outlined in blue). The participant tapped the predicted shape with the stylus. Shape selection was followed by a low-pitched auditory tone. No direct feedback was given regarding accuracy, but it could be inferred by the participant comparing their prediction with the actual new position of the dot. There were five different rules in the task (with a total of 46 moves). The first four rules were only based on the position of the shape. For the fifth rule, both the position and colour of the shape were important. The change from one rule to another was not signalled. To make accurate

predictions the participant needed to detect the rule change and work out the new rule.

Scores

Participants scored 1 point for each move correctly predicted, with a maximum move score of 46. The first move in each new rule was not scored.

Figure drawing task

Procedure

The participant was asked to use the stylus to draw a figure composed of simple geometric shapes on the tablet. The task has two conditions. In the copy condition, the participant was asked to copy the figure while the figure remained at the top of the screen for the duration of the copying. In the recall condition administered immediately afterwards, the participant was asked to draw the same composite figure again, this time from memory. The drawing accuracy was scored manually offline after completion of testing using a dedicated figure scoring software application and the scoring manual.

Scores

The figure consisted of twenty components. Participants scored a maximum of 3 for each component, 1 point each for the component presence, accuracy and position. There were three types of components: container (lines defining the edges of the enclosing rectangle); divider (lines that create partitions of the container component); and detail (distinct features inside partitions of the container component). An element was present if it appeared anywhere in the drawing. A component was accurate if it was drawn with reasonable accuracy as expected from a person with typical drawing ability. Reasonable allowances were made for

slight inaccuracies that could be attributed to a lack of drawing proficiency or stylus slippage, or obvious attempts to correct such inaccuracies. A component was in the correct position if the corresponding lines were in the same position relative to their nearest neighbours as in the template drawing. Each individual drawing mistake was penalised only once.

Selection task

Procedure

Participants were presented with a distribution of black-and-white drawings of three types of vegetables (10 items of each type) and three types of fruit (10 items of each type) and asked to use the stylus to select only the fruits (targets), ignoring the vegetables (distractors). Upon selecting an item, visual feedback of the selection was given in the form of a square frame around the item. There were two conditions for this task: (i) the visible condition, in which the visual feedback remained on the screen once an item had been selected, and (ii) the invisible condition, in which the visual feedback only appeared briefly following the stylus tap before disappearing. The distribution of fruit and vegetables was different for two conditions (see Figure 39 for the visible condition distribution). For the invisible condition participants had to remember which items they had selected previously to avoid selecting items more than once.

Scores

Participants scored 1 for each correctly selected target (maximum of 30 for each condition). The number of false positives (distractors selected) was counted (maximum of 30 for each condition). In the invisible condition, scores tallying the number of targets revisited (maximum of 30) and the number of distractors revisited (maximum of 30) were also recorded.

Digit recall task

Procedure

Participants were asked to repeat out loud a series of digit sequences of increasing length (from 2 to 9 digits' long). Digits from 1 to 9 were used. For each sequence, the examiner read the digits out loud slowly and clearly. The task consisted of two conditions: (i) forwards, in which participants should repeat the sequence in the same order as they heard it, and (ii) backwards, in which participants should repeat the sequence in reverse order. As participants recalled digits, the examiner used the stylus to tap the digits on the tablet in the order recalled by the participants. The accuracy (maximum span) was automatically calculated after this input. If participants recalled a sequence of a certain length correctly, they proceeded to the next level in which the length of the sequence was one digit longer. Participants were allowed three attempts at different sequences of a certain length. If they failed all three attempts, the task ended.

Scores

The digit span was given by the length of the longest sequence the participant recalled correctly in each condition (minimum of 0, maximum of 9).

Appendix 4: Justification for choice of measures for each task

Trails

I derived various measures using the trails task. I wanted to use it as a measure of set-shifting ability. Therefore, it made sense to derive a switch cost measure which measures the cost of the executive demand to shift on performance (Monsell, 2003). With the more traditional version of the trails task (numbers and letters), many authors choose to use a trails duration switch cost score which accounts for

the lengthened duration taken for the switch condition relative to the baseline non-switch condition (Arbuthnott & Frank, 2000). I chose to use the trails switch accuracy cost score which looks at any relative decrease in accuracy that occurs on the switch condition relative to the non-switch or baseline condition. There were various reasons for my choice. Firstly, it was recommended by the developers of this particular geometric version of the task (Demeyere et al., 2019; Rosenberg et al., 2018). Secondly, it is less dependent on processing speed than a duration-based measure. This is important in the context of HIV when processing speed may be slow due to HIV-associated neurocognitive disorder. Thirdly, it was less prone to measurement error than duration-based measures. Duration was recorded automatically by the OCS-EF software; however, the fieldworker had to click the 'next' button at the top of the screen to cue task completion.

Another measure that I considered using was the efficiency cost. Efficiency is a measure that combines accuracy and duration (accuracy/duration e.g. number of correct connections per second). This is similar to the rate residual score which calculates the residualised difference between switch and non-switch trials in the rates of correct responses per second (M. M. Hughes, Linck, Bowles, Koeth, & Bunting, 2014). This is a parsimonious measure that reduces the number of outcome measures needed for researchers wanting to generate an overall measure of task performance taking accuracy and duration into account. It may also be useful to distinguish between the top performers who achieved at ceiling for accuracy on both the baseline and switching conditions of the task. It is also useful for researchers wanting to use parametric measures because it is more likely to be normally distributed as it combines positively skewed duration with negatively skewed accuracy. This measure is not often used for the trails task in

the literature; however, it could be a measure for researchers to consider using in the future especially when utilising this task with young, healthy populations who perform at ceiling on accuracy. I chose not to use this measure because it has seldom been used for this task in the literature making it less comparable with other studies. It also has similar issues to duration-based measures, as described in the above paragraph.

Iowa Gambling Task

For the Iowa Gambling Task, the net score was chosen because it was the score used by the authors of the Children's Gambling Task implementation on which the OCS-EF version was based (A. Kerr & Zelazo, 2004). It has often been used in adolescent and adult populations (Cauffman et al., 2010; Gansler, Jerram, Vannorsdall, & Schretlen, 2011). It is also easily comparable across different constructions of the task even if they differ in terms of number of trials, the value of rewards etc.

Emotional go/no-go

There are multiple measures that can be derived from an emotional go/no-go task that focus on either go trials (go accuracy, omission errors) or no-go trials (no-go accuracy, commission errors). Sensitivity measures like d-prime, the chosen measure in this thesis, are useful because they are parsimonious and combine performance on both go and no-go trials. This is important because there are limitations of looking at go or no-go accuracy in isolation due to response bias. Someone can achieve 100% no-go accuracy by simply not responding to any stimuli or having a bias towards non-response. Conversely, one can achieve 100% go accuracy by responding to every stimulus without differentiating stimuli or

having a bias towards responding. This combined measure is not affected by response bias (Stanislaw & Todorov, 1999).

Rule-finding

There are two accuracy measures that can be derived from the OCS-EF rule-finding task. The first is the total number of rules acquired (out of 5). The second is the total number of correct moves (out of 46). They both measure accuracy but I chose to derive a proportion accuracy score using the total correct moves because it has greater variability and is thus more sensitive in detecting individual differences.

Selection

For the selection task, I chose the invisible proportion accuracy score as the executive measure. The visible condition is a measure of selective attention. The invisible condition has more executive demands than the visible condition because it requires memorisation of previously selected targets to avoid re-selection. It also requires planning to select targets in a systematic way to avoid re-selection. Re-selection of previously selected targets (e.g. due to poor visuospatial working memory or planning) is penalised.

Figure drawing

For the figure drawing task, I chose the figure recall proportion accuracy score as the executive measure. The recall condition has more executive demands than the copy condition because it requires construction based on memorisation of the previously drawn figure placing demands on visuospatial working memory. It also requires planning to draw the figure elements in a systematic way which is less prone to error (Watanabe et al., 2005).

Digit recall

For the digit recall task, I chose the backwards digit span as the executive measure. The backwards condition of the digit recall has greater executive demands than the forwards condition because it requires manipulation in additional to storage of memorised numbers (Baddeley, 2012).

Appendix 5: Study 2 pairwise correlation matrix between cognitive task outcome measures

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
(1) Digit span forwards	1.000												
(2) Digit span backwards	0.295*	1.000											
	0.000												
(3) Go/no-go d-prime	-0.049	-0.010	1.000										
	0.168	0.791											
(4) Iowa net score	-0.061	0.017	0.136*	1.000									
	0.087	0.631	0.000										
(5) Trails baseline accuracy	0.107*	0.127*	0.096*	0.042	1.000								
	0.003	0.000	0.007	0.234									
(6) Trails switch accuracy	-0.050	0.028	0.177*	0.139*	0.256*	1.000							
	0.157	0.441	0.000	0.000	0.000								
(7) Trails switch accuracy	-0.083*	-0.015	0.153*	0.122*	-0.081*	0.916*	1.000						
cost	0.021	0.684	0.000	0.001	0.025	0.000							
(8) Trails switch duration	0.114*	0.092*	0.007	-0.008	0.172*	0.002	-0.049	1.000					
cost	0.001	0.010	0.841	0.818	0.000	0.959	0.177						
(9) Selection visible	0.140*	0.081*	0.091*	-0.032	0.011	0.009	0.003	0.073*	1.000				
accuracy	0.000	0.023	0.011	0.368	0.758	0.801	0.945	0.041					
(10) Selection invisible	0.124*	0.062	0.107*	-0.062	0.143*	0.091*	0.064	0.095*	0.302*	1.000			
accuracy	0.001	0.084	0.003	0.084	0.000	0.011	0.078	0.008	0.000				
(11) Figure copy accuracy	0.075*	0.102*	0.004	0.014	0.237*	0.188*	0.092	0.065	0.050	0.085*	1.000		
	0.036	0.004	0.918	0.703	0.000	0.000	0.011	0.068	0.160	0.017			
(12) Figure recall accuracy	0.087*	0.119*	-0.001	-0.010	0.257*	0.200*	0.115*	0.041	0.042	0.146*	0.604*	1.000	
	0.015	0.001	0.850	0.776	0.000	0.000	0.001	0.253	0.243	0.000	0.000		
(13) Rule-finding accuracy	-0.033	0.087*	0.196*	0.154*	0.143*	0.149*	0.083*	0.098*	0.060	0.003	0.106*	0.155*	1.000
	0.351	0.015	0.000	0.000	0.000	0.000	0.021	0.006	0.091	0.939	0.003	0.000	

Key: * $p < 0.05$; upper values are Pearson's correlation coefficients; lower values are p values

Appendix 6: Study 2 kernel density plots of shifts from baseline to test condition

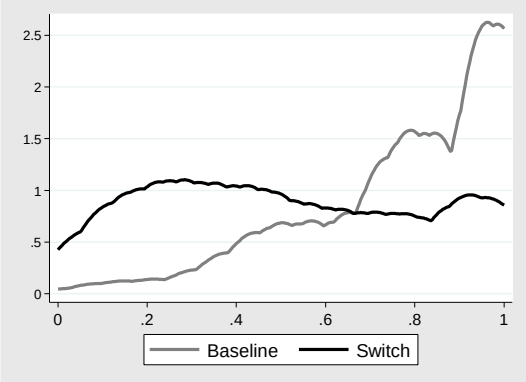


Figure A. Kernel density plot of trails accuracy by condition

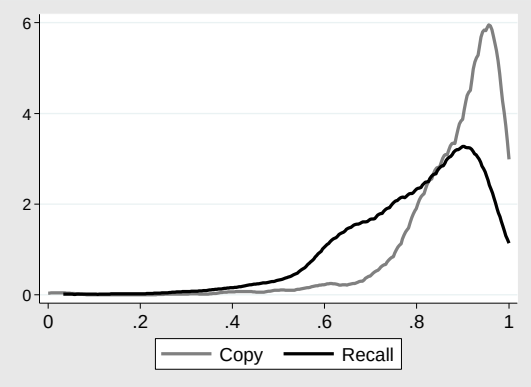


Figure B. Kernel density plot of figure drawing accuracy by condition

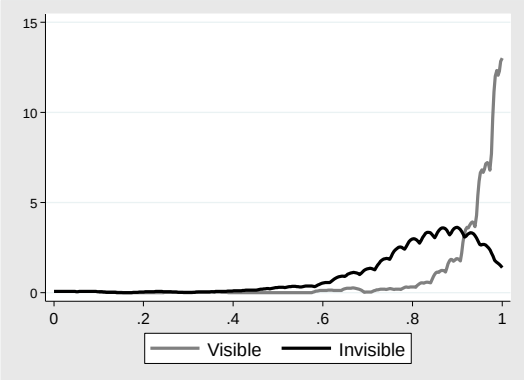


Figure C. Kernel density plot of selection task accuracy by condition

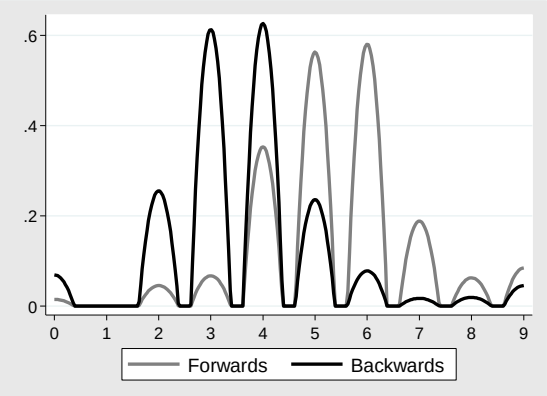


Figure D. Kernel density plot of digit recall maximum span by condition

Appendix 7: Study 2 additional exploratory factor analysis using the 7 OCS-EF tasks

Method: Principal factors exploratory factor analysis of the same 7 variables included in the confirmatory factor (only using valid data) in Stata 14 with oblique promax rotation allowing correlated factors.

Results:

Number of observations included = 786

Table 42. Proportion of variance explained by each factor in the rotated factor solution

Factor	Variance	Proportion
Factor 1	0.52461	1.1964
Factor 2	0.46119	1.0518
Factor 3	0.15664	0.3572

Table 43. Pattern matrix of rotated factor loadings and unique variances

Variable	Factor 1	Factor 2	Factor 3	Uniqueness
Trails switch	0.3140	0.1698	0.0250	0.8283
Rule-finding	0.2791	0.1630	-0.0807	0.8463
Digits backwards	-0.0710	0.2725	-0.0163	0.9381
Invisible selection	0.0959	0.1499	0.2719	0.8818
Go/no-go	0.4295	-0.0694	0.0546	0.8409
Iowa Gambling Task	0.1844	-0.0315	-0.2091	0.9131
Figure recall	0.0405	0.3910	0.0772	0.8209

Table 44. Factor rotation matrix

Factor	Factor 1	Factor 2	Factor 3
Factor 1	0.8754	0.8023	0.0358
Factor 2	-0.4433	0.4657	0.7165
Factor 3	-0.1926	0.3735	-0.6967

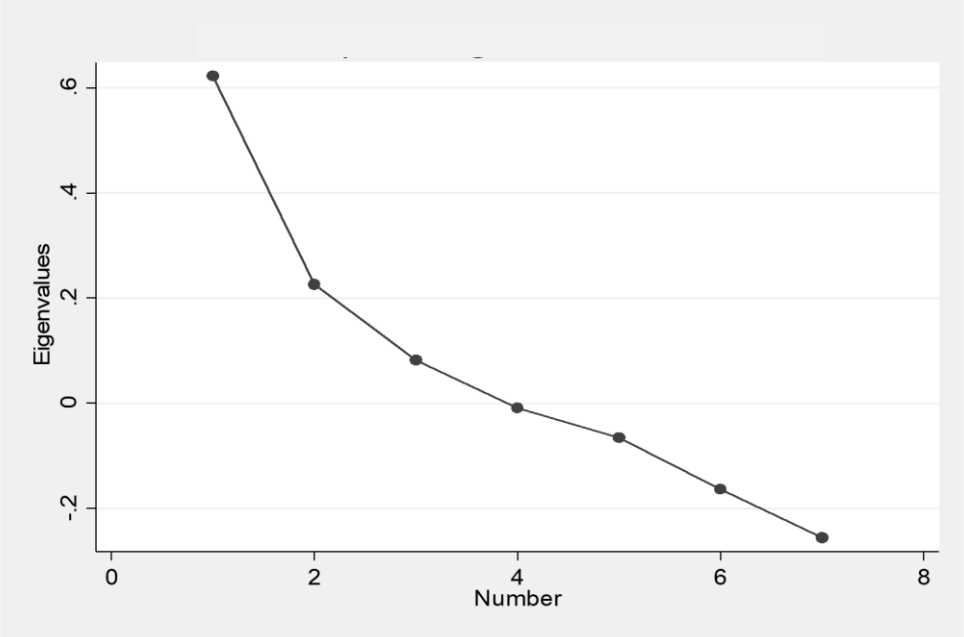


Figure 7. Scree plot of Eigenvalues after exploratory factor analysis

Retention of factors: I retained two factors based on the elbow of the Scree plot (Figure 48) occurring after the second factor and the fact that the first two factors explained a large proportion of the variance.

Interpretation of rotated factor solution:

- Factor 1: inhibitory control / task switching factor (trails switch, rule-finding, emotional go/no-go & Iowa Gambling load onto Factor 1)
- Factor 2: working memory factor (figure recall, digit span backwards and invisible selection load onto Factor 2; trails switch and rule-finding cross-load onto Factor 2)

Appendix 8: Study 3 results tables

Table A. Attention and executive function task scores in HIV-positive cases compared to matched HIV-negative controls

	Controls (HIV-negative)			Cases (HIV-positive)				Bivariable mean comparisons		Multivariable analysis
Characteristic	**Unadj. mean (95% CI)**	**Adj. mean (95% CI)**	**n**	**Unadj. mean (95% CI)**	**Adj. mean (95% CI)**	**n**	**Effect size (Hedge's g, 95% CI)**	**n**	**Unadj. p value**	**Adj. p**
Digits forwards	5.47 (5.23, 5.72)	5.47 (5.23, 5.70)	150	5.27 (4.95, 5.58)	5.28 (4.94, 5.61)	75	-0.14 (-0.42, 0.14)	225	t = 1.00 p = 0.3203	0.352
Digits backwards	3.95 (3.67, 4.22)	3.94 (3.67, 4.21)	150	3.32 (2.96, 3.68)	3.33 (2.95, 3.71)	75	-0.38 (-0.66, -0.10)	225	t = 2.69 p = 0.0076**	0.010*
Trails baseline accuracy	0.76 (0.72, 0.80)	0.75 (0.71, 0.80)	146	0.76 (0.70, 0.82)	0.77 (0.71, 0.83)	71	0.01 (-0.27, 0.29)	217	z = 0.02 p = 0.9859	0.689
Trails switch accuracy	0.51 (0.46, 0.55)	0.51 (0.46, 0.56)	146	0.55 (0.47, 0.63)	0.55 (0.48, 0.62)	71	0.15 (-0.14, 0.43)	217	z = -0.85 p = 0.3968	0.314
Trails switch accuracy cost	0.64 (0.59, 0.69)	0.64 (0.59, 0.69)	136	0.64 (0.56, 0.72)	0.63 (0.56, 0.71)	69	0.00 (-0.29, 0.29)	205	z = -0.12 p = 0.9046	0.903
Trails switch duration cost	1.19 (1.08, 1.29)	1.18 (1.07, 1.30)	146	1.15 (0.98, 1.32)	1.15 (0.99, 1.31)	71	0.05 (-0.23, 0.34)	217	t = 0.37 p = 0.7143	0.733
Rule-finding accuracy	0.49 (0.45, 0.52)	0.49 (0.45, 0.53)	153	0.46 (0.41, 0.51)	0.47 (0.42, 0.53)	77	-0.11 (-0.39, 0.16)	230	t = 0.81 p = 0.4168	0.533
Iowa net score	0.27 (0.17, 0.37)	0.30 (0.19, 0.40)	152	0.23 (0.08, 0.37)	0.27 (0.13, 0.41)	76	0.06 (-0.21, 0.34)	228	z = 0.37 p = 0.7084	0.735
D prime	2.06 (1.90, 2.21)	2.05 (1.89, 2.21)	153	2.02 (1.81, 2.24)	2.06 (1.84, 2.28)	77	-0.03 (-0.31, 0.24)	230	t = 0.23 p = 0.8151	0.927

Selection visible accuracy	0.95 (0.93, 0.96)	0.95 (0.93, 0.97)	146	0.93 (0.90, 0.96)	0.93 (0.91, 0.96)	75	-0.15 (-0.43, 0.13)	221	z = 1.216 p = 0.2239	0.333
Selection invisible accuracy	0.80 (0.77, 0.83)	0.80 (0.77, 0.83)	146	0.82 (0.78, 0.86)	0.82 (0.78, 0.86)	75	0.15 (-0.13, 0.42)	221	z = -1.304 p = 0.1922	0.352
Figure copy accuracy	0.88 (0.85, 0.90)	0.87 (0.85, 0.90)	150	0.86 (0.83, 0.89)	0.86 (0.83, 0.89)	77	-0.12 (-0.39, 0.16)	227	z = 1.829 p = 0.0674	0.526
Figure recall accuracy	0.78 (0.76, 0.81)	0.78 (0.75, 0.81)	150	0.77 (0.73, 0.81)	0.78 (0.74, 0.81)	77	-0.08 (-0.35, 0.20)	227	z = 0.822 p = 0.4114	0.832

Key: Unadj. = unadjusted; adj. = adjusted; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table B. Attention and executive function task scores by CD4 cell count classification in HIV-positive cases

		CD4 cell count ≥ 350 (n = 58)		CD4 cell count < 350 (n = 10)		Effect size	Mean comparisons		Multivariable regression analysis	
Cognitive Task	**Outcome**	**Unadjusted mean (95% CI)**	**Adjusted mean (95% CI)**	**Unadjusted mean (95% CI)**	**Adjusted mean (95% CI)**	**Hedge's g (95% CI)**	**n**	**Unadjusted p**	**n**	**Adjusted p**
Digit recall	Forwards span	5.32 (4.95, 5.68)	5.31 (4.93, 5.70)	4.80 (3.74, 5.86)	4.82 (3.90, 5.74)	-0.36 (-1.02, 0.31)	72	t = -1.06 p = 0.2949	64	0.327
	Backwards span	3.49 (3.08, 3.90)	3.49 (3.06, 3.92)	2.70 (1.67, 3.73)	2.70 (1.67, 3.72)	-0.50 (-1.17, 0.17)	72	t = -0.16 p = 0.8755	64	0.159
Trails	Baseline accuracy	0.78 (0.71, 0.85)	0.78 (0.72, 0.84)	0.69 (0.52, 0.85)	0.66 (0.52, 0.81)	-0.11 (-0.61, 0.39)	63	z = -1.34 p = 0.1793	60	0.150
	Switch accuracy	0.59 (0.51, 0.67)	0.59 (0.50, 0.68)	0.45 (0.15, 0.75)	0.45 (0.25, 0.66)	-0.44 (-1.11, 0.24)	63	z = -1.17 p = 0.2413	60	0.227
	Switch accuracy cost	0.69 (0.61, 0.77)	0.68 (0.59, 0.77)	0.53 (0.21, 0.85)	0.54 (0.34, 0.75)	-0.48 (-1.15, 0.20)	61	z = 0.79 p = 0.4312	61	0.202
	Switch duration cost	1.21 (0.99, 1.42)	1.21 (1.00, 1.41)	0.97 (0.73, 1.21)	0.98 (0.50, 1.45)	-0.32 (-0.99, 0.35)	63	t = 1.32 p = 0.1924	63	0.381
Rule-finding	Accuracy	0.45 (0.39, 0.50)	0.45 (0.39, 0.51)	0.62 (0.43, 0.81)	0.62 (0.47, 0.76)	0.77 (0.09, 1.44)	68	t = 2.27 p = 0.0263*	65	0.033*
Iowa Gambling Task	Net score	0.22 (0.06, 0.39)	0.22 (0.05, 0.40)	0.30 (-0.22, 0.82)	0.30 (-0.11, 0.72)	0.12 (-0.55, 0.78)	67	z = 1.47 p = 0.1419	67	0.725
Emotional go/no-go	D-prime	2.01 (1.75, 2.27)	2.01 (1.74, 2.28)	2.00 (1.25, 2.74)	1.99 (1.33, 2.65)	-0.01 (-0.68, 0.65)	68	t = -0.04 p = 0.9688	65	0.952
Selection	Visible accuracy	0.94 (0.92, 0.97)	0.94 (0.91, 0.98)	0.87 (0.66, 1.07)	0.86 (0.77, 0.95)	-0.55 (-1.22, 0.13)	66	z = -0.68 p = 0.5000	64	0.091
	Invisible accuracy	0.84 (0.79, 0.88)	0.84 (0.79, 0.89)	0.73 (0.56, 0.89)	0.73 (0.61, 0.84)	-0.61 (-1.28, 0.07)	66	z = -1.60 p = 0.1095	64	0.088
Figure drawing	Copy accuracy	0.86 (0.83, 0.89)	0.86 (0.83, 0.89)	0.81 (0.68, 0.94)	0.81 (0.73, 0.89)	-0.41 (-1.08, 0.25)	68	z = -0.49 p = 0.6269	65	0.246
	Recall accuracy	0.78 (0.73, 0.82)	0.78 (0.73, 0.82)	0.76 (0.61, 0.91)	0.75 (0.65, 0.86)	-0.11 (-0.77, 0.56)	68	z = 0.03 p = 0.9793	65	0.646

Key: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table C. Attention and executive function task scores by viral load classification in HIV-positive cases

		VL < 1000 copies/ml (n = 26)		VL ≥ 1000 copies/ml (n = 49)		Effect size	Hypothesis testing		Regression analysis	
Cognitive Task	**Outcome**	**Unadjusted mean (95% CI)**	**Adjusted mean (95% CI)**	**Unadjusted mean (95% CI)**	**Adjusted mean (95% CI)**	**Hedge's g (95% CI)**	**n**	**Unadjusted p**	**n**	**Adjusted p**
Digit recall	Forwards span	5.13 (4.71, 5.54)	5.09 (4.49, 5.70)	5.35 (4.90, 5.81)	5.37 (4.95, 5.79)	0.16 (-0.32, 0.65)	72	t = -0.65 p = 0.5154	64	0.470
	Backwards span	3.25 (2.87, 3.63)	3.20 (2.50, 3.89)	3.31 (2.78, 3.85)	3.34 (2.86, 3.82)	0.04 (-0.45, 0.52)	72	t = -0.16 p = 0.8755	64	0.744
Trails	Baseline accuracy	0.75 (0.64, 0.85)	0.73 (0.63, 0.84)	0.77 (0.70, 0.85)	0.78 (0.71, 0.85)	0.11 (-0.39, 0.61)	68	z = -0.66 p = 0.5094	60	0.494
	Switch accuracy	0.58 (0.44, 0.73)	0.57 (0.43, 0.72)	0.55 (0.45, 0.65)	0.55 (0.45, 0.65)	-0.10 (-0.60, 0.39)	66	z = 0.55 p = 0.5845	60	0.791
	Switch accuracy cost	0.68 (0.54, 0.82)	0.67 (0.52, 0.82)	0.62 (0.51, 0.72)	0.62 (0.52, 0.73)	0.20 (-0.30, 0.70)	66	z = 0.79 p = 0.4312	66	0.609
	Switch duration cost	1.25 (0.94, 1.56)	1.19 (0.90, 1.49)	1.03 (0.85, 1.22)	1.06 (0.86, 1.27)	0.33 (-0.17, 0.83)	68	t = 1.32 p = 0.1924	68	0.484
Rule-finding	Accuracy	0.47 (0.38, 0.57)	0.46 (0.37, 0.56)	0.46 (0.39, 0.53)	0.46 (0.40, 0.53)	-0.07 (-0.54, 0.41)	74	t = 0.27 p = 0.7846	65	0.992
Iowa Gambling	Net score	0.33 (0.06, 0.60)	0.28 (0.01, 0.55)	0.15 (-0.03, 0.33)	0.17 (-0.02, 0.36)	0.28 (-0.20, 0.76)	73	z = 1.47 p = 0.1419	73	0.522
Emotional go/no-go	D-prime	2.16 (1.78, 2.54)	2.15 (1.73, 2.57)	1.91 (1.63, 2.20)	1.92 (1.63, 2.21)	-0.25 (-0.73, 0.23)	74	t = 1.03 p = 0.3057	65	0.383
Selection	Visible accuracy	0.95 (0.91, 0.98)	0.94 (0.89, 1.00)	0.92 (0.88, 0.97)	0.92 (0.89, 0.96)	-0.18 (-0.66, 0.31)	73	z = 0.59 p = 0.5554	64	0.596
	Invisible accuracy	0.82 (0.76, 0.88)	0.83 (0.75, 0.91)	0.84 (0.79, 0.89)	0.82 (0.77, 0.88)	0.11 (-0.38, 0.59)	72	z = -0.49 p = 0.6241	64	0.886
Figure drawing	Copy accuracy	0.84 (0.80, 0.89)	0.84 (0.79, 0.89)	0.87 (0.83, 0.90)	0.87 (0.83, 0.90)	0.20 (-0.28, 0.68)	74	z = -1.38 p = 0.1674	65	0.357
	Recall accuracy	0.77 (0.70, 0.84)	0.76 (0.69, 0.82)	0.77 (0.72, 0.82)	0.78 (0.73, 0.83)	0.01 (-0.47, 0.48)	68	z = -0.16 p = 0.8727	65	0.614

Key: VL = viral load; * p < 0.05; ** p < 0.01; *** p < 0.001

Appendix 9: AHEAD Study screening information sheet for minor participants aged 12-14 years old

Researcher Details: Dr Kirsten Rowe and Dr Ryan Wagner.

Contact details: Tel: XXX XXX XXXX. Cell: XXX XXX XXXX

Purpose of study: To understand how the brain works in young people going to the clinics and to see if taking part in a drumming group can help a young person to concentrate better.

Introduction: Good day. We would like to ***invite*** you and your caregiver to take part in a screening questionnaire for the 'AHEAD Study' to see if you could take part. Your caregiver will answer questions which will help us to decide if you may take part. You do not have to take part in the screening process if you do not want to do so. If you have any questions, please ask us.

1. What information will I need to share as part of the screening process?

We will ask your caregiver a few questions about your medical history. The questionnaire will take about 10 minutes. We may need to see your clinic folder and your clinic card to answer some of the questions.

2. What will happen after the questionnaire is finished?

We will tell you and your parent/guardian if you may take part. If you *are* suitable, we will invite you and your caregiver to take part in the study. We will need to give you both more detailed information about the study and what taking part will involve. You can then decide whether to take part. No one will force you to take part if you do not wish to take part. Your caregiver will need to sign a form to give us permission for you to be allowed to take part.

3. What will happen to my information? Will it be kept a secret?

All your information, including personal and medical data, will be kept a secret. The information will be stored on a secure password-protected electronic database on the computer which only the study team will see.

4. Has the study been reviewed by an ethics committee?

This clinical study protocol has been submitted to and approved by ethics committees from the University of the Witwatersrand, the University of Oxford, and the Mpumalanga Department of Health.

5. What if I have any questions or concerns?

If you or your caregiver have any questions about this study or you are worried about something to do with the study, please feel free to call one of the study doctors at any time during the study: Dr Kirsten Rowe (XXX XXX XXXX) or Dr Ryan Wagner (XXX XXX XXXX). You may also contact the Chair of the University of Witwatersrand Human Research Ethics Committee at: XXX XXX XXXX.

Appendix 10: AHEAD Study screening information sheet for caregivers of minor participants (younger than 18 years old)

Researcher Details: Dr Kirsten Rowe and Dr Ryan Wagner

Contact details: Tel: XXX XXX XXXX. Cell: XXX XXX XXXX

Purpose of study: To understand how the brain works in young people going to the clinics and to see if taking part in a drumming group can help a young person to concentrate better.

Introduction: Good day. We would like to ***invite*** you and your child to participate in screening for the AHEAD Study to see if your child could take part in the study. We will ask you a few questions to see if your child may take part. If you have any questions, please feel free to ask us.

1. What information will I need to share as part of the screening process?

We will ask you a few questions about your child's medical history. The questionnaire will take about 10 minutes.

2. What will happen after the questionnaire is finished?

After the questionnaire is finished, we will be able to tell you whether your child may take part. We will share more detailed information with you and your child about the study and what taking part in the study will involve so that you can make a final decision together about whether your child will take part.

3. What will happen to our information? Will it be kept a secret?

All your and your child's personal and medical information will be kept a secret. The data will be stored on a secure password-protected electronic database which will only be seen by the study team.

4. Has the study been reviewed by an ethics committee?
This clinical study protocol has been submitted to and approved by ethics committees from the University of the Witwatersrand, the University of Oxford, and the Mpumalanga Department of Health.

5. What if I have any questions or concerns?
If you have any questions about this study or want to raise a concern, you should discuss them with one of the study doctors: Dr Kirsten Rowe (XXX XXX XXXX) or Dr Ryan Wagner (XXX XXX XXXX). You may also contact the Chair of the University of Witwatersrand Human Research Ethics Committee at: XXX XXX XXXX.

Appendix 11: AHEAD Study participant eligibility screening questionnaire

Inclusion criteria If you answer No to any of these questions, your child is not eligible to participate.	
1. Is your (child's) HIV status known?	Yes / No
2. Are you willing to share your (child's) HIV status with the study team?	Yes / No
3. Is your child (/are you) between the ages of 12 and 19 years old?	Yes / No
4. Does your child (/do you) currently live or attend clinic in the MRC/Wits Agincourt HDSS study villages: Belfast, Lillydale, Lillydale A, Lillydale B, Somerset A, Somerset B, Somerset C, Justicia, Justicia A, Justicia B, Huntington, Cunningmoore A, Cunningmoore B, Kildare A, Kildare B, Kildare C, Ireagh A, Ireagh B, Ireagh C, Croquet Lawn A, Newington C, or Rolle?	Yes / No
5. Will your child (/you) be staying in these villages for the next 6 months?	Yes / No
Exclusion criteria If you answer Yes to any of these questions, your child is not eligible to participate (except for question 4 where the child is eligible if the condition is under control).	
1. Is your child (/are you) deaf or hard of hearing?	Yes / No
2. Does your child (/do you) currently have a severe infection such as TB?	Yes / No
3. Is your child (/are you) currently more than 4 months' pregnant?	Yes / No / Not Applicable / Don't know
4. Does your child (/do you) currently receive treatment for any medical conditions e.g. asthma or diabetes? If the answer is Yes, does the doctor/nurse at the clinic say this condition is currently under control?	Yes / No Yes / No / Don't know
5. Is the child (/are you) known to have an intellectual disability due to cerebral palsy, Down's syndrome or another disease?	Yes / No / Don't know
6. Has the child (/have you) had fits in the last 7 years?	Yes / No
7. Has the child (/have you) had a brain infection in the last year?	Yes / No
8. Has the child (/have you) ever had brain cancer?	Yes / No
9. Has the child (/have you) ever had a stroke?	Yes / No
10. Has the child (/have you) ever had an injury to the head that caused him/her to be unconscious for more than 5 minutes, or have a fit, or where the skull was broken or where he/she needed an operation?	Yes / No

Appendix 12: AHEAD Study full participant information sheet for participants aged 15 to 17 years old

Researcher Details: Dr Kirsten Rowe and Dr Ryan Wagner.

Contact details: Tel: XXX XXX XXXX. Cell: XXX XXX XXXX.

Purpose of study: To understand how the brain works in young people going to the clinics and to see if taking part in a drumming group can help a young person to concentrate better.

To the potential participant: Please ask the study team to explain anything that you do not understand.

Introduction: Hello. We would like to ***invite*** you to take part in the AHEAD Study. Before you and your caregiver decide if you will take part, it is important that you understand what it will mean if you take part, including what could go wrong. If you have any questions, please feel free to ask us. You may not take part in another study or music group where you play a musical instrument while you take part in this study.

1. What's the study about?

Growing up with a disease can affect your ability to concentrate and remember things. This study will test how your disease affects your brain and see if taking part in a drumming group could help your brain to work better. Half of the teenagers who take part will be in the drumming groups and the other half (the control group) will not.

2. How big is the study and how long will it last for?

There will be about 60 teenagers taking part. The study will run for 4 months from July-October 2018. The busiest part will be during Term 3 (August and September 2018) if you are in a drumming group. During this period, the drumming groups will meet for an hour a week for 8 weeks in a row. Everyone will have another visit in October so you will have about 13 visits in total if you are in the drumming group and 5 visits if you are in the control group.

3. What's involved for me?

A computer will randomly put you in one of the two groups. You will have an equal chance of ending up in each group. You cannot choose which group you will be in. We will tell you which group you are in after you have joined the study.

At the start of the study, you and your caregiver will each fill in a survey. These surveys will take about 60 minutes to fill in. They will ask some questions about your background, lifestyle, feelings and behaviour. All the surveys will be available in English and Tsonga. The study team will use a medical form to get information about your disease from the clinic folder.

You will need to do some tests on the electronic tablet which will take about 40 minutes in total. They are a bit like computer games and will test how your brain works. We do not want you to be tired or hungry for the tests so will only let you do them after a good night's sleep. We will give you a snack before the tasks. If you are in the drumming group, you will also need to fill in a short survey about your expectations before the drumming starts.

During August and September, there will be 8 weeks of group sessions once a week for an hour. You and your caregiver will need to arrange your own transport and we will pay

you back for this. The drumming sessions will involve hand drumming in a circle led by a trained drumming teacher. The control group will not take part in the drumming sessions.

If you can't make it to a session, please let us know. If you feel that taking part is causing you problems, please let us know so we can try to help you. We would also then like you to fill in a survey about how you found the sessions.

At the end of the study, you and your caregiver will need to fill in surveys again. This will take about 40 minutes. If you took part in the drumming, you will need to fill in a 20-minute survey about how it was and how we could make it better. You will need to do the brain tests on the tablet again.

4. What will happen to my information? Will you tell anyone?

We will not tell anyone unless we find out something that could cause you or someone else to get hurt e.g. if you tell us that someone is hurting you, we will tell someone who is responsible for protecting children (e.g. the police) so they can make sure that you are kept safe. If you get certain diseases e.g. TB, we will have to report this to the clinic. Your information will be kept on a secure electronic database only seen by the study team.

5. Will taking part cause me any problems?

There is always a chance of teenagers bullying or teasing each other but the drumming groups will be supervised to make sure that this doesn't happen. Your HIV status will only be shared with members of the study team. It will not be shared with anyone else. When the results of the research are shared, your name or other personal details will not be shared with anyone. People will not be able work out that this information comes from you.

Some of the questions about your feelings might make you feel upset. If you are very upset, we will do our best to help you feel better or refer you for counselling. If you are in the drumming group, your hands may feel sore especially after the first session. If you listen to the drumming teacher's instructions and don't drum too hard then you probably won't get pain or sores on your hands. If you drum too hard or practise too long each day, especially when you first start to play, then there is a small chance that you might get sores on your hands. We will check your hands at the start of each drumming session to make sure you don't have a sore. If you do, you may not be allowed to drum during that session. If you are asked to sit out, you may still watch and sing along so that you can learn the rhythms and songs. If you sit with your back up straight (like the teacher shows you) then you shouldn't get a sore back. Spending time on the study could cause you inconvenience especially if you have a lot of work at that time. Since the drumming groups have not been run in the area before, we cannot predict if they will cause you any other problems that we have not expected. You or your caregiver should contact the study team straight away if you have any problems during the study.

6. Will taking part help me at all?

No. Drumming groups have helped young people and adults in other parts of the world to concentrate better or feel happier, but it might not do the same for you.

7. Do I have to take part?

No. It is up to you and your caregiver to decide. You may also stop at any time if you do not wish to take part anymore. Stopping early would not affect your treatment at the clinic in any way.

8. Will my caregiver or I have to pay for anything? Will I be paid to take part?

No, you will not be paid. The study is paid for by study grants. You or your caregiver will need to pay for your transport to the different venues for the study visits, but we will pay you back for this.

9. What if I have any questions or if I am worried about something?

If you or your caregiver have any questions about this study or you are worried about something to do with the study, please call us: Dr Kirsten Rowe (XXX XXX XXXX) or Dr Ryan Wagner (XXX XXX XXXX). You may also contact the Chair of the University of Witwatersrand Human Research Ethics Committee at: XXX XXX XXXX. If you are feeling upset, you can also contact XX, the social worker at Agincourt CHC, on XXX XXX XXXX during office hours.

Appendix 13: AHEAD Study full information sheet for caregivers of participants younger than 18 years old

Researcher Details: Dr Kirsten Rowe and Dr Ryan Wagner

Contact details: Tel: XXX XXX XXXX. Cell: XXX XXX XXXX.

Purpose of study: To understand how the brain works in young people with chronic diseases going to the clinics and to see if taking part in a drumming group can help a young person to concentrate better.

To the caregiver of the potential participant: Hello. We would like to ***invite*** you to consider participating with your child in the AHEAD Study. Before making a decision, we would like to explain what taking part will involve for you and your child, including what could go wrong. If you have any questions, please feel free to ask us.

1. What's the study about?

Growing up with a disease can affect someone's ability to concentrate and remember things. This study will test how your child's disease affects his/her brain and to see if a drumming group could help him/her to concentrate better. Half of the teenagers who take part will be in the drumming groups and the other half (the control group) will not.

2. How big is the study and how long will it last for?

There will be about 60 teenagers taking part. The study will run for 4 months from July-October 2018. The busiest part will be during Term 3, if your child is in a drumming group, because the drumming groups will meet for an hour a week for 8 weeks in a row. Everyone will have another visit in October so your child will have about 13 visits (drumming group) or 5 visits (control group) in total. You will have a maximum of 4 visits.

3. What's involved for me and for my child?

A computer will randomly put your child in one of the two groups. He/she will have an equal chance of ending up in each group. You cannot choose the group. We will tell you which group he/she is in after you join the study.

At the start of the study, you and your child will each fill in an hour-long survey on an electronic tablet. It will ask questions about your background, lifestyle (including the use of alcohol and drugs), feelings, behaviour and recent stressful life experiences. Your child will also be asked about his/her lifestyle (including the use of alcohol and illicit drugs),

feelings and behaviour. The surveys will be available in English and Tsonga. The study team will use a separate medical form to get information from the clinic folder.

Your child will need to do 7 tests on the electronic tablet (about 40 minutes in total). They are a bit like computer games and will test how the brain works. We do not want your child to be tired or hungry for the tests, so we recommend a good night's sleep before the tests. We will also give him/her a snack beforehand. If he/she is in the drumming group, he/she will also need to fill in a survey about expectations for the group.

During August and September, there will be 8 weeks of group sessions once a week for an hour. Your child will need to arrange his/her own transport and we will pay you back for this. The drumming sessions will involve hand drumming in a circle led by a trained drumming teacher. The control group will not take part in the drumming sessions.

If your child can't make it to a session, please let us know. If you feel that taking part is causing your child problems, please let us know so we can try to help. At the end of the study, you and your child will need to fill in surveys again. This will take about 40 minutes. If your child took part in the drumming, he/she will need to fill in a 20-minute survey about how it was and how we could make it better. He/she will need to do the brain tests on the tablet again at the end.

4. What will happen to our information? Will it be kept a secret?

All your information will be kept strictly confidential. We will only tell someone if you we think that your child or someone else could be in danger. Your information will be kept on a secure electronic database only seen by the study team. The information will be reviewed by representatives of the University of Oxford and the University of the Witwatersrand. They will only use it to fulfil their obligations for this study. You will be told if we find out something important about you, but we will not tell anyone (except those mentioned above) without your written permission. There are a few exceptions to this confidentiality rule e.g. if your child is at risk of harm (e.g. from substance abuse or mental illness requiring referral to the clinic for treatment) or where others are at risk of harm (e.g. if your child gets TB). The anonymous study findings will be published in an academic journal and the student researcher's thesis. If they suggest that a drumming group is useful, a larger study may happen afterwards to test it in more people.

5. Will taking part cause my child any problems?

There is always a chance of teenagers bullying or teasing each other but the drumming groups will be supervised to make sure that this doesn't happen. Your child's HIV status will only be shared with members of the study team. It will not be shared with anyone else. When the results of the research are shared, your and your child's personal details will not be shared with anyone. People will not be able work out that this information comes from you.

Some of the questions about feelings or stress might make you or your child feel upset. If either of you is very upset, we will do our best to help you feel better or refer you for counselling. If your child is in the drumming group, his/her hands may feel sore especially after the first session. If he/she drums too hard or practises too long each day, especially at the beginning, then there is a small chance that he/she could get sores on his/her hands. We will check his/her hands at the start of each drumming session to make sure there are no sores. If he/she has sores, he/she can still watch and listen without playing. Drumming should not cause backache unless your child sits incorrectly. Spending time on the study could cause you and your child inconvenience especially if you have a lot of work at that time. Since the drumming groups have not been run here before, we cannot predict if they

will cause any other problems. You should contact us straight away if you have any problems during the study.

6. Will taking part help my child?

No. Drumming groups have helped young people and adults in other parts of the world to concentrate better or feel happier, but it might not do the same for your child.

7. Does my child have to take part?

No. It is up to the two of you to decide whether to take part. You may also leave the study early and this will not affect his/her treatment at the clinic in any way.

8. Will I have to pay for anything? Will I be paid for my child to take part?

No, you will not be paid. The study is paid for by study grants. You will need to pay for your child's transport, but we will pay you back for this.

9. What if I have any questions or concerns?

If you have any questions or want to raise a concern at any time during the study, you should first discuss them with one of the study doctors: Dr Kirsten Rowe (XXX XXX XXXX) or Dr Ryan Wagner (XXX XXX XXXX). You may also contact the Chair of the University of Witwatersrand Human Research Ethics Committee at: XXX XXX XXXX. If you are feeling distressed, you can also contact XX, the social worker at Agincourt CHC, on XXX XXX XXXX during office hours.

Appendix 14: AHEAD Study drumming programme weekly schedule

Component	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Pre-session	Name tags Pre-intervention expectations questionnaire	Name tags Practise drumming and/or socialise	Practise drumming and/or socialise	Practise drumming and/or socialise	Practise drumming and/or socialise	Practise drumming and/or socialise	Practise drumming and/or socialise	Practise drumming and/or socialise
Technique	Teaching posture, how to play 3 tones & associated vocalisations (vocal drumming) & how to keep alternating left & right hands between beats.	Revise. Cycle: 4 repeats of each tone. Repeat cycle with vocal drumming. Remind re alternating hands.	Revise (as in Week 2). Then get into pairs & practise technique. Give each other feedback on technique. Facilitator walks to each pair & checks technique.	Revise Cycle: 4 repeats of each tone. Repeat cycle with vocal drumming.	-	-	-	-
Norms	Each participant contributed a group norm. Facilitator added key norms if not already mentioned.	Revise. People who missed last week add theirs.	Revise (only if needed due to violation)	Revise (only if needed due to violation)	Revise (only if needed due to violation)	Revise (only if needed due to violation)	Revise (only if needed due to violation)	Revise (only if needed due to violation)

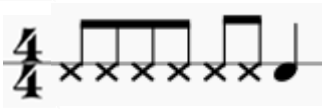
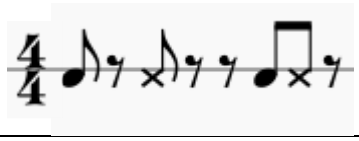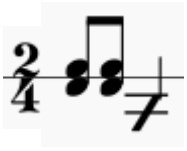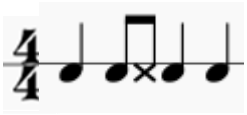
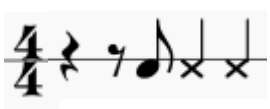
Greeting song 'Avuxeni vanghana' ('Hello, friends')	If no suggestions, then 'Avuxeni vanghana' a song composed by the facilitator: Rhythm 1 alone then add singing (call and response). Lead singer initially facilitator then adolescents were asked to volunteer to lead.	Test to see if remember. Rhythm 1 alone. Singing alone. Rhythm & singing combined.	Test to see if remember. Rhythm 1 alone. Singing alone. Rhythm & singing combined. Add Rhythm 2. Divide into 2 subgroups who each play a rhythm & then switch.	15 minutes Singing alone. Rhythm 1 alone. Rhythm 2 alone. Both rhythms. Rhythms & singing combined. Subgroups switch.	15 minutes. Singing alone. Teach Rhythm 3. Teach Rhythm 4. Subgroups: Group 1 plays Rhythm 3; Group 2 plays Rhythm 4. Groups switch rhythms.	15 minutes. Rhythm 1 & 2 with subgroups & switching. Rhythm 3 & 4 with subgroups & switching.	15 minutes. Rhythm 1 & 2 together in subgroups then switch. Rhythm 3 & 4 together in subgroups then switch.	10 minutes. Rhythm 1 & 2 together in subgroups then switch. Rhythm 3 & 4 together in subgroups then switch.
Icebreaker and/or game	Introduction song	Introduction song. 'Find your match' icebreaker where participants find someone with the same: 1. favourite colour	Each pull another person's name from a hat, find that person & tell them something you like about them. Get into pairs & find as many new sounds on	2 minutes. Single paradiddle alternating hands on the bass tone: 'left right left left' then 'right left right right'. Repeat.	5 minutes. Double paradiddle alternating hands on the bass tone: 'left right left right left left' then 'right left right left right right'. Repeat.	5 minutes. African thunderstorm game. Build up with facilitator bringing in 1 person at a time like a Mexican wave. Starting with softer sounds and building up to louder sound with each pass	5 minutes. Triple paradiddle alternating hands on the bass tone: 'left right left right left right left left' then 'right left right left right left	-

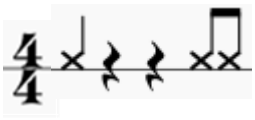
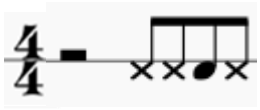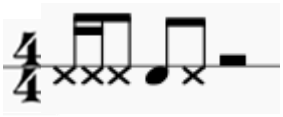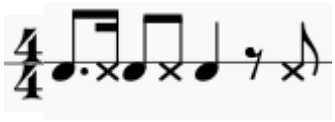
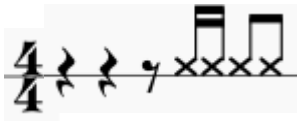
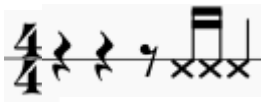
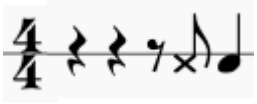
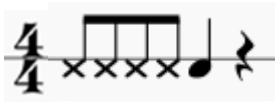
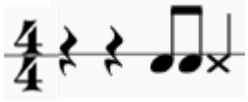
		2. favourite sports team 3. favourite sport to play 4.favourite fruit Re-introduce themselves. Lastly, find a partner & identify & share with the group 3 things in common with partner.	the djembe as possible & then share these with group.			around the circle: stroking, light patting, beating, knuckles. Then dying down in the reverse order.	right right'. Repeat. Paradiddle pyramid: 2 x single, 2 x double then 2 x triple paradiddles.	
Improvisation	-	'Call & response improvisation game': Introduce linking rhythm. Go around circle & each participant creates rhythm & repeats twice. Group repeats it back twice. Linking rhythm x 4.	'Call & response improvisation game: Revise linking rhythm. Facilitator & supervisor alternate in leading 'calls' with responses from group.	'Call & response improvisation game: Revise linking rhythm. Facilitator & supervisor alternate in leading 'calls' with responses from group. Participants each take turns to	-	-	-	-

		Next person's turn.		create rhythms.				
Core song 1	-	'Kanimamba' or 'Club controller'. Teach melody, lyrics & Rhythm 1 and 2.	Revise Rhythm 1 & Rhythm 2. Practise playing each rhythm & switching between rhythms as a whole group.	15 minutes. Rhythm 1. Add Rhythm 2. Subgroups play rhythms together. Subgroups switch rhythms. Take turns dancing along if they wish.	15 minutes: Practise Rhythm 1 & 2. Learn Rhythm 3. 3 subgroups: play the 3 rhythms simultaneously. Subgroups each take turns doing each rhythm.	15 minutes: Practise Rhythms 1, 2 & 3. Subgroups – playing 3 rhythms simultaneously. Switching so each subgroup has played each rhythm.	15 minutes: Practise Rhythms 1, 2 & 3. Subgroups allocated rhythms & play them then switch twice.	20 minutes: Practising performing Rhythms 1, 2 & 3 in subgroups with switching at a designated time.
Core song 2	-	'UJesu uyalalela'. Teach melody, lyrics & Rhythm 1.	Revise Rhythm 1 & teach Rhythm 3. Play rhythms separately & switch.	Revise Rhythms 1 & 3.	20 minutes: Revise Verse 1 with Rhythm 1 only. Verse 2 with Rhythm 3 only.	20 minutes: Teach Rhythm 2 for Verse 1 & Rhythm 4 for Verse 2.	20 minutes: Revise Verses 1 & 2 with Rhythms 1-4.	20 minutes: Practise performing Verses 1 & 2 with Rhythms 1-4.
Farewell song 'Wahamba nathi'' ('You walked with us')	Learn melody, lyrics & Rhythm 1.	Revise melody, lyrics & Rhythm 1. Teach Rhythm 2. Play Rhythms 1 & 2 separately.	Group 1: Rhythm 1 Group 2: Rhythm 2 Groups switch rhythms.	Group 1: Rhythm 1 Group 2: Rhythm 2 Groups switch rhythms a few times.	Group 1: Rhythm 1 Group 2: Rhythm 2 Groups switch rhythms a few times.	5 minutes: Group 1: Rhythm 1 Group 2: Rhythm 2 Groups switch rhythms a few times.	5 minutes: Group 1: Rhythm 1 Group 2: Rhythm 2 Groups switch rhythms a few times.	5 minutes: Group 1: Rhythm 1 Group 2: Rhythm 2 Groups switch rhythms a few times.

Homework setting & wrapping up	Practise 3 tones. Think of a song you could teach the group.	Practise 3 tones. Create rhythms to teach group. Practise core songs.	Practise 3 tones. Create rhythms to teach group. Practise core songs.	Practise core songs' rhythms.	Practise core songs' rhythms.	Practise core songs' rhythms.	Practise core songs' rhythms. Reminded re next week last week & told re optional showcase with another group in Week 9.	5 minutes: Goodbye & thank you. Reminder to practise core songs' rhythms & bring recycling to make instruments if attending optional showcase.
Post-session	Pack up drums Snack & beverage Taxi fare and/or lift home	Pack up drums Snack & beverage Taxi fare and/or lift home	Pack up drums Snack & beverage Taxi fare and/or lift home	Pack up drums Snack & beverage Taxi fare and/or lift home	Pack up drums Snack & beverage Taxi fare and/or lift home	Pack up drums Snack & beverage Taxi fare and/or lift home	Pack up drums Snack & beverage Taxi fare and/or lift home	Pack up drums Snack & beverage Taxi fare and/or lift home

Appendix 15: AHEAD Study notated rhythms of songs and games

Standard musical notation	Box notation with vocal drumming names							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Welcome song ('Avuxeni vanghana')	ke	-	ke	-	du	-	-	-
Rhythm 1: 								
Rhythm 2: 	ke	ke	ke	ke	ke	ke	du	-
Rhythm 3: 	-	-	-	-	-	du	-	ke
Rhythm 4: 	du	ke ke	du	ke ke	du	-	-	ke ke
Norms rhythm 	du	-	ke	-	-	du	ke	-
Introduction song  (soft version: two-handed du on lap & click not clap)	du / du	du / du	cl-ap	-				
Improvisation game linking rhythm 	du	ke	du	-				
First core piece option 1: 'UJesu uyalalela'	du	-	du	ke	du	-	du	-
Rhythm 1: 								
Rhythm 2: 	-	-	-	du	ke	-	ke	-

Rhythm 3: 	pa	-	-	-	-	-	pa	pa
First core piece option 2: 'Ngcwele somandla' Rhythm 1: 	ke	ke	du	ke	-	-	-	-
Rhythm 2: 	-	-	-	-	ke	ke	du	ke
Rhythm 3: 	ke ke	ke	du	ke	-	-	-	-
'Club Controller' / 'Kanimambo' <u>Section 1</u> Rhythm 1: 	du	- ke	du	ke	du	-	-	ke
Rhythm 2: 	-	-	-	-	-	pa pa	pa	pa
Rhythm 3: 	du	-	du	-	du	-	du	-
<u>Section 2</u> Rhythm 1: 	-	-	-	-	-	ke ke	ke	-
Rhythm 2: 	-	-	-	-	-	ke	du	-
Farewell song ('Wahamba nathi') Rhythm 1: 	ke	ke	ke	ke	du	-	-	-
Rhythm 2: 	-	-	-	-	du	du	ke	-

Appendix 16: AHEAD Study song lyrics

Song	Lyrics
Greeting song	Avuxeni, vanghana (Hello, friends) Aye, aye, aye, aye (Hi)
Introduction song	Hi mina … Ndzi huma (My name is … I come from …) Risimu/kumbe muyimbeleri loyi ndzi nwi rhandzaka i .. (My favourite song/singer is ….)
UJesu uyalalela	uJesu uyalalela (Jesus listens) Aphendule umkhuleko (He answers prayers) uletha konke nguJesu ngomkhuleko (Ask anything, Jesus will answer you)
Ngcwele somandla	Ngcwele ngcwele somandla (Holy of holies) Siyakudumisa (We praise you) Ngcwele ngcwele somandla (Holy of holies) Sibabaza wena Nkosi yethu (We thank you, our Lord) ubukhulu bakho abulinganiseki (Your greatness is not equalled) Amandla akho somandla ayababazeka (Your strength is mighty) Uthando lwakho somandla (Your love, Almighty,) Lungangezilwande (is as vast as the oceans) Indalo yonke somandla ibabaza wena (the whole world praises You)
Club controller	Section 1: Angazi ngenze njani (I don't know what to do) ngoba lengoma iyang controller (because this song is controlling me) Section 2: Ibambe, ibambe into yakho (hold, hold your thing)
Khanimambo	Xana wena wanwi rhandza Yeso (Do you love Jesus?) Ahh khanimambo (Yeah, thank you) Akuya tilweni aswilavi mali swilava mintirho (to go to heaven doesn't require money, it requires deeds) Kuya ka Tatana aswilavi mali swilava mintirho (to go to the Father doesn't require money, it requires deeds) kuya ekaXikwembu aswilavi mali swilava mintirho (to go to God doesn't require money, it requires deeds) Ekuya ka Tatana aswilavi mali swilava mintirho (to go to the Father doesn't require money, it requires deeds) kuya ka Jehova aswilavi mali swilava mintirho (to go to Jehovah doesn't require money, it requires deeds) ekuya tilweni aswilavi mali swilava mintirho (to go to heaven doesn't require money, it requires deeds)
Farewell song ('Wahamba nathi')	Zulu section: Wahamba nathi (You walked with us) Siyabonga (We thank you) Tsonga section: Wafamba na yina (You walked with us) Akukhensa (We thank you)

Appendix 17: AHEAD Study participant pre-cognitive testing checklist

Please answer honestly. If you answer Yes to question 3 or No to questions 1, 2 or 5, we will postpone your cognitive tasks until another day. If you answer No to question 4, we will provide you with a snack prior to the cognitive screening.	
1. Are you currently feeling well?	Yes / No
2. Did you sleep well last night and for at least 7 hours?	Yes / No
3. Have you used any alcohol or substances in the last 12 hours?	Yes / No
4. Have you eaten today? If the answer is No, the participant must be given a snack prior to the cognitive screening.	Yes / No
5. Are you comfortable with doing the tablet-based tasks today?	Yes / No

Appendix 18: AHEAD OCS-EF cognitive task modifications

Trails

A duration cut-off of 180 seconds for each task condition was built into the software. The button to stop the timer and move to the next screen had a built-in lock period of 1 second to prevent accidental skipping of a task section by double-clicking on the button.

Iowa Gambling Task

This task started with a positive 'balance' of 6000 points rather than zero points, like in the previous version. This meant that the lowest possible end score was 100 points with a maximum score of 11900 points. This was to avoid having total scores that could be negative numbers which would require sufficient numeracy for their appropriate interpretation when weighing up risk and reward in this task.

Emotional go/no-go

The three female faces in the initial OCS-EF version were African-American models from the NimStim database; however, they looked like South African mixed race or ‘coloured’ people and one of the model’s calm facial expressions was sometimes mistaken for an angry expression. There was no male version of the task with male faces. Six new black African facial stimuli, three male (numbers 033, 036, 039) and three female (numbers 037, 039, 044), were therefore chosen from the Chicago Face Database (Ma, Correll, & Wittenbrink, 2015). We used the three male faces for a new male version of the task (used to assess adolescent boys) and the three female faces for the new female version of the task (used to assess adolescent girls). The faces were selected to look as similar as possible to local black African faces in the Agincourt subdistrict of Mpumalanga, South Africa, and to have clear, unambiguous facial expressions.

Appendix 19: AHEAD RACER cognitive task descriptions

RACER (Rapid Assessment of Cognitive and Emotional Regulation) is a touch-screen tablet-based application which was developed by Margaret Sheridan and Amar Hamoudi to assess cognitive function, including EF, in the field in large samples of children in LMICs. It is designed to be easy to administer by trained lay people or fieldworkers and suitable for use in children with low literacy levels. The tasks use simple shapes and do not rely on content knowledge. The two EF tasks are both quick to administer (1-4 minutes). They are administered with the tablet in landscape orientation with the examiner seated next to the participant so that the stimuli and on-screen instructions are upright for both the examiner and the participant. Input is with the dominant hand’s index or middle finger for both the examiner and the participant. The examiner has a separate set of standardised

written instructions, translated into the local language, Tsonga in the AHEAD Study, to ensure that administration is standardised. Each task has practice rounds built in during which task comprehension can be assured prior to the 'test' itself. They include baseline trials with minimal or no EF demands and more challenging EF trials. The outcome measure for each task is the comparison between performance on the EF trials and baseline trials.

Task 1: Dot location recall

This visuospatial working memory task has 52 trials. In each trial, participants are shown one, two or three stimuli (black dots on the screen). Each dot appears in one of nine locations on an invisible 3 x 3 grid. The stimuli appear on the screen for 2000 milliseconds during which time participants should memorise their locations. After this period, the screen goes blank for 100 milliseconds (short-delay trials) or 3000 milliseconds (long-delay trials). There were 26 short-delay trials and 26 long-delay (working memory) trials. After the delay, participants are asked to touch the screen exactly where they remember the dots to have appeared. Trials with only one dot are low-load trials whereas trials with two or three dots are high-load trials because they contain a greater amount of spatial information to memorise. Long-delay trials also place greater demands on the working memory than short-delay trials because the mental rehearsal needs to occur for a longer period of time. See Figure 49 for an example of the configuration of stimuli on the screen. Response accuracy is measured as the Euclidean distance (in pixels) from the recorded touch location to the centre of the nearest stimulus. These distances are recorded automatically by the tablet. The final working memory outcome variable is the difference between the mean accuracy on low-load short-delay trials and the mean accuracy on high-load long-delay trials: working memory score =

[mean distance from target on low-load short-delay trials] – [mean distance from target on high-load long-delay trials]. The degree to which a longer delay impairs performance is taken to be an estimate of working memory. A higher score indicates better working memory performance.

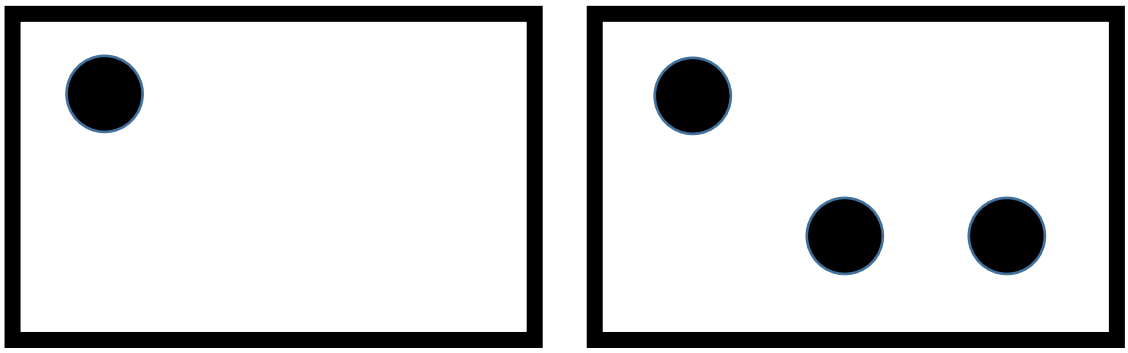


Figure 8. AHEAD Study RACER dot recall spatial working memory task: examples of stimulus configurations in low-load (left) and high-load (right) trials

Task 2: Simon task

The Simon task is a measure of cool or non-affective inhibitory control based on the Simon or stimulus-response compatibility effect. This effect describes the phenomenon of higher accuracy and lower response times when there is congruence between stimuli and the expected response, and decreased accuracy and slower reaction times when there is incongruence or a mismatch between features of the stimulus and the required response (e.g. response required on the opposite side to the stimulus) (O'Leary & Barber, 1993; Simon & Rudell, 1967). In this version of the task, there were 60 same-side (congruent) trials and 60 opposite-side (incongruent) trials. Stimuli with different colours and patterns appear one at a time on either the left or right side of the screen. For same-side trials, participants are instructed to touch the centre of the dot (i.e. the same side) as quickly as possible. For opposite-side trials, participants are instructed to touch the centre of the opposite side of the screen, which is marked with a small cross sign, as quickly as possible. This incongruence between the side of the stimulus

and the side of the response requires inhibition of the prepotent tendency to touch the same side as the stimulus and thus assesses inhibitory control. See Figure 50 for the on-screen appearance of different trial types. Reaction times on each trial are recorded automatically by the tablet. The final inhibitory control outcome variable is the difference between the mean reaction time on same-side (congruent) trials and opposite-side (incongruent) trials: inhibitory control score = [mean congruent trial reaction time] – [mean incongruent trial reaction time]. The degree to which the requirement of inhibition slows performance is taken as an estimate of the individual's inhibitory control performance. A higher score indicates better inhibitory control performance.

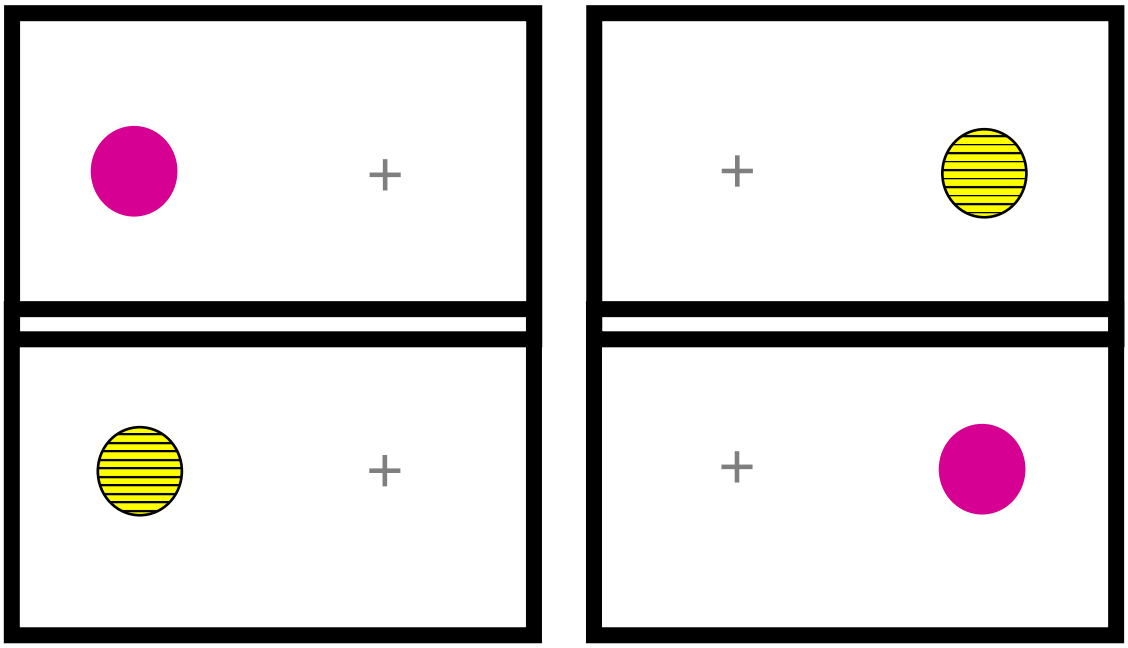


Figure 9. AHEAD Study RACER Simon inhibitory control task: examples of same-side trials with purple-pink dot stimuli and opposite-side trials with striped yellow-and-black dot stimuli

Appendix 20: AHEAD Study MRC/Wits Agincourt Health and Socio-demographic Surveillance System asset index form

Column	Data type	Description	Codes (if other than numeric, or numeric has additional meaning)	
Household	Number	Unique household id		
ObsYear	Number	Year data was collected		
Construct	Yes/No	Indicates whether or not the main dwelling structure is still under construction		
Walls	Text	Gives the construction materials of the walls	1 2 3 4 5 6 7 Q X	Brick Cement Other Modern Stabilised mud Traditional mud Wood Other Informal Query Unknown
Roof	Text	Gives the construction materials of the roof	1 2 3 4 5 Q X	Tiles Corrugated iron Other modern Thatch Other informal Query Unknown

Floor	Text	Gives the construction materials of the floor	1 2 3 4 5 6 7 8 Q X	Tiles Cement Modern carpet Wood Other modern Dirt Mat Other Traditional Query Unknown
SepKit	Yes/No	Indicates whether or not there is a kitchen separate from the sleeping function		
SepLiv	Yes/No	Indicates whether or not there is a living room separate from the sleeping function		
ToiletFac	Text	Gives the status of the toilet facility	1 2 3 4 Q X	In house In yard Other house Bush Query Unknown
ToiletType	Text	Gives the toilet type	1 2 3 4 Q X	Modern VIP Pit Toilet None Query Unknown
WaterSup	Text	Gives the status of the main water supply	01 02 03	Tap in house Tap in yard Tap in street

			04 05 06 07 08 09 10 11 QQ XX	Truck Cement well Traditional well Pond River Dam Rainwater tank Other Query Unknown
WaterAvail	Text	Gives the availability of the water supply	1 2 3 4 5 Q X	Always Most of the time Few hours a day Irregular, not every day Very irregular Query Unknown
DistMetre	Number	Gives the number of metres to the main water supply. If WaterSup is code 1 or 2, then not applicable		
DistMin	Number	Gives the number of minutes required to walk to the main water supply. If WaterSup is code 1 or 2, then not applicable.		
PowerLight	Text	Gives the main power supply for lights and appliances	1 2 3 4 5 6 Q X	Electricity Battery/Generator Solar Power Paraffin Candles Other Query Unknown

PowerCook	Text	Gives the main power supply for cooking	1 2 3 4 5 Q X	Electricity Gas Bottle Paraffin Wood Other Query Unknown
Fridge	Text	Gives fridge ownership status	1 2 3 4 Q X	Yes No Broken, to be fixed soon Broken, no plans to fix Query Unknown
TV	Text	Gives TV ownership status	1 2 3 4 Q X	Yes No Broken, to be fixed soon Broken, no plans to fix Query Unknown
CellPhone	Text	Gives cell phone ownership status	1 2 3 4 Q X	Yes No Broken, to be fixed soon Broken, no plans to fix Query Unknown
Cattle	Text	Gives cattle ownership status	1 2 3 4	None 1-10 11-40 More than 40

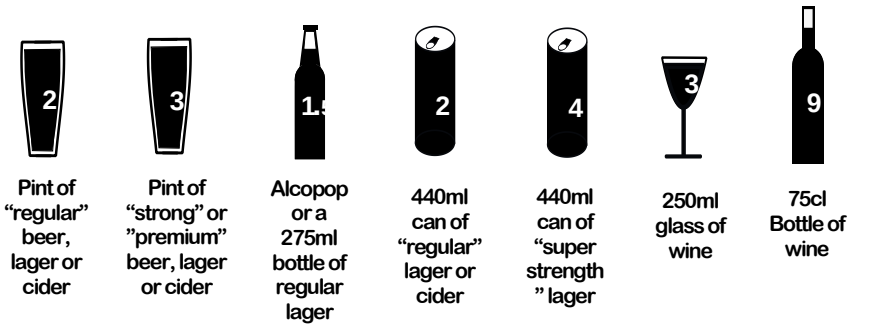
			5 Q X	Yes, but number unknown Query Unknown
Goats	Text	Gives goats ownership status	1 2 3 4 5 Q X	None 1-10 11-40 More than 40 Yes, but number unknown Query Unknown
Poultry	Text	Gives poultry ownership status	1 2 3 4 5 Q X	None 1-10 11-40 More than 40 Yes, but number unknown Query Unknown

Appendix 21: AHEAD Study adolescent baseline questionnaire

Sociodemographic information	
1. What is your home language?	Tsonga (Shangaan) / Zulu / Sepedi (Northern Sotho) / Venda / Other If other, please specify
2. Which hand do you use to write?	Right / left / both
3. What is your nationality?	South African / Mozambican / Other If other, please specify
4. What race do you identify yourself as?	Black / Coloured / White / Indian / Other / Prefer not to say If other, please specify
Education history	
5. What is the highest grade you have completed so far?	R / 1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10 / 11 / 12 / post-secondary
6. Are you currently attending school? If the answer is No, skip the next question.	Yes / No
7. Which grade are you currently in?	R / 1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10 / 11 / 12
8. Have you ever had to repeat a grade? If the answer is No, skip the next question.	Yes / No
9. Which grade/s did you repeat? Circle the applicable grade/s.	R / 1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10 / 11 / 12
10. What was your last mathematics mark (percentage) at school?	0-100
Musical and creative arts history	
11. Have you learnt to read music or musical notation?	Yes / No
12. Have you ever learnt to play a musical instrument before? If the answer is No, skip the next three questions.	Yes / No
13. Which musical instrument/s have you learnt to play? Select all that apply.	Drum played with a drumstick Drum beaten by hand Drum kit Other percussive instrument/s e.g. marimba, cymbals, triangle, chimes String instrument e.g. guitar Keyboard / piano Wind instrument e.g. flute, recorder Brass instrument e.g. trumpet, trombone Traditional African instrument

	Other If other, please specify.
14. Where did you learn to play the musical instrument/s? Select all that apply.	School Church Community group or organisation Home Other If other, please specify.
15. How long did you spend playing a musical instrument regularly i.e. at least once a week in term time?	< 1 month / 1-3 months / 3-6 months / 6-12 months / 1-2 years / 2-4 years / 4-6 years / >6 years
16. Do you currently sing in a choir or with a group of people on a regular basis i.e. at least once a week in term time? If the answer is No, please skip the next two questions.	Yes / No
17. Where is/are the singing group/s taking place? Select all that apply.	School Church Community group or organisation Home Other If other, please specify
18. How long have you been singing in a group regularly i.e. at least once a week in term time?	< 1 month / 1-3 months / 3-6 months / 6-12 months / 1-2 years / 2-4 years / 4-6 years / >6 years
19. Have you previously sung in a choir or with a group of people on a regular basis i.e. at least once a week in term time? If the answer is No, please skip the next two questions.	Yes / No
20. Where did the singing group/s take place? Select all that apply.	School Church Community group or organisation Home Other If other, please specify
21. How long did you spend singing with a group regularly i.e. at least once a week in term time?	< 1 month / 1-3 months / 3-6 months / 6-12 months / 1-2 years / 2-4 years / 4-6 years / >6 years
22. Do you currently dance (dancing includes rhythmic movements in a marching band or	Yes / No

rhythmic gymnastics) with a group or take part in a dance class on a regular basis i.e. at least once a week in term time? If the answer is No, please skip the next two questions.	
23. Where is/are the dancing group/s taking place? Select all that apply.	School Church Community group or organisation Home Other If other, please specify
24. How long have you been dancing in a group or dance class regularly i.e. at least once a week in term time?	< 1 month / 1-3 months / 3-6 months / 6-12 months / 1-2 years / 2-4 years / 4-6 years / >6 years
25. Have you previously taken part in a dance class or danced with a group of people on a regular basis i.e. at least once a week in term time? If the answer is No, please skip the next two questions.	Yes / No
26. Where did the dancing group/s or class/es take place? Select all that apply.	School Church Community group or organisation Home Other If other, please specify
27. How long did you spend dancing with a group regularly i.e. at least once a week in term time?	< 1 month / 1-3 months / 3-6 months / 6-12 months / 1-2 years / 2-4 years / 4-6 years / >6 years
Medical history	
28. 18-19-year-old participants with HIV: Did you get HIV from your mother?	Yes / No / Prefer not to say
29. Have you ever taken treatment for your disease?	Yes / No / Prefer not to say
30. Are you currently taking treatment for your disease?	Yes / No / Prefer not to say
31. How old were you when you started treatment?	Age (continuous in years from 0-19 years old) / Unknown
32. Has your treatment changed at all in the past?	Yes / No / Don't know / Not applicable
33. Have you ever forgotten to take your treatment?	Yes / No / Prefer not to say
34. How often do you usually forget to take your treatment?	Never / Once a year / Once a month / A few times each month

	/ Once a week / A few days per week / Almost every day
35. Have you ever stopped taking your treatment for more than a week? If no, skip the next two questions.	Yes / No / Prefer not to say
36. How many times has this happened?	Never / Once / More than once
37. What were the reasons for not taking the treatment for more than a week? Tick all that apply. If other, please specify.	I forgot to take my treatment. No one reminded me to take my treatment. I am tired of taking treatment every day. I don't like taking the treatment. The treatment gave me bad side effects. I was sick. The doctor/nursing sister told me to stop the treatment. Other reason:
Mental health and behaviour	
Alcohol (AUDIT) **and substance use history** **1 unit:**  **More than 1 unit:** 	
38. How often do you have a drink containing alcohol? If you answer Never, skip the next nine questions.	Never / Monthly or less / 2-4 times a month / 2-3 times a week / 4 or more times a week
39. How many units of alcohol do you drink on a typical day when you are drinking?	0 - 2 / 3 - 4 / 5 - 6 / 7 - 9 / 10 or more
40. How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never / less than monthly / monthly / weekly / daily or almost daily
41. How often during the last year have you found that you were not able to stop drinking once you had started?	Never / less than monthly / monthly / weekly / daily or almost daily

42. How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never / less than monthly / monthly / weekly / daily or almost daily
43. How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never / less than monthly / monthly / weekly / daily or almost daily
44. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never / less than monthly / monthly / weekly / daily or almost daily
45. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never / less than monthly / monthly / weekly / daily or almost daily
46. Have you or somebody else been injured as a result of your drinking?	Never / less than monthly / monthly / weekly / daily or almost daily
47. Has a relative or friend, doctor, or other health worker been concerned about your drinking or suggested that you cut down?	Never / less than monthly / monthly / weekly / daily or almost daily
48. Have you ever used illicit drugs? If the answer is No, skip the next question.	Yes / No / Unknown / Prefer not to say
49. Have you used any illicit drugs in the last month?	Yes / No / Unknown / Prefer not to say
Your emotions and behaviour	
50. Have you ever been diagnosed with a mental illness such as depression or anxiety? If the answer is No, skip the next question.	Yes / No / Unknown / Prefer not to say
51. Are you currently on treatment for this mental illness?	Yes / No / Unknown / Prefer not to say
SRQ-20: The following questions are related to certain problems that may have bothered you in the last 30 days. If you think the question applies to you and you had the described problem in the last 30 days, answer 'Yes'. If the answer does not apply to you and you did not have the described problem in the last 30 days, answer 'No'. If you are unsure, please give the best answer you can.	
52. Do you often have headaches?	Yes / No
53. Is your appetite poor?	Yes / No
54. Do you sleep badly?	Yes / No
55. Are you easily frightened?	Yes / No
56. Do your hands shake?	Yes / No
57. Do you feel nervous, tense or worried?	Yes / No
58. Is your digestion poor?	Yes / No
59. Do you have trouble thinking clearly?	Yes / No
60. Do you feel unhappy?	Yes / No
61. Do you cry more than usual?	Yes / No
62. Do you find it difficult to enjoy your daily activities?	Yes / No
63. Do you find it difficult to make decisions?	Yes / No
64. Is your daily work suffering?	Yes / No

65. Are you unable to play a useful part in life?	Yes / No
66. Have you lost interest in things?	Yes / No
67. Do you feel that you are a worthless person?	Yes / No
68. Has the thought of ending your life been on your mind?	Yes / No
69. Do you feel tired all the time?	Yes / No
70. Do you have uncomfortable feelings in your stomach?	Yes / No
71. Are you easily tired?	Yes / No
72. If you said 'Yes' to any of the problems above, how difficult have these problems made it for you to take care of things at home, or get along with other people?	Not difficult at all / A bit difficult / Very difficult / Extremely difficult
Social support (MSPSS)	
73. There is a special person who is around when I am in need.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
74. There is a special person with whom I can share joys and sorrows.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
75. My family really tries to help me.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
76. I get the emotional help & support I need from my family.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
77. I have a special person who is a real source of comfort to me.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
78. My friends really try to help me.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
79. I can count on my friends when things go wrong.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
80. I can talk about my problems with my family.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree

81. I have friends with whom I can share my joys and sorrows.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
82. There is a special person in my life who cares about my feelings.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
83. My family is willing to help me make decisions.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
84. I can talk about my problems with my friends.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree

Appendix 22: AHEAD Study caregiver baseline questionnaire

Sociodemographic history	
1. What is your relationship to the participant?	Biological mother / biological father / adopted mother / adopted father / grandmother / grandfather / aunt / uncle / cousin / other If other, please specify
2. What is your nationality?	South African / Mozambican / Other If other, please specify
3. Are you currently married?	Yes / No / Prefer not to say
4. What is your highest level of education?	No formal education / Some primary school / Completed primary school / Some high school / Completed high school / Post-secondary training (e.g. apprenticeship, diploma or degree) / Other If other, please specify
5. Are you currently employed? If the answer is No, skip the next question.	Yes / No
6. Are you employed on a full-time or part-time basis?	Full-time / part-time / other If other, please specify
7. How would you rate your household compared to others in your local community?	One of the poorest / Poor / Below average / Average / Above average / Rich / One of the richest / Unknown / Prefer not to say
Child's medical history	

8. Did the child's mother use drugs or drink alcohol while she was pregnant with him/her?	Yes / No / Don't know
9. Was the child born early or prematurely i.e. before the mother was 9 months' pregnant?	Yes / No / Don't know
10. Did the child need to sleep in hospital for a few days/weeks after being born due to illness?	Yes / No / Don't know
11. If the child is HIV-positive, did he/she get HIV from his/her mother?	Yes / No / Don't know
12. Does the child know his/her HIV status?	Yes / No / Don't know
Your emotions and behaviour	
13. Have you ever been diagnosed with a mental illness such as depression or anxiety? If the answer is No, skip the next question.	Yes / No / Unknown / Prefer not to say
14. Are you currently on treatment for this mental illness?	Yes / No / Unknown / Prefer not to say
SRQ-20: The following questions are related to certain problems that may have bothered you in the last 30 days. If you think the question applies to you and you had the described problem in the last 30 days, answer 'Yes'. If the answer does not apply to you and you did not have the described problem in the last 30 days, answer 'No'. If you are unsure, please give the best answer you can.	
15. Do you often have headaches?	Yes / No
16. Is your appetite poor?	Yes / No
17. Do you sleep badly?	Yes / No
18. Are you easily frightened?	Yes / No
19. Do your hands shake?	Yes / No
20. Do you feel nervous, tense or worried?	Yes / No
21. Is your digestion poor?	Yes / No
22. Do you have trouble thinking clearly?	Yes / No
23. Do you feel unhappy?	Yes / No
24. Do you cry more than usual?	Yes / No
25. Do you find it difficult to enjoy your daily activities?	Yes / No
26. Do you find it difficult to make decisions?	Yes / No
27. Is your daily work suffering?	Yes / No
28. Are you unable to play a useful part in life?	Yes / No
29. Have you lost interest in things?	Yes / No
30. Do you feel that you are a worthless person?	Yes / No

31. Has the thought of ending your life been on your mind?	Yes / No
32. Do you feel tired all the time?	Yes / No
33. Do you have uncomfortable feelings in your stomach?	Yes / No
34. Are you easily tired?	Yes / No
35. If you said 'Yes' to any of the problems above, how difficult have these problems made it for you to take care of things at home, or get along with other people?	Not difficult at all / A bit difficult / Very difficult / Extremely difficult

Appendix 23: AHEAD Study clinical data extraction form

Targeted information	**Data found in clinical records**
Clinical diagnoses (select all that apply)	HIV / Asthma / Diabetes mellitus Type 1 / Diabetes mellitus Type 2 / Eczema / Epilepsy / Rheumatic heart disease / Depression / Anxiety / ADHD / Hypothyroidism / Hyperthyroidism / Rheumatoid arthritis or SLE / Other
If other, what other diagnosis?	Type response here.
Non-ART medications (select all that apply)	Vitamins or supplements / Isoniazid prophylaxis / Cotrimoxazole prophylaxis / Analgesia / Drug-sensitive TB medication / Drug-resistant TB medication / Insulin / Oral antidiabetic medications / Anticonvulsant or mood stabiliser / Asthma inhaler / Oral prednisone / Topical dermatological treatments / Antidepressant / Anxiolytic / None / Other
If other, what other medications?	Type response here.
HIV testing and diagnosis	
Date of last recorded HIV test	DD/MM/YYYY
Method/s used to test and/or confirm the diagnosis	HIV PCR / HIV ELISA / HIV rapid testing
Result of last HIV test	Negative / Positive
Age at diagnosis (select one)	< 1 month old / 1-6 months old / 6-12 months old / 1-3 years old / 3-5 years old / 5-10 years old / 10-15 years old / >15 years old
Clinical data	
History of HIV encephalopathy	Yes / No / Unknown
WHO stage at diagnosis	1 / 2 / 3 / 4 / Unknown
Haematological and biochemical data	

Lowest ever (nadir) recorded absolute CD4+ cell count	Cells per microlitre
Lowest ever (nadir) CD4% of lymphocytes	%
Highest ever (peak) recorded viral load	Number of copies per millilitre
Highest ever (peak) recorded log viral load	Log value
Date of the most recent CD4+ cell count	DD/MM/YYYY
Most recent CD4+ cell count	Cells per microlitre
Most recent CD4% of lymphocytes	%
Date of the most recent viral load	DD/MM/YYYY
Value of most recent viral load	Number of copies per millilitre
Value of most recent log viral load	Log value
Treatment-related information	
Ever treated with antiretroviral therapy	Yes / No
Date of clinical data extraction	DD/MM/YYYY
Date of ART initiation	DD/MM/YYYY
Duration of ART	Calculated value: (date of clinical data extraction – date of ART initiation)
Current antiretroviral regimen (select all drugs the participant is currently taking)	Fixed-dose combination (FDC) of tenofovir, emtricitabine, efavirenz / Fixed-dose combination (FDC) of dolutegravir, abacavir, lamivudine / Dolutegravir (DTG) / Tenofovir (TDF) / Abacavir (ABC) / Zidovudine (AZT) / Emtricitabine (FTC) / Lamivudine (3TC) / Efavirenz (EFV) / Nevirapine (NVP) / Lopinavir/Ritonavir (LPV/r) / Ritonavir (RTV) / Atazanavir (ATV) / Unknown
First antiretroviral regimen (select all drugs the participant was taking)	Fixed-dose combination (FDC) of tenofovir, emtricitabine, efavirenz / Fixed-dose combination (FDC) of dolutegravir, abacavir, lamivudine / Dolutegravir (DTG) / Tenofovir (TDF) / Abacavir (ABC) / Zidovudine (AZT) / Emtricitabine (FTC) / Lamivudine (3TC) / Efavirenz (EFV) / Nevirapine (NVP) / Lopinavir/Ritonavir (LPV/r) / Ritonavir (RTV) / Atazanavir (ATV) / Unknown
Second antiretroviral regimen (select all drugs the participant was taking)	Fixed-dose combination (FDC) of tenofovir, emtricitabine, efavirenz / Fixed-dose combination (FDC) of dolutegravir, abacavir, lamivudine / Dolutegravir (DTG) / Tenofovir (TDF) / Abacavir (ABC) / Zidovudine (AZT) / Emtricitabine (FTC) / Lamivudine (3TC) / Efavirenz (EFV) / Nevirapine (NVP) / Lopinavir/Ritonavir (LPV/r) / Ritonavir (RTV) / Atazanavir (ATV) / Unknown

Third antiretroviral regimen (select all drugs the participant was taking)	Fixed-dose combination (FDC) of tenofovir, emtricitabine, efavirenz / Fixed-dose combination (FDC) of dolutegravir, abacavir, lamivudine / Dolutegravir (DTG) / Tenofovir (TDF) / Abacavir (ABC) / Zidovudine (AZT) / Emtricitabine (FTC) / Lamivudine (3TC) / Efavirenz (EFV) / Nevirapine (NVP) / Lopinavir/Ritonavir (LPV/r) / Ritonavir (RTV) / Atazanavir (ATV) / Unknown
Any reported neuropsychiatric side effects If yes, select the side effects experienced.	Yes / No Dizziness / light-headedness / insomnia / fatigue / headaches / nightmares or bad dreams / impaired concentration / hallucinations or psychosis / depression / anxiety / other
Adherence	
Previous virological failure. If no, skip the next question. If yes, how many times has the participant previously been in virological failure?	Yes / No Never / Once / More than once
Any reported non-adherence based on missed appointments, pill counts etc.	Yes / No
How many times has there been reported non-adherence?	Never / Once / More than once

Appendix 24: AHEAD Study pre-intervention expectations questionnaire

Expectations Please select the statement that best describes how you feel. Please be honest.	
How would you describe your overall feeling towards the upcoming programme?	Very positive / positive / neutral / negative / very negative
If you could rate your excitement for the upcoming programme on a scale from 1 to 10 (0 = not at all excited; 10 = the most excited you have ever been about something), what score would you give it?	1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10
How do you think the programme will affect your ability to do the cognitive tasks on the tablet?	Get a lot better / get a bit better / stay the same / get worse / get a lot worse
How do you think the programme will affect your ability to concentrate at school or work?	Get a lot better / get a bit better / stay the same / get worse / get a lot worse

How do you think the programme will affect your overall mood or feelings?	It will improve a lot / It will improve a little / It will stay the same / It will get worse / It will get a lot worse

Appendix 25: AHEAD Study early study exit questionnaire

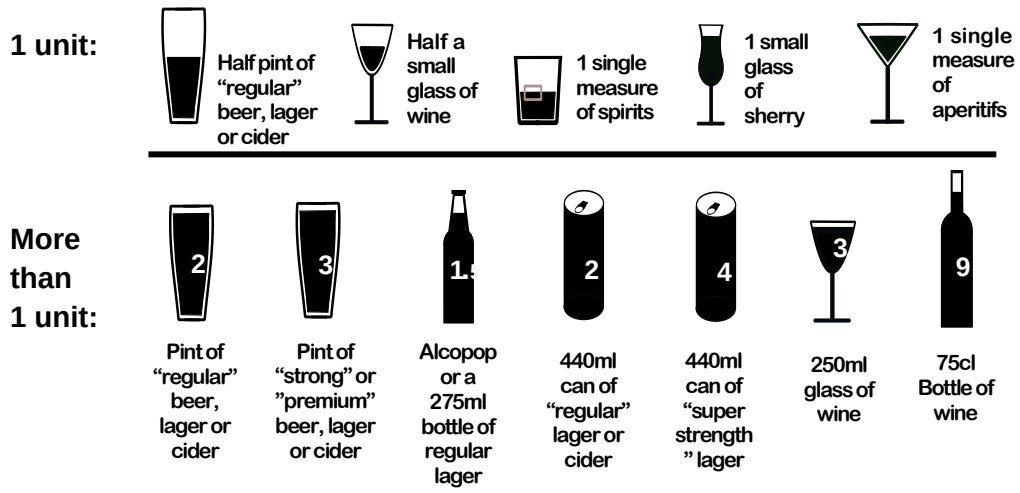
Acceptability Please be honest with your feedback. It is very important that you are honest so that we can find out what was easy and what was hard about taking part in the programme. We can then make sure that we improve the programme if it is run again. It will give us an accurate picture of how things went in the study for when we write up the results.	
1. How would you describe your overall feeling towards the programme	Very positive / positive / neutral / negative / very negative
2. If you could rate your enjoyment of the programme on a scale from 1 to 10 (1 = not at all enjoyable; 10 = highly enjoyable), what score would you give it	1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10
3. Would you recommend this programme to other people your age?	Yes / Maybe / No
4. Would you continue with this programme or take part again if you had the chance?	Yes / Maybe / No
5. Was there anything about the programme that you enjoyed or liked? If you answered No, skip the next question.	Yes / No / Don't know
6. What about the programme did you enjoy or like?	
7. Was there anything that you found strange or did *not* enjoy about taking part? If the answer is No, skip the next question.	Yes / No / Don't know
8. What about the programme did you find strange or not enjoy?	
9. Did you have any negative experiences (or did anything bad happen to you) due to taking part in the study? If the answer is No, skip the next question.	Yes / No
10. Please describe these negative experiences.	
11. Do you have any suggestions for how we could make the programme better? If the answer is No, skip the next question.	Yes / No
12. What are your suggestions for how we could improve the programme or make it better?	

13. What is your main reason for leaving the study early?	
14. Are there any other reasons why you are stopping the study early?	
15. Is there anything else you would like to tell us about your experience of taking part in the study?	

Appendix 26: AHEAD Study adolescent endline questionnaire

Medical history	
HIV-related history	
1. Are you currently taking medication?	No / Yes / Don't know / Prefer not to say
2. Has your treatment changed at all in the last 3 months?	No / Yes / Don't know / Prefer not to say
3. Have you forgotten to take your treatment at all in the last 3 months? If the answer is No, skip the next question.	No / Yes / Don't know / Prefer not to say
4. How often did you forget to take your treatment?	Once a month / A few times each month / Once a week / A few days per week / Almost every day / Don't know / Not applicable / Prefer not to say
5. Did you ever stop taking your treatment for more than a week in the last 3 months? If the answer is No, skip the next question.	No / Yes / Don't know / Prefer not to say
6. What were the reasons for not taking the treatment for more than a week? Tick all that apply. If other, please specify.	I forgot to take my treatment. No one reminded me to take my treatment. I am tired of taking treatment every day. I don't like taking the treatment. The treatment gave me bad side effects. I was sick. The doctor/nursing sister told me to stop the treatment. Other reason:
Mental health and behaviour	

Alcohol (AUDIT) **and substance use history**



7. How often do you have a drink containing alcohol? If you answer Never, skip the next nine questions.	Never / Monthly or less / 2-4 times a month / 2-3 times a week / 4 or more times a week
8. How many units of alcohol do you drink on a typical day when you are drinking?	0 - 2 / 3 - 4 / 5 - 6 / 7 - 9 / 10 or more
9. How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never / less than monthly / monthly / weekly / daily or almost daily
10. How often during the last year have you found that you were not able to stop drinking once you had started?	Never / less than monthly / monthly / weekly / daily or almost daily
11. How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never / less than monthly / monthly / weekly / daily or almost daily
12. How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never / less than monthly / monthly / weekly / daily or almost daily
13. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never / less than monthly / monthly / weekly / daily or almost daily
14. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never / less than monthly / monthly / weekly / daily or almost daily
15. Have you or somebody else been injured as a result of your drinking?	Never / less than monthly / monthly / weekly / daily or almost daily
16. Has a relative or friend, doctor, or other health worker been concerned about your drinking or suggested that you cut down?	Never / less than monthly / monthly / weekly / daily or almost daily

17. Have you used any illicit drugs in the last 3 months? If the answer is No, skip to question 25.	Yes / No / Unknown / Prefer not to say
18. Have you used any illicit drugs in the last month?	Yes / No / Unknown / Prefer not to say
Your emotions and behaviour (SRQ-20)	
The following questions are related to certain problems that may have bothered you in the last 30 days. If you think the question applies to you and you had the described problem in the last 30 days, answer 'Yes'. If the answer does not apply to you and you did not have the described problem in the last 30 days, answer 'No'. If you are unsure, please give the best answer you can.	
19. Do you often have headaches?	Yes / No
20. Is your appetite poor?	Yes / No
21. Do you sleep badly?	Yes / No
22. Are you easily frightened?	Yes / No
23. Do your hands shake?	Yes / No
24. Do you feel nervous, tense or worried?	Yes / No
25. Is your digestion poor?	Yes / No
26. Do you have trouble thinking clearly?	Yes / No
27. Do you feel unhappy?	Yes / No
28. Do you cry more than usual?	Yes / No
29. Do you find it difficult to enjoy your daily activities?	Yes / No
30. Do you find it difficult to make decisions?	Yes / No
31. Is your daily work suffering?	Yes / No
32. Are you unable to play a useful part in life?	Yes / No
33. Have you lost interest in things?	Yes / No
34. Do you feel that you are a worthless person?	Yes / No
35. Has the thought of ending your life been on your mind?	Yes / No
36. Do you feel tired all the time?	Yes / No
37. Do you have uncomfortable feelings in your stomach?	Yes / No
38. Are you easily tired?	Yes / No
39. If you said 'Yes' to any of the problems above, how difficult have these problems made it for you to take care of things at home, or get along with other people?	Not difficult at all / A bit difficult / Very difficult / Extremely difficult / Not applicable
Social support (MSPSS)	
40. There is a special person who is around when I am in need.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
41. There is a special person with whom I can share joys and sorrows.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral /

	Mildly agree / Strongly agree / Very strongly agree
42. My family really tries to help me.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
43. I get the emotional help & support I need from my family.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
44. I have a special person who is a real source of comfort to me.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
45. My friends really try to help me.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
46. I can count on my friends when things go wrong.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
47. I can talk about my problems with my family.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
48. I have friends with whom I can share my joys and sorrows.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
49. There is a special person in my life who cares about my feelings.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
50. My family is willing to help me make decisions.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree
51. I can talk about my problems with my friends.	Very strongly disagree / Strongly disagree / Mildly disagree / Neutral / Mildly agree / Strongly agree / Very strongly agree

Appendix 27: AHEAD Study caregiver endline questionnaire

Your emotions and behaviour	
1. In the last 3 months, have you been diagnosed with a mental illness such as depression or anxiety? If the answer is No, skip the next question.	Yes / No / Don't know / Prefer not to say
2. Are you currently on treatment for this mental illness?	Yes / No / Unknown / Prefer not to say
SRQ-20: The following questions are related to certain problems that may have bothered you in the last 30 days. If you think the question applies to you and you had the described problem in the last 30 days, answer 'Yes'. If the answer does not apply to you and you did not have the described problem in the last 30 days, answer 'No'. If you are unsure, please give the best answer you can.	
3. Do you often have headaches?	Yes / No
4. Is your appetite poor?	Yes / No
5. Do you sleep badly?	Yes / No
6. Are you easily frightened?	Yes / No
7. Do your hands shake?	Yes / No
8. Do you feel nervous, tense or worried?	Yes / No
9. Is your digestion poor?	Yes / No
10. Do you have trouble thinking clearly?	Yes / No
11. Do you feel unhappy?	Yes / No
12. Do you cry more than usual?	Yes / No
13. Do you find it difficult to enjoy your daily activities?	Yes / No
14. Do you find it difficult to make decisions?	Yes / No
15. Is your daily work suffering?	Yes / No
16. Are you unable to play a useful part in life?	Yes / No
17. Have you lost interest in things?	Yes / No
18. Do you feel that you are a worthless person?	Yes / No
19. Has the thought of ending your life been on your mind?	Yes / No
20. Do you feel tired all the time?	Yes / No
21. Do you have uncomfortable feelings in your stomach?	Yes / No
22. Are you easily tired?	Yes / No
23. If you said 'Yes' to any of the problems above, how difficult have these problems made it for you to take care of things at home, or get along with other people?	Not difficult at all / A bit difficult / Very difficult / Extremely difficult / Not applicable

Appendix 28: AHEAD Study drumming participant endline acceptability questionnaire

Acceptability Please be honest with your feedback. It is very important that you are honest so that we can find out what was easy and what was hard about taking part in the programme. We can then make sure that we improve the programme if it is run again. It will give us an accurate picture of how things went in the study for when we write up the results.	
1. How would you describe your overall feeling towards the programme?	Very positive / positive / neutral / negative / very negative
2. If you could rate your level of satisfaction with the programme on a scale from 0 to 10 (0 = absolutely hated it; 10 = absolutely loved it), what score would you give it	0 / 1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10
3. Did you practise drumming? If no, skip the next question.	Yes / No
4. How often did you practise?	Once a week / 2-3 times a week / 4-5 times a week / Every day
5. How do you think the programme affected your ability to do the brain tasks on the tablet?	It helped a lot / it helped a little / it made no difference / it made me do worse / it made me do a lot worse
6. How do you think the programme affected your ability to concentrate at school or work?	It helped a lot / it helped a little / it made no difference / it made it worse / it made it a lot worse
7. How do you think the programme affected your overall mood or feelings?	It helped a lot / it helped a little / it made no difference / it made it worse / it made it a lot worse
8. Would you recommend this programme to other people your age?	Yes / Maybe / No
9. Would you continue with this programme or take part again if you had the chance?	Yes / Maybe / No
10. What about the programme did you enjoy or like?	
11. Was there anything you did *not* enjoy about taking part? If the answer is No, skip the next question.	Yes / No
12. Please specify what you did *not* enjoy.	
13. Did anything bad happen because you took part in this study? If the answer is No, skip the next question.	Yes / No
14. Please describe these negative experiences.	
15. Did you miss any of the 8 sessions? If the answer is No, skip the next two questions.	Yes / No
16. How many sessions did you miss?	Whole number

17. What were the reasons for missing the session/s?	
18. Do you have any suggestions for how we could make the programme better? If the answer is No, skip the next question.	Yes / No
19. What are your suggestions for how we could improve the programme or make it better?	
20. Is there anything else you would like to tell us about your experience of taking part in the study?	

Appendix 29: AHEAD Study fieldworker job advertisement content

FIELD & DATA SECTION - JOB OPPORTUNITIES

The MRC/Wits Agincourt Research Unit is an exceptional health and population research Centre providing an extensive data resource resulting from years of longitudinal health and socio-demographic surveillance. It currently nests a number of observational and intervention studies - all undertaken with an interdisciplinary network of leading international scientists in the Agincourt sub-district in rural north-east South Africa. A new study will be starting in July 2018, looking at the effect of drumming on brain function in adolescents with chronic diseases attending the clinics. The Unit is currently inviting applications for a short-term contractual fieldworker position for this study.

AHEAD (Adolescent Executive Functioning and Drumming) Study

1 x evaluation & drumming intervention fieldworker

Job expectations:

Availability:

- Available for job interview in Agincourt during the week of 25-28 June 2018.
- Willing to attend training (likely in Kildare or Lillydale) from 2-6 July 2018 for Modern African Classical Drumming and study-specific training.
- Willing to practise playing the djembe drum (loaned to the fieldworker for the duration of the study) for a minimum of 1-2 hours per week from July-October 2018.
- Available full-time during July, August and October 2018 and three days a week during September 2018.

Qualifications:

- Grade 12 certificate (NQF Level 5)

Residence:

- Applicants must be residing within the HDSS villages; Agincourt, Khayalami, Croquet lawn, Cunningmoore A & B, Dumphries A, B & C, Rolle C, Kumani, MP Stream, Makaringe, Kildare A, B & C, Lillydale A & B, Ireagh A, B & C, Huntington, Newington B & C, Somerset A, B & C, Justicia A & B, Xanthia, Belfast, Rholane.

Recommended past experience:

- Prior experience of working on a study within the MRC/Wits Agincourt Research Unit.
- Prior experience of working with teenagers.
- Prior musical experience (e.g. drumming or playing another musical instrument, singing in a group).

Personal abilities:

A successful candidate for this position will be creative, musical, have a good sense of rhythm, be passionate about music and able to engage and empower youth. The individual should be respectful, empathetic and have good listening skills. The individual should be confident, friendly, professional, able to follow instructions, self-motivated, and must have good communication skills in both English and Xitsonga. The individual must be flexible, able to work well within a team, and be able to maintain participants' confidentiality strictly, both on and off the job. Short-listed applicants must be willing to take part in the drumming training from 2-6 July and lead a drumming circle on the last day of training as part of the selection process.

The successful candidate will be notified on Saturday 7 July and be required to participate in further study-specific training from 9-10 July 2018. Only candidates who complete the training successfully will be considered for a short-term contract with the MRC/Wits Agincourt Research Unit from July-October 2018.

If you have the required qualifications listed above and would like to apply, please send your CV (including your full name and contact details), names and contact details of 3 referees, certified copies of Certificates, ID copy, and motivation letter stating why you are interested in the position and deliver it to the Agincourt site office in a box placed at the entrance of the main office.

Enquiries should be forwarded to XX at **XXX XXX XXXX / XXX XXX XXXX** or **xxxx.xxxx@wits.ac.za** between 08h00 and 16h30 weekdays.

Closing date: 20 June 2018 @ 16h30

Appendix 30: AHEAD Study fieldworker interview questions

SECTION A: BACKGROUND QUESTION

1. Briefly tell us about yourself (Background and career History)? (5)

SECTION B: ORGANISATIONAL FIT QUESTIONS

1. The AHEAD Adolescent Drumming Study will involve recruiting 60 teenagers from the clinics and leading weekly drumming groups for half of them. Why do you wish to join the project as a Fieldworker and what makes you a suitable candidate? (5)
2. What do you think are the most important qualities and abilities that a person should possess to be successful in this position? (5)
3. Tell us about any musical or creative experience you have. (5)
4. Please sing a song verse for us. (5)
5. Please copy me as I tap out a few rhythms. (5)

SECTION C: INSIGHT AND UNDERSTANDING

1. Fieldwork requires personal motivation, taking initiative and building relationships. Please tell us how you will apply these qualities in your work as Fieldworker? (5)
2. How would you describe your leadership style? (5)
3. What is confidentiality, and why is it important? (5)
4. Describe a difficult problem you have had to deal with (in the field) and how you solved that problem. (5)

SECTION D: HR QUESTIONS

1. Do you have a valid driver's license? Yes/No
2. Are you comfortable and able to travel within Bushbuckridge and surrounding areas? Yes/No
3. Are you willing and available to work on weekends? Yes/No
4. Are you willing to reside in Bushbuckridge? Yes/No
5. Did you bring certified copies of your qualifications or any other courses? Yes/N
6. Are you currently employed? Yes/No. What is your notice period (30 days or calendar month)?
7. Are you studying anything at the moment? Yes/No
8. How much time do you need off for your studies?
9. Are your references contactable? (Please confirm references on the CV) (If there are no references on the CV, please ask the candidate to provide you with one contactable reference).
10. Do you have any questions that you would like to ask? (Note the questions asked) (Pro-activeness, initiative)

Appendix 31: AHEAD Study assessment fieldworker training

The assessment fieldworkers who were responsible for screening and recruitment, baseline and endline assessments, received 24 hours (three days) of study-specific training prior to initiation of participant recruitment including didactic teaching and practical learning through role-play. They received written material to study from and refer to throughout the study including: the study protocol, participant information sheets, questionnaires, and informed consent and assent forms. The training covered the following topics: being a fieldworker including team dynamics and leadership style, expectations, communication, professionalism, respect for autonomy and confidentiality; study rationale; study design; screening and recruitment; the different participant information sheets and how to inform caregivers and participants; the informed consent and assent process; randomisation and data management; participant questionnaires; caregiver questionnaires; the referral process to healthcare facilities; adverse event reporting; the psychological distress standard operating procedure (SOP); confidentiality; cognitive assessments; and the acceptability questionnaires; study timeline and logistics with regard to venues, transport, the daily schedule and work hours; practicalities regarding study phones and calling participants and caregivers, participant reimbursement for taxi fare and completion of the log, recordkeeping, attendance register, sick leave and safety reporting. Their knowledge was assessed with a written and practical test following the completion of training. If they did not achieve 75% on this test, they had to receive further training prior to commencement of recruitment.

Appendix 32: AHEAD Study group drumming facilitation training

Objectives

General objectives

Primary objective:

To train the fieldworkers in the art of djembe drumming circle facilitation so that they acquire the knowledge, skills and attitudes necessary to facilitate therapeutic drumming circles that train executive functioning for 12-19-year-old adolescents as part of the AHEAD Study.

Secondary objectives:

1. To train the local Creative Arts or choral educators in the art of djembe drumming so that they can use the techniques learnt to teach other educators and learners in their respective schools about drumming.

2. To train the local public-sector occupational therapist / occupational therapy technician in the art of djembe drumming so that they can use the techniques learnt in a therapeutic context with clients in local clinics and/or hospitals.

Specific objectives

Knowledge:

- Posture and technique – playing the djembe drum
- Basic beats (base, tone, slap) on the djembe drum
- Other possible beats and techniques for playing the djembe e.g. using fingertips or thumbs, the edges of the drum, different hand positions/postures

Skills:

- Ability to play the djembe drum – basic and more complex rhythms
- Ability to read drumming musical notation
- Ability to improvise on the djembe drum
- Ability to lead a djembe drumming circle

Attitudes:

- Enthusiastic and able to engage and inspire the youth
- Confidence without being intimidating or overbearing
- Encouraging and empowering attitude
- Flexible and creative

The focus will be on teaching the attendees to facilitate a group drumming programme for learners/adolescent participants/clients (12-19-year-olds) which comprises the following elements:

- A combination of core taught rhythms and improvised rhythms
- Progressively increasing complexity and level of difficulty over a number of weeks

- Simple to more complex rhythms
- Unison to polyrhythmic pieces where different subgroups are playing different rhythms
    - Memorisation of a progressively increasing number of rhythms (executive function: working memory)
    - Switching between various memorised rhythms upon demand (executive function: task switching)
    - Improvisation of rhythms by the adolescent participants (executive function: cognitive flexibility)

- Switching between unison and polyrhythmic structures (executive functions: task switching, inhibitory control)

The group drumming programme should develop the following skills in the adolescent participants:

- Working memory or updating: the ability to hold information (e.g. rhythms) in mind and then do something with this information (e.g. play the rhythm on the drum); the ability to update the information (rhythms) held in mind constantly (e.g. memorise a new rhythm that you now need to play)
- Inhibitory control: the ability to block out distractions (e.g. competing rhythms) and focus on maintaining one's own action (rhythm) without copying someone else's action (rhythm)
- Task switching or cognitive flexibility: the ability to switch flexibly between one task (rhythm) and another when required to do so without reverting to the previous action (rhythm) by mistake; the ability to work creatively (e.g. improvising one's own rhythms)

Daily schedule

Date	**Activities**
Mon 2 July	9:15: Participants arrive & register 9:30: Introductions 10:00: Tutorial by Dr Rowe: Objectives of training & the adolescent drumming programme 10:30: Practical training: posture, basic beats. Dr Nkosi leads an introductory djembe drumming circle for an hour. 11:30: Tea 12:00: Practical training (experiential learning): learning core basic rhythms 12:30: Practical training: how to teach core basic rhythms 13:30: Lunch 14:00: Training: drumming notation theory & putting it into practice 16:30: Pack-up and departure

Tues 3 July	9:30: Tutorial by Dr Rowe: executive function training & increasing complexity 10:30: Training: Revision of core basic rhythms & learning core complex rhythms 11:30: Tea 12:00: Training: drumming notation theory & putting it into practice 13:30: Lunch 14:00: Practical training: improvisation (how to improvise & how to encourage others to do so) 15:00: Combining core & improvised rhythms 16:30: Pack-up and departure
Wed 4 July	9:30: Tutorial by Dr Rowe: Musical training & the brain; drumming & the brain 10:30: Drumming circle led by Dr Nkosi incorporating simple & complex rhythms, alternation of rhythms, polyrhythms 11:30: Tea 12:00: Practical sessions: Taking turns to lead the group for 15 minutes 13:30: Lunch 14:00: Practical sessions: Taking turns to lead the group for 15 minutes 15:30: Drumming notation – practice 16:30: Pack-up and departure
Thu 5 July	9:30: Tutorial by Dr Rowe: attitudes to encourage & empower youth 10:30: Drumming circle led by Dr Nkosi incorporating simple & complex rhythms, alternation of rhythms, polyrhythms 11:30: Tea 12:00: Practical sessions: Taking turns to lead the group for 15 minutes 13:30: Lunch 14:00: Practical sessions: Taking turns to lead the group for 15 minutes 15:30: Drumming notation – practice 16:30: Pack-up and departure
Fri 6 July	9:30: Tutorial by Dr Rowe: AHEAD Study 10:30: Drumming circle led by Dr Nkosi incorporating simple & complex rhythms, alternation of rhythms, polyrhythms 11:30: Tea 12:00: Assessments: Taking turns to lead the group for 15 minutes 13:30: Lunch 14:00: Assessments: Taking turns to lead the group for 15 minutes 15:30: Final words: Dr Nkosi on facilitating a drumming circle with teenagers 16:00: Dr Rowe: Conclusions and thanks 16:30: Pack-up and departure

Photographs from AHEAD Study group drumming facilitation training





Appendix 33: AHEAD Study intervention fieldworker assessment schedules

Continuous assessment by me, the supervisor and participant-observer

Criterion	1	2	3	4	5	Subtotal
Initiative						/5
Enthusiasm						/5
Interpersonal interactions & communication (encouraging others etc.)						/5
Confidence						/5
Punctuality						/5
Effort						/5
Musicality						/5
Leadership						/5
Creativity						/5
Professionalism (e.g. use of phone, interrupting)						/5
TOTAL						**/50**

Musical assessment at end of drum training by drumming trainer, Dr Nkosi

Criteria	Excellent 8-10	Good 5-7	Poor/Average 0-4	Final Mark
Posture	Drumming posture was encouraged including how to hold a drum.	Drumming posture and holding of the drum was partly given attention.	Posture and positioning of the drum was not given attention.	**/10**
Tone sensitivity	Low, high and slap tones were used and played audibly.	Only high and low tones were used.	The tones were not given attention and the sound was not clean.	**/10**
Rhythm sensitivity	Rhythms were executed with precision.	Rhythms were played averagely without paying attention to their configuration.	Rhythms were poorly executed and worked on.	**/10**
Ensemble balance sensitivity	The first and the second rhythms were well-balanced including the vocals.	The first and the second rhythms were not synchronised efficiently.	There is no clear relationship between the rhythms given.	**/10**

Criteria	Excellent 8-10	Good 5-7	Poor/Average 0-4	Final Mark
Energy/creation of good learning environment	The facilitator worked efficiently and demonstrated the rhythms.	The facilitator gave average attention to the ensemble and did not demonstrate how the rhythms should be executed.	The facilitator did not demonstrate the skills needed.	**/10**
Modern African Classical Drumming (notated rhythms) sight reading				**/50**
Total score				**/100**

Appendix 34: AHEAD Study data management and quality assurance procedures

Data collection

Each participant was assigned a unique study specific numerical identifier at study entry which was used to identify the participant in study databases. All identifying details (participant name, clinic name, clinic folder number, date of birth, address, and contact details) were recorded in a separate encrypted Microsoft Access database at study entry. This database was accessible to the PI, the fieldworkers and the Agincourt data team for study-related purposes during the study e.g. to contact a participant regarding a missed visit.

There was no paper version of the case report form (CRF). It was made up of various electronic forms (identifiable data, enrolment data including consent and randomisation) in REDCap with direct entry of data into these electronic forms via an electronic tablet. Electronic data collection has numerous advantages over a paper-based system (Thriemer et al., 2012). The questionnaire and clinical record data collection forms were designed in REDCap. REDCap is a secure web-based

software platform allowing electronic data capture with an intuitive interface, tracing of the data trail, and automated data labelling and export (Harris et al., 2009).

The data was later exported as comma-separated values (CSV) files. After cleaning and collation of the data, the CSV files were imported into Stata 14 for data analysis. Separate Stata datasets (with the extension. dta) were created for each of the following: participant baseline questionnaire data; caregiver baseline questionnaire data; participant baseline clinical data; participant baseline cognitive data; participant endline questionnaire data; caregiver endline questionnaire data; participant endline cognitive data. The unique participant identifier was used in each dataset so that the datasets could be merged for analysis. The Stata syntax for the commands used to implement the data analysis was saved as Stata do-files (with the extension .do).

The cognitive data was collected through an electronic tablet. The raw data was imported into a CSV file for cleaning, collation and deriving of summary variables. This CSV file was imported into Stata 14 for data analysis.

Documentation and metadata

Accompanying documentation included all the questionnaires and data extraction forms, the cognitive task instructions, and a data dictionary explaining each of the cognitive and questionnaire variables.

Ethics and legal compliance

Permission for accessing South African Department of Health data in the form of clinical records was obtained from the Mpumalanga Provincial Health Research Committee, and the heads of the health facilities. Due to the sensitive nature of the HIV-related data, I, as the trained clinician on the team, obtained the information

in a confidential manner. Folders were viewed in private rooms at the health facilities and data was extracted using the clinical data extraction form on REDCap. The use of standardised questionnaires and batteries designed by other authors or researchers were appropriately acknowledged and cited, and permission obtained where necessary.

Storage and backup

The Wits REDCap server was used to host the various study forms and collect the data. The server is upgraded and maintained by the Wits REDCap team to ensure that it remains secure and free from bugs. I performed data transfer from the tablets manually at the end of each workday. The data was exported in a CSV format. All the primary data files as well as the accompanying documentation and metadata were saved on my encrypted laptop hard drive in a password-protected folder as well as on two encrypted password-protected external hard drives. These hard drives were kept with me during office hours during the study and locked away securely each night to ensure that no unauthorised access occurred. I took the hard drives with anonymised data on them back to the Department of Psychiatry, University of Oxford, after study completion where they were stored in a locked cabinet in my locked office.

Data access

The computer and tablets used for the data collection and storage were password-protected and encrypted. Only the investigators and other members of the study team at the MRC/Wits Agincourt Research Unit and at the University of Oxford had access to the login details for the project-specific REDCap account and the electronic devices. The passwords were complex involving a combination of letters in upper and lower case, symbols, and numbers.

Direct access will be granted to authorised representatives from the University of Oxford and the University of the Witwatersrand for monitoring and/or audit of the study if necessary to ensure compliance with the university regulations.

Selection and preservation

Any journal publications arising from the study, as well as this thesis will be uploaded to the Oxford University Research Archive, a permanent secure institutional repository. This will enable long-term curation as deposited items are held in the Bodleian Libraries archival store. Every item is assigned a persistent URL. Identifiable data (including all physical and electronic source documents) will be archived safely at the MRC/Wits Agincourt Research Unit for five years after which it will be destroyed in an appropriate and secure manner. All data that was retained by me and returned to the University of Oxford will be stored in a locked cabinet in the University of Oxford Department of Psychiatry for 3 years after publication of study findings. It will then be destroyed by the research group securely through standard departmental procedures.

Data sharing

The Oxford University Research Archive is accessible by any researchers who are interested in viewing the study findings. Approved members of the study team were given access to the data via the secure REDCap server.

Responsibilities and resources

All members of the research team were jointly responsible for executing this data management plan. The resources required were: a laptop and two electronic tablets with the necessary software capabilities; two external hard drives; and a secure and efficient wireless network with Internet access.

Dissemination of results

I presented the findings at AIDS Impact and the International HIV Paediatrics Workshop prior to the IAS Conference 2019. I also aim to publish the findings in a peer-reviewed journal. For any publications or presentations arising from the study, the four authorship criteria of the International Committee of Medical Journal Editors (ICMJE) must be met for each paper. To qualify as an author, an individual must: make substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data; draft the work or revise it critically for important intellectual content; approve the final version of the manuscript for publication; and agree to be held accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (ICMJE, 2017). People who contributed to the work but do not meet all four of the above criteria for authorship will be acknowledged in the acknowledgements section of any paper or presentation arising from the study.

With regards to disseminating the study findings at the local level in the MRC/Wits Agincourt HDSS study site, there are various meetings that the unit's Public Engagement Office carries out annually to disseminate research findings from recent studies conducted there. These include a community feedback meeting within each village in the study site; as well as a meeting for various key stakeholders including the staff from the health care facilities within the study site, and representatives from the local and provincial Departments of Health. The acronym 'AHEAD' will be described as 'Adolescent Executive Function and Drumming' to avoid the association with HIV and potential stigmatisation of participants.

Quality assurance

The study was conducted in accordance with relevant regulations and standard operating procedures of the MRC/Wits Agincourt Research Unit. Quality control measures included fieldworker self-checks, cross-checks, and random checks by me. Data integrity was checked after each data upload to the REDCap server. Any inconsistencies were then resolved with the fieldworker immediately. Collated data was checked by Julia Ruiz Pozuelo, a fellow DPhil student who assisted with data analysis for publication, to help identify any inconsistencies and deal with them prior to data analysis.

Appendix 35: AHEAD Study ethical considerations

I ensured that this study was conducted in accordance with the principles of the Declaration of Helsinki 2013 (*World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, 2013), relevant regulations, the ICH Good Clinical Practice (GCP) guidelines as well as the South African Good Clinical Practice Guidelines 2006 Second Edition (*Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa*, 2006; *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) Current Step 4 version dated 9 November 2016*, 2016).

Participant confidentiality

The fieldworkers received training in confidentiality as part of their study-specific training. They ensured that participants' anonymity was maintained during the study. The participants were identified by a participant ID number only on all study documents and the electronic database, except for the consent and assent forms, the case report form, the identifiable data database, and session attendance

registers. All identifying details were recorded in a separate encrypted Microsoft Access database and only accessible to me and other approved members of the study team for study-related purposes during the study. The study's electronic data was stored on a secure password-protected REDCap server. All paper documents were stored securely and only accessible by study staff and authorised personnel. The study complied with the Protection of Personal Information Act No. 4 of 2013 ("Protection of Personal Information Act," 2013). No identifying data was published in this thesis, neither will it be published in any other peer-reviewed publications arising from the study. Participants and caregivers were assured that confidentiality would be breached only if the study team felt that they were at risk of harm (e.g. suicidal ideation or psychotic depression requiring referral to the local mental health services, or suspected child abuse), where a condition warranted mandatory reporting (e.g. a notifiable disease such as tuberculosis), or where a court order dictated that information be released.

To reduce the risk of inadvertent disclosure of the HIV status of potential and actual participants, recruitment took place at the clinics where adolescents with and without HIV are seen so that it was not possible to know which participants have HIV and which participants do not have HIV. The weekly drumming sessions were held indoors behind closed doors in church halls or clinic rooms without public access.

A big concern in adolescents with behaviourally acquired HIV could be disclosure of their HIV status, and their sexual behaviour by implication, to their caregivers. This is less of an issue with perinatally acquired HIV where caregivers usually know the adolescent's HIV status and have assisted with HIV care, often for many years. 18-19-year-old adolescents who had not disclosed to their caregivers did not need

to invite a caregiver to participate in the study if they did not wish to do so. However, in the case of 12-17-year-old participants who acquired HIV sexually and had not disclosed to a caregiver, consent would need to be obtained from their caregivers for participation. These adolescents would likely have self-selected out of participation. If they did wish to participate, they were supported in disclosing their HIV status to their caregivers. Similarly, if adolescents had not yet been disclosed to and were unaware of their own HIV status at eligibility screening, caregivers and the clinic nurse responsible for seeing the HIV-positive patients were encouraged to begin the process of disclosure and told the reasons for it being vitally important including the adolescent's right to information about his/her own health, disease ownership and responsibility, adherence to treatment, and building a relationship of trust between adolescents and caregivers as well as clinic nursing staff. Training sessions were held at three of the local clinics towards the end of the study, including teaching on and distribution of the South African National Department of Health guidelines on HIV status disclosure.

Potential risks of participation and how these were mitigated

Despite the high prevalence of HIV in the study area, HIV is still a stigmatised illness. If I had been an HIV-positive adolescent taking part in the study, my main concern would have been accidental disclosure of my HIV status to others within the study or the community. I would have been afraid that my HIV status might have been discovered by my peers. For this reason, the original protocol was amended to include any adolescents with chronic diseases, with or without HIV, from the clinics. This meant that people who took part in the 'drumming study' were not automatically labelled as having HIV because it was not known as an HIV study. The trained fieldworkers signed confidentiality agreements where they

swore to keep the HIV status of participants confidential. All study and health facility staff as well as the CAB were asked to refer to the study by the acronym AHEAD because it did not include the term ‘HIV’.

Certain questions in the questionnaire regarding mental health had the potential to trigger psychological distress in the adolescent and/or the caregiver (including a post-traumatic stress reaction in someone with post-traumatic stress disorder). If this occurred, the study team followed the MRC/Wits Agincourt Research Unit’s Psychological Distress SOP which included appropriate referral to local health services for further assessment and management if this was deemed necessary. Participants were referred to the local social worker for further counselling if this was considered necessary. Participants with more severe mental health symptoms (e.g. psychosis, suicidal ideation) were referred to the Psychiatry Clinic at Tintswalo Hospital.

The study may have caused inconvenience to the caregivers of participants who did not normally attend the clinic but now needed to do so to complete informed consent forms, and baseline and endline questionnaires. They were reimbursed for their travel expenses. The study may have caused inconvenience to participants who had to travel to a central venue within the Agincourt HDSS weekly for 8 weeks during the second term, September school holiday, and third term of 2018. They did not receive monetary compensation (as per the MRC/Wits Agincourt Research Unit policy); however, intervention arm participants were given snacks and beverages at each drumming session. All participants were given snacks and beverages at their cognitive assessment visits. They were also reimbursed for their travel expenses.

Any adolescent who is a member of a group of adolescents is at risk of being a target of bullying by another member of the group. The chances of this occurring were minimised by the group being supervised by a fieldworker and/or drumming facilitator throughout each weekly session. Any incidents occurring in drumming sessions were managed appropriately.

Participants in the intervention arm may have experienced some discomfort in their hands after their initial drumming session/s. If the participants followed the facilitator's instructions and did not drum too hard during the early sessions, this discomfort should have been minimal and will have diminished with time as the participants' hands become accustomed to regular drumming. However, if participants did not listen to the facilitator and drummed harder than instructed or spent more than the recommended amount of time drumming each day, there was a small chance that they could have developed blisters on the palms of their hands. The drumming group participants' hands were inspected at the start of each session to make sure that they did not have open blisters or sores that could cause dangerous exposure of the shared drum skin to infectious body fluids. If a participant had a sore or blister, the wound was cleaned and dressed with a plaster using the first aid kit that was taken to each drumming session. They were not allowed to drum during that particular session but were allowed to sit in the session, listen and sing along so that they could learn the new rhythms and songs for that week. They were also referred to their local clinic to obtain antiseptic ointment and dressings to prevent the blisters or sores from becoming infected.

To minimise the risk of spread of infectious diseases within the drumming groups, the drumming participants were asked not to attend sessions if they were experiencing symptoms such as a fever, productive (wet) cough, vomiting or

diarrhoea. If a participant came along to a session but was found to be coughing productively, have a high fever, or experiencing other symptoms suggestive of an infectious illness, the participant's caregiver was alerted (in the case of minor participants) and the participant was referred to the nearest local clinic or primary care facility for further assessment and management.

South Africa has high rates of crime. The drumming sessions took place in the late afternoons while it was still light so they should not have endangered participants any more than their usual after-school afternoon activity. The doors to the rooms where the sessions took place were closed to prevent unwanted entry. The drumming facilitators and I both carried mobile phones with the local emergency number (112) saved on speed-dial for rapid alerting of the police if an attempted incident of crime occurred. Similarly, it made it possible for an ambulance to be called quickly should one of the participants have fallen ill during the session and required emergency medical attention.

Road transportation always carries the risk of road traffic accidents. The South African Road Accident Fund (RAF) provides compulsory cover to all users of South African roads against injuries sustained or death arising from accidents involving motor vehicles within the borders of South Africa. This cover is in the form of indemnity insurance to persons who cause the accident, as well as personal injury and death insurance to victims of motor vehicle accidents and their families. If any participants had been involved in any incidents of crime or road traffic accidents during travel to and from the study visits, the incident would have been reported to the local authorities in accordance with local laws as well as to me by the fieldworker/s.

The fieldworkers and I kept a record of any adverse events occurring during the execution of the study. Any adverse events occurring in the field had to be reported to me immediately. Serious adverse events in this study included: caregiver or participant death; caregiver or participant physical illness requiring admission to hospital for seven days or more; severe mental illness (including psychosis, intentional self-harm, or suicidal ideation); serious social harm to the caregiver or the participant (including domestic violence, or child abuse). Adverse events in this study included: stigma purportedly arising due to participation in the study; caregiver or participant reports of other negative consequences of study participation (e.g. family conflict, or a decline in academic performance). I reported any adverse events to the MRC/Wits Agincourt Research Unit field research manager, Dr Xavier Goméz-Olivé, and the Unit's management team. A meeting was arranged to discuss the event, the likely causality, and determine whether it was safe for the participant/s to continue with the study. I am registered as an independent medical practitioner with the Health Professions Council of South Africa (registration number MP0785172) and took professional responsibility for the referral of any cases of physical or mental illness arising during the study.

Benefits of study participation

The screening for mental health and substance use disorders that occurred as part of the caregiver and participant baseline assessment and the endline assessment of participants allowed the identification of problems that may not otherwise have been detected or might have taken longer to be discovered. This allowed referrals to be made to the local mental health services through the clinics where recruitment took place.

Payments and inducements

Caregivers were reimbursed for their travel expenses after the baseline and endline visits. Participants were given snacks and beverages at each weekly session. They were also reimbursed for their travel expenses each week. The amount varied according to distance travelled and was based on fixed taxi fare rates set by the local taxi unions.

Other ethical considerations

Adolescents, particularly during early adolescence, are a vulnerable population group because they are still developing and many of them are not yet competent to provide consent to participate in research. This meant that they were vulnerable to coercion by caregivers into taking part in a study even if they did not wish to do so. This were protected against by the fieldworkers addressing the adolescents themselves along with their caregivers during the recruitment and informed consent process. The adolescents were given a participant information sheet that is simple to understand and were given the opportunity to ask questions and to think about whether they wanted to participate if they were not sure. It was made clear that it was their choice to participate and that they were under no obligation to participate just because their caregiver had consented. Minor participants signed written assent forms to confirm that they also agreed to participate.

The research team referred any participants or caregivers to appropriate services if any physical or mental health disorders requiring treatment were diagnosed. A participant or caregiver with a score of 20 or more on the AUDIT alcohol screening questionnaire triggered referral to the local hospital for assessment for possible alcohol dependence. A participant who screened positive for illicit drug use in the

last month underwent full screening and a brief intervention using the World Health Organization's Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) package. A participant or caregiver with a score of 13 or more on the SRQ-20 triggered referral to the local hospital for further assessment and management for a possible anxiety and/or mood disorder. Any participant or caregiver who screened positive for suicidality on the mental health screening had a risk assessment done and was referred to the local hospital if necessary. This allowed further clinical management as deemed appropriate after thorough evaluation.

If it could be concluded on reasonable grounds that a minor participant had been abused in a manner causing physical injury, emotionally abused, sexually abused, or deliberately neglected, the suspected abuse was reported to a police officer at the local South African Police Service (SAPS) Office. This was in line with the mandatory reporting of suspected non-accidental injury or neglect of children required by the Children's Act No. 38 of 2005 ("Children's Act No. 38 of 2005," 2005).

Appendix 36: AHEAD Study facilitator post-intervention feedback on non-musical components of intervention

Component	Structure used	Rationale for chosen structure	Feedback from drumming facilitator and/or supervisor
Session duration	1 hour per session	Music therapist recommendation.	-Too short to get through the daily programme & allow the participants time to socialise.

			-Longer sessions tiring for younger participants.
Timing of various activities within the session	Initially target durations were not set, but later they were set at 5-15 minutes per activity or song with a watch for timekeeping.	-Good time management → whole programme covered. -Facilitator watch → easier timekeeping without phone use.	-Time management improved after better planning with target durations for each activity and the facilitator wearing a watch for timekeeping.
Participant snacks and beverages	2-3 items of fruit (apple, orange, banana) and one 200ml box of fruit juice per participant	-Help motivate attendance. -Encourage healthy eating.	-Allowed participants to come straight from school. -Prevented hunger, fatigue & low energy levels during sessions.
Session reminders	Telephonic call or text message (if no answer) the day before	-Confirm time, venue, transport arrangements, planned attendance. -Avoid poor attendance due to forgetfulness.	-Likely helped keep up attendance. -Perhaps didn't allow them to show ownership & commitment. -Without reminders, some still remembered, while others forgot.
Venue	Clinic adolescent room (1 group) or church halls (3 groups)	-Central/convenient -Safe -Available -Affordable -Appropriate in terms of size, furniture, amenities	-Church halls better – larger & own fans. -Clinic: small room → cramped as group grew; destigmatised coming to clinic even if healthy young

			person (additional attendees joined)
Group size	Allocations: 7-9 per group Reality: 3-12 per group (varied by day)	Music therapist recommendation of maximum adolescent:facilitator ratio of 10:1	-Smaller groups: quieter; less energy → harder for facilitator to maintain energy; more individual attention & interaction with adolescents by facilitator. -Larger groups: louder; more energy → easier for facilitator; facilitator less able to give individual attention & interact one-to-one with adolescents.
Group age range	12-19-years-old with no separation of age groups.	Small sample: logistically easiest to divide groups by location.	-Tough on youngest & oldest if in different life stages e.g. one has baby, other accompanied by caregiver. -May be better to split into primary & secondary school adolescents, or 12-14-year-olds & 15-19-year-olds.
Group gender composition	-3 mixed groups -1 all-female group (1 male allocated to group never attended)	Challenge gender stereotypes re females & drumming.	-All-female group more homogenous (all 14-19-years-old) → faster group cohesion &

			friendship formation vs mixed groups. -Having someone else in group similar in age & of the same sex seemed to help participants make friends & feel comfortable.
Group structure or formation	Always seated in a circle & all on the same level.	-Promote equality. -Promote unity. -Build self-esteem. -Non-threatening. -Non-hierarchical.	-Worked well to maintain sense of unity & equality within the groups.
'Find your match' icebreaker	-Reintroduce names with each new partner. -Find someone else who shares your: Favourite colour Favourite sports team Favourite sport Favourite fruit -Find a partner & find 3 things you have in common then report back to whole group.	-Build trust. -Start to build relationships.	Facilitator felt the icebreakers helped the group to 'open up' to each other and talk to each other. She would suggest starting each session with an icebreaker to help them become friends.
'Name out of hat' icebreaker	Each person to pull someone's name out of hat, find the person & tell the person some things	-Build trust. -Start to build relationships.	This icebreaker was shorter than the 'find your match' but still a useful way to get the adolescents talking to each other.

	you like about them.		
Observers	-1 peer (friend/family member) allowed to accompany each adolescent if requested & spare drum available. -Caregiver: allowed to sit outside the room. -Infants: allowed on adolescent's back if not disruptive. -Clinic staff: 1 allowed per session if drum available.	Safer travel to venue. Put adolescent at ease or make more comfortable at first.	-Peers: seemed to help some individuals feel more comfortable, relaxed, confident; created bigger, more energetic group. -Caregivers: distracting & makes it uncomfortable knowing they are there. -Infant: one at one session → distraction & noise -Nurse: one at one clinic-based session → young, friendly, enthusiastic, participated well.
Drumming facilitator	1 facilitator ± 1 supervisor Desired characteristics sought: -Confident -Musical -Young -Dynamic & enthusiastic -Engaging -Compassionate -Energetic -Positive	-Music therapist recommendation. -Facilitator inexperienced → supported by supervisor. -Facilitator characteristics vital to lead the sessions successfully.	The drumming facilitator had all the characteristics sought in an intervention fieldworker. Weaknesses: -Poor time management initially → improved -Reflecting the group's energy i.e. losing energy in quiet groups &

	-Open & responsive to feedback -Fun -Respectful & commands respect -Teachable -Daily practice, rhythm creation & co-operation.		gaining energy from loud groups. -Better at relating to other extraverts. Strengths (apart from desired characteristics listed): -Good at building relationships with the participants. -Non-judgemental & accepting. -Hardworking -Self-motivated & self-directed -Independent -Reliable -Inspiring -Role model for the adolescents
Setting the group norms	Group norms to be set by leaders (if not already mentioned by participants in their 'setting the norms' rhythmical exercise): -'Respect one another.' -'Listen to one another.' -'No mobile phone use during sessions.'	-Music therapist recommendation. -Chance for the group to build team identity & set norms to make the sessions a safe space for all participants.	Many of the norms were already mentioned by the adolescents. Facilitator just added whatever was missed.

	-'What happens in the group stays in the group.' -'There is no wrong answer.' -'Care for one another.' -'We are not competing. We are a team. Work together for the group to be better.'		

Appendix 37: AHEAD Study drumming facilitator post-intervention feedback on musical components of the intervention

Component	Structure used	Rationale for chosen structure	Feedback from drumming facilitator and/or supervisor
Pre-session practice & improvisation	-Allow adolescents to decide what to play & improvise. -Practise previous week's material.	-Not part of formal session. -Give participants opportunity to practise what they would like to or catch up on missed material. -Encourage creativity.	-Sometimes the adolescents danced or made up many of their own rhythms. -Some were more open to share in this unstructured setting. -Conversations occurred & friendships developed.
Teaching drumming posture & technique	-Teach 3 basic notes on djembe drum with their vocal drumming counterparts: bass	-Encourage consistent & correct posture & technique → improved comfort, tonal quality, uniformity.	-Some participants confused the bass & tone, particularly as the rhythms became more

	(du), tone (ke), slap (pa). -Teach for 10 minutes in first session with revision in next few sessions.	-Enable increased working memory load by having 3 distinct notes for rhythmical composition. -Drumming trainer advised vocal drumming to assist with learning & memorising notes.	complex with hand alternation. -Constant revision required. -May have been useful to spend longer on this initially. -Many participants seemed to struggle to vocalise simultaneously.
Drum choice	All used djembe drums of varying sizes (12-inch, 13-inch & 14-inch heads).	-Djembe has 3 different basic notes (& many more possible notes) → possible to make more complex rhythms → increased working memory load. -Prototype African single-membrane drum.	-Versatile drum with good sounds. -Might have been fun & challenging to add other percussive instruments.
Welcome song	-Recurring rhythm played by all simultaneously. -Each person in circle gets a turn to say: their name, where they are from, their favourite song, their favourite musical artist. -Version 1 at first: loud; hand claps & bass notes on drum. Version 2 later: softer; clicks & lap slaps. -Done in first two sessions.	-Music therapist recommendation. -Welcome each participant to circle. -Icebreaker. -Introductions.	-Version 1 too loud → difficult to hear soft people -Version 2 better to hear people introduce themselves.
Setting the group norms rhythmical exercise	-Recurring rhythm played by all simultaneously. -Each person in circle gets a turn to	-Music therapist recommendation. -Chance for the group to build team identity & set norms to make	-Good way to make sure everyone's opinion is heard & valued equally.

	suggest the group norm they would like the group to adopt. -Done in first two sessions.	the sessions a safe space for all participants.	-These were their chosen norms: -'Always love each other.' (5) -'Be happy.' (4) -'No phones.' (2) -'Respect each other.' (2) -'Focus on what you are doing.' (2) -'Play and have fun.' (2) -'Help each other.' (1) -'Listen to each other.' (1) -'Don't laugh at or tease each other.' (1) -'Maintain order and discipline.' (1) -'Good time management and punctuality'. (1) -'No skipping of sessions.' (1) -'Understand each other.' (1) -'Always dance.' (1)
Hello or greeting song	-Participants asked to suggest a song. If no suggestions, used facilitator-composed song 'Avuxeni vanghana! Aye!' (meaning 'Hello friends! Hi!').	-Music therapist recommendation. -Common thread in programme. -Greeting. -Way to start each session. -Cue to foster focused attention.	-Good to be in local language → comfortable & 'at home'.
Goodbye song	-Participants asked to suggest a song. If no suggestions, used a well-known local song sung in local languages, Zulu 'Wahamba nathi' / Tsonga	-Music therapist recommendation. -Common thread in programme. -Farewell. -Way to close off each session.	-Familiar & non-threatening song.

	'Wafamba na yina' ('Go with us').		
Number of songs	-2-3 additional songs per group introduced from second session. -2-4 different rhythms per song.	-Music therapist recommendation. -Increase working memory load by memorising multiple songs & rhythms.	-Having 4 songs in total is enough especially with multiple rhythms for each. -Difficult to practise them all sufficiently in only 7 sessions.
Song choice & diversity	-Adolescents shared their favourite songs in first session. -We selected 2-3 of these favourite songs for each group to practise & composed 2-4 rhythms per song which we gradually added & then made subgroups play different rhythms simultaneously then switch rhythms. -Adolescents chose the final 2 self-selected songs. -Adolescents offered the opportunity to lead songs.	-Empowering adolescents by giving them the choice. -Validating their preferences & opinions. -Building their confidence.	-In some groups, no adolescents wanted to lead songs; in others, different adolescents took turns to lead songs. -Facilitator felt that leading songs "helped them feel part of what was happening. It made them gain confidence."
Homework to practise	-Every week: Practise what you learnt today. -First week: Practise your favourite song to teach the group.	-Practice → improved technique & potentially greater benefits of learning to play the drum.	-Some adolescents had clearly practised & others hadn't. -Some adolescents came to sessions early to practise.
Paradiddle technical exercises	-Session 4: Accelerating single paradiddles as 'last man standing' competition.	-Gradually increasing executive function demands through accelerating oscillations (task switching) & longer	-Adolescents loved these technical exercises. We should add more of them.

	-Session 5: Accelerating double paradiddles. -Session 7: Accelerating triple paradiddles & paradiddle pyramid.	rhythmical sequences to memorise & execute (working memory).	
'African thunderstorm' exercise	-Build up in Mexican wave fashion (1 bar between each new person joining in). -Rubbing hands → clicking → soft clap → loud clap → lap slap. -Then gradually fade out again in reverse order.	-Inhibitory control demands. -Fun way to build up tension & then release it as the sound waxes & wanes.	-Works better in larger groups. -Participants really enjoyed this activity & found it fun.
Heartbeat rhythm exercise	-Feel your pulse & start beating on your drum in time with your heartbeat.	-Recommended in R.L. Friedman's book 'The Healing Power of the Drum'. -Focuses attention in the present moment. -Decreases stress.	-Helped the facilitator to feel calm & relaxed. -Helped supervisor feel calm & be present in the moment.
Burst of sound exercise	-Everyone improvises on the drum simultaneously.	-Recommended in R.L. Friedman's book 'The Healing Power of the Drum'. -Opportunity for creative expression & emotional expression without judgement. -Not performance-oriented.	-Facilitator: "It allowed everyone to feel independent and not judged."
Rhythm creation or improvisation exercise	-Recurring core linking rhythm alternating with individual improvised rhythms copied by the group. -Group copies whatever the individual does in their slot e.g. rhythm, silence, laugh.	-Music therapist recommendation. -Develops creativity. -Affirming: anything you do is accepted & mimicked by the group.	Facilitator: "Everyone felt like a leader. I believe it builds confidence because everyone had to copy exactly what you did."

Drumming technique critique in pairs	-Adolescents sit in pairs facing each other. -Take turns to do 4 repetitions of each of the 3 basic notes. -Critique and correct each other.	-Non-threatening way to improve technique. -Learn to give & receive feedback. -Builds relationships.	-Less intimidating to be corrected one-to-one by a peer than by the facilitator in front of the whole group.
Making up new sounds on the drum in pairs	-Adolescents sit in pairs facing each other. -Try to create as many new notes/sounds on the djembe (apart from the 3 basic notes) together as possible. -Each pair shares 2 of their sounds with whole group.	-Builds relationships. -Develops creativity. -Encourages cognitive flexibility. -Challenges rigidity.	-Many struggled to come up with new sounds. -Good for bonding. -Facilitator: "It should be done at each session to keep them using their minds creatively to come up with new things."
Spontaneous traditional or modern dancing before or during session	-Adolescents allowed to dance briefly in the middle of the circle if they felt like it.	-Encourage creative expression. -Build confidence.	-Facilitator: "It was great. It made everyone happy and not shy." -Familiarity of the traditional dances → relaxation, enjoyment, unity.

Appendix 38: AHEAD Study summary of drumming facilitator reflection on the facilitation process

The highlights of the drumming programme for the facilitator were:

- Seeing the group improve and grow in confidence.
- Seeing the group make friends and talk to each other.

The negative aspects of the drumming programme for the facilitator were:

- Poor punctuality and attendance on some days.

- Poor engagement by some participants or groups. Low energy and unwilling to sing or lead songs.

Lessons learned by facilitator re drumming group facilitation based on her post-programme completion reflection form:

- Confidence and self-motivation: Maintain confidence and energy even if the group does not give the same positivity and energy back.
- Consistency: Treat all participants and groups the same even if their energy levels and engagement differ.
- Attitude towards and belief in the group: Keep believing in the group even if participants seem demotivated or uninterested.
- Unconditional acceptance: Allow them to be themselves.
- Time management within the session: Stick to the proposed time allocations for each activity. Wear a watch and use it to manage time. Start at the agreed starting time.
- Empowerment of participants: Use participant ideas because it makes them feel part of the programme.
- Flexibility: Allow the group members to do what they enjoy e.g. don’t force them to sing if they prefer drumming without any singing. Repetition sometimes necessary so that people don't get left behind.
- Permission to enjoy: Allow them to have fun.
- Preparation: Practise enough and prepare your material in advance for the session.

- Patience: Be patient with the participants. Trust can take time to build. While some may feel comfortable to talk early on, others will be slow to warm up to the facilitator and the group.
- Providing feedback: Give each participant feedback by walking around the circle and stopping at each person briefly while they are all playing rather than just picking on one person.
- Self-control: Do not lose control or lose your temper.
- Focus: Stay calm and focused. Try not to think about personal worries while facilitating the session.
- Responsiveness: Some groups may take longer to master simple rhythms or techniques and need more time practising these before progressing to more complex rhythms, polyrhythms and rhythm switching. Be responsive and adapt the programme to the needs of the group.

Appendix 39: AHEAD Study drumming facilitator participant continuous assessment rubric

Give the participant a score for each of the six criteria from 1 (worst) to 10 (best). Write descriptions, where applicable, in last two columns.

	1. Confidence	**2. Effort & energy**	**3. Drumming technique**	**4. Drumming rhythmical accuracy**	**5. Interaction with peers**	**6. Interaction with facilitator**	**Adolescent's own feedback or comments**	**Other comments or anecdotes**
Week 1								
Week 2								
Week 3								
Week 4								
Week 5								
Week 6								
Week 7								
Week 8								

Appendix 40: AHEAD Study drumming facilitator participant continuous assessment weekly group mean scores on the assessed criteria

