Neurodevelopmental and Behavioural Outcome of the HIV-Exposed Uninfected Infant and Child

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Dissertation presented in fulfilment of the degree of Doctor of Philosophy (PhD) in the Faculty of Medicine and Health Sciences at Stellenbosch University.

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March 2020

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated), and that I have not previously in its entirety, or in part, submitted it for obtaining any qualification.

The research in this thesis was performed at the Family Clinical Research Unit, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa and Tygerberg Hospital. The financial assistance of the HOPE Cape Town trust and Harry Crossley Fund towards this research is hereby acknowledged, as well as the infrastructure and data provided by the Mother and Infant Health Study. Opinions expressed and conclusions arrived at, are those of the author and are not necessarily to be attributed to the funders.

Date: March 2020

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SUMMARY

The first 1000 days of life represents a crucial phase for cognitive, language and emotional development. Indeed, early childhood development provides a foundation for educational and vocational success. Early screening and detection of developmental delay is therefore important, as timely intervention can improve school readiness. The human immunodeficiency virus (HIV) pandemic has been identified as a contributor to early developmental delay in low-and middle-income countries. In South Africa, successful vertical HIV-transmission prevention programmes have led to a substantial decrease in mother-to-child transmission rates. As a result, approximately one in four newborns are HIV-exposed but uninfected (HEU). However, the impact of both HIV exposure and anti-retroviral therapy on neurodevelopmental outcomes of HEU infants remains poorly understood. In particular, few prospective studies have combined developmental and behavioural assessments from infancy to early childhood.

In response to this knowledge gap, a pilot study was performed to explore the feasibility of using the Griffiths Mental Development Scales to assess outcome in HEU compared to HIV-unexposed uninfected (HUU) infants. Following the initial pilot phase, mother-infant dyads were better matched for home language, cultural and maternal social characteristics and we extended infant assessments to include cognitive, motor, language and behavioural domains using the Bayley Scales of Infant and Toddler Development-3rd edition (BSID), as well as the Alarm Distress Baby Scale. The BSID was repeated at two-year follow-up, and behaviour was assessed using the Strengths and Difficulties Questionnaire. Despite similar performance in BSID motor, language and cognitive domains, more behavioural problems were reported by mothers of HUU children at 2-3 years old. Childhood stunting was associated with poorer motor and behavioural outcome, irrespective of HIV exposure.

Based on initial findings, we further explored the use of the Molteno Adapted Scale (MAS) screening tool, and its correlations with the BSID at 11-14 months and 2-3 years of age in our study cohort. There was moderate correlation between the major domains of these tests; however, we were unable to test the diagnostic accuracy of the MAS, as too few participants had significant developmental delays. There was also increased discrepancy in scores of the assessment tools at the lower and upper ranges of the spectrum, which could potentially lead to under-identification of children at risk for delay. Lastly, we assessed the diagnostic accuracy of the Goodenough Drawing test screening tool (DAP) in a group of at-risk children at five years of age. The diagnostic accuracy of the DAP was sufficiently promising to justify its use as a research tool to detect visuo-perceptual and fine motor delay.

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High attrition rates and a small sample size were important limitations in our study. However, a major strength lies in the observation of the need for developmental surveillance and support for all children regardless of HIV exposure, especially those from socio-economically disadvantaged communities. Our findings could help South African policy makers justify initiatives encouraging multi-sectoral collaboration such as the Framework for Nurturing Care, aligning with both the fourth Sustainable Development Goal and the National Development Plan for 2030, which aims to “leave no child behind”.

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OPSOMMING

Die eerste 1 000 dae van ’n mens se lewe is ’n deurslaggewende fase vir kognitiewe, taal- en emosionele ontwikkeling. Vroeë kinderontwikkeling bied trouens ’n grondslag vir opvoedkundige en beroepsukses. Vroeë sifting en die identifisering van ontwikkelingsagterstande is gevolglik belangrik, aangesien tydige ingryping skoolgereedheid kan verbeter. Menslike immuniteitsgebrekvirus- (MIV) infeksie is as ’n bydraer tot agterstande in vroeë ontwikkeling geïdentifiseer in lae- en midde-linkomste-lande. In Suid-Afrika het suksesvolle vertikale MIV-oordragvoorkomingsprogramme tot ’n aansienlike afname in moeder-kind-oordragkoerse gelei. Ongeveer een uit elke vier pasgeborenes is gevolglik MIV-blootgestelde dog onbesmette babas (sogenaamde HEU’s). Die invloed van MIV-blootstelling en antiretrovirale behandeling op HEU-babas se neuro-ontwikkelingsuitkomste word egter steeds nie behoorlik verstaan nie. In die besonder kombineer weinig beoogde studies ontwikkelings- en gedragsevaluerings vanaf babatyd tot die vroeë kinderjare.

Na aanleiding van hierdie kennisgaping is ’n loodstudie onderneem om die haalbaarheid van die gebruik van die Griffiths Mental Development Scales by die evaluering van uitkomste in HEU’s met uitkomste in MIV-nieblootgestelde babas (sogenaamde HUU’s) te vergelyk. Ná afloop van die loodsfase is moeder-baba-diades beter gepaar volgens huistaal, kulturele en moederlike sosiale kenmerke, terwyl ons baba-evaluerings uitgebrei het om kognitiewe, motoriese, taal- en gedragsdomeine aan die hand van die derde uitgawe van die Bayley Scales of Infant and Toddler Development® (BSID), asook die Alarm Distress Baby Scale in te sluit. Die BSID is in ’n tweejaaropvolgtoets herhaal, terwyl gedrag aan die hand van die “*Strengths and Difficulties Questionnaire*” geëvalueer is. Ondanks soortgelyke prestasies in die BSID- motoriese, taal- en kognitiewe domein, het moeders van HUU-kinders op 2- tot 3-jarige ouderdom meer gedragsprobleme gerapporteer. Belemmerde groei by kinders is met ’n swakker motoriese en gedragsuitkoms in verband gebring, ongeag blootstelling aan die MIV.

Op grond van die aanvanklike bevindings, het ons verder die gebruik van die “*Molteno Adapted Scale- (MAS-)*” siftingsinstrument en die korrelasies daarvan met die BSID op 11 tot 14 maande en 2 tot 3 jaar in ons studiekohort ondersoek. Daar was matige korrelasie tussen hierdie toetse se belangrikste domeine. Ons kon egter nie die diagnostiese akkuraatheid van eersgenoemde groep toets nie, aangesien te min deelnemers beduidende ontwikkelingsagterstande ervaar het. Daar was ook groter afwykingsverskille in die tellings van die evalueringsinstrumente vir die onderste en boonste reikwydtes van die spektrum, wat moontlik tot die onderidentifikasie van kinders wat aan

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die risiko van agterstande blootgestel is, kan lei. Laastens het ons die diagnostiese akkuraatheid van die "*Goodenough–Harris Drawing Test*" (DAP) siftingsinstrument in 'n groep van vyfjarige risikokinders beoordeel. Die diagnostiese akkuraatheid van die DAP was belowend genoeg om die gebruik daarvan as 'n navorsingsinstrument te regverdig, met die oog op die opsporing van visueel-perseptuele en fynmotoriese agterstande.

Hoë afslytingskoerse en 'n klein steekproefgrootte was belangrike beperkings in ons studie. 'n Belangrike sterk punt lê egter in die observasie van die behoefte aan ontwikkelingsbewaking en -steun vir alle kinders, ongeag hul blootstelling aan MIV, veral dié uit sosio-ekonomies benadeelde gemeenskappe. Ons bevindings kan Suid-Afrikaanse beleidmakers help met die motivering van inisiatiewe ter bevordering van multisektorale samewerking, soos die Raamwerk vir Sorgsame Versorging, wat strook met die vierde Volhoubaarheidsontwikkelingsdoelwit (SDG) en met die Nasionale Ontwikkelingsplan vir 2030, wat wil verseker dat "geen kind agterweë gelaat word nie".

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DEDICATION

I dedicate this work to my husband, Jacques and sons, Frank and Robert.

"Our children are the rock on which our future will be built, our greatest asset as a nation. They will be the leaders of our country, the creators of our national wealth, who care for and protect our people."
Nelson Rolihlahla Mandela (3 June 1995)

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CHAPTER 1: Introduction

1.1. Background

HIV remains a major public health challenge. In 2017, the number of people living with HIV (PLWH) globally was estimated at 36.9 million (31.1 million–43.9 million) of whom 21.7 million (19.1 million–22.6 million) had access to antiretroviral therapy (ART) (UNAIDS, 2018). Vertical HIV-Transmission Prevention (VTP) programmes have caused a significant fall in mother-to-child transmission. As such, there is now an expanding population of approximately 14.8 million HIV-exposed but uninfected (HEU) children worldwide, of whom an estimated one million are born annually in Sub-Saharan Africa (UNAIDS, 2018). Researchers have identified vulnerabilities in these infants, such as differences in innate immunity, increased morbidity and mortality, as well as poorer growth, all of which could affect their long-term health, cognitive and emotional wellbeing (Evans, Jones, & Prendergast, 2016). Low- and middle-income countries (LMIC) have limited public health, education and social support systems, increasing the susceptibility of HEU infants to sub-optimal outcomes (Evans et al., 2016).

South Africa, which is classified as an upper middle-income country (UMIC), has an estimated HIV prevalence rate of 13% (2018), with an estimated 7.52 million PLWH (UNAIDS, 2018). For adults aged 15–49 years, this translates to approximately 20.4% of the population and one-fifth of women of reproductive age (15-49 years) being affected (UNAIDS, 2019). Fortunately, provincial health services have rolled out a comprehensive combination antiretroviral therapy (cart) programme, including VTP, which has improved long-term life expectancy of PLWH. National South African data (2017) also showed a significant reduction in mother–to-child transmission to less than 3% (Goga et al., 2018). There are currently an estimated 3.5 million HEU children living in South Africa, and going forward, this group will receive increased ART exposure, both *in-utero* and during prolonged breastfeeding, and consequently require surveillance (UNAIDS., 2019)., The HEU child faces unique biological and environmental risks, which could affect their cognitive and emotional development (Filteau, 2009). Early research by Drotar et al., (1997) in Uganda showed no difference in outcome between HEU and HIV-unexposed (HUU) infants. In contrast, Van Rie et al., (2008) found that HEU infants from Democratic Republic of Congo (DRC) had poorer motor, mental, and expressive speech development (Van Rie, Mupuala, & Dow, 2008). Findings in Africa regarding neurodevelopmental outcome of HEU children remain conflicting (Chaudhury et al., 2017; Le Roux et al., 2018; Ngoma et al., 2014; Wedderburnet al., 2019).

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1.2 Problem Statement and Study Rationale

There is still uncertainty as to whether neurodevelopmental and behavioural outcomes differ in the HEU infant and child in LMIC, or even an UMIC, such as South African review by Sherr et al., (2014) highlighted methodological shortfalls in early studies, such as lack of suitable comparison groups, and failure to use validated measures of cognitive function (Sherr, Croome, Parra Castaneda, & Bradshaw, 2014). Studies have also varied with respect to inclusion of well-matched control groups, and choice of child development assessment tools (CDAT). In addition, changing ART regimens, ambivalent attitudes towards breastfeeding, and additional confounding variables may have influenced findings reported to date. McHenry et al., (2018) in a meta-analysis of studies using the Bayley Scales of Infant and Toddler Development scales, reported poorer neurodevelopmental outcome in HEU compared to HUU children. However, the studies from LMIC were deemed "lower-quality" versus those from high-income countries (HIC), where no developmental difference was found (McHenry et al., 2018).

Developmental assessment is defined as "the psychological examination of a child's abilities over a broad spectrum of behaviour, including motor, social and cognitive traits" (Allan, 1992). However, few studies have included the emotional and behavioural assessment of the pre-school HEU child, which represents a critical phase offering a window of opportunity for early intervention (Britto et al., 2017; MCaloon & Lazarou, 2019; Walkeret al., 2011). As a child's developmental trajectory may change over time depending on innate and environmental factors, longitudinal follow-up is necessary. There is also a need for affordable and appropriate developmental and behavioural screening tools, which can be used to detect delay in infants and pre-school children in resource-limited settings (Semrud-Clikeman et al., 2016). Testing children from disadvantaged communities in LMIC settings presents challenges: there may be language and cultural differences; they may have had fewer learning opportunities and experience problems with motivation; while time-pressure and unfamiliarity with the test situation may also prove a concern. Most tools have originated from, and been standardised on, HIC populations, and it is thus important to select tests suited to the local context (Kammerer, Isquith & Lundy, 2013). Moreover, psychometrists or psychologists are a scarce resource in LMIC, and the responsibility often falls upon healthcare professionals to detect and quantify developmental delay in pre-school children. International experts in early child development (ECD), who were canvassed on global ECD research priorities for 2025, included the need for appropriate tools for assessment in resource-limited settings (Dua et al., 2019).

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1.3 Aims and Objectives

The main research aim was to explore the impact of HIV exposure on neurodevelopment and behavioural outcomes over time in a group of South African infants from an impoverished community in relation to biological, environmental and psychosocial risk factors. Our primary objective was to compare the neurodevelopmental and behavioural performance of HEU children with that of HUU children from a similar socio-economic and cultural background during the first 3 years of life, and to identify risk factors for poorer outcome. A secondary objective was to evaluate CDAT, which could be used to evaluate this population of infants and pre-school children in resource-limited healthcare settings. We hypothesized that there would be a difference in neurodevelopmental and behavioural outcome between infants and children who were HIV-exposed but uninfected and HIV-unexposed.

1.4 Structure of Dissertation

This thesis is presented in publication format and structured according to sequence of individual sub-studies, each with a corresponding objective and hypothesis.

Chapter 2 *Neurodevelopmental and behavioural outcomes of the HIV-exposed infant and young child in Low- and Middle-income countries: a narrative review.*

Research findings are mixed regarding neurodevelopmental outcome of the HEU infant and pre-school child in LMIC. This narrative review provided an overview of existing evidence on the developmental and behavioural outcome of HEU infants and pre-school children in relation to risk and protective factors. We also describe the use of CDAT in the LMIC context to evaluate this vulnerable population, and how heterogeneity has hindered study comparisons (McHenry et al., 2018). Progress in the field of assessment has included adaptation of established tools for resource-constrained settings, creation of country-specific tools, and the recent collaborative development of international CDAT. These developments could allow for global comparisons of child development and evaluation of early intervention programmes in future (Fernandes et al., 2014).

Chapter 3 *Neurodevelopmental status of HIV-exposed but uninfected children: a pilot study (2012). Ethics no: N08/10/289*

This pilot study explored the feasibility of evaluating development in HEU toddlers using an HUU comparison group from a similar community. The neurodevelopmental sub-study was part of larger

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prospective cohort study which compared morbidity of HEU with that of HUU infants recruited from the post-natal ward of Tygerberg academic hospital. Both HEU and HUU participants were assessed at 18 months on all five subscales of the Griffiths Mental Developmental Scales 0-2 years (GMDS) (Griffiths, 1996). In this pilot study, we hypothesised that there would be poorer developmental outcome in HEU versus HUU toddlers at 18 months.

Chapter 4 *Neurodevelopmental outcome of HIV-exposed but uninfected infants in the Mother and Infant Health study, Cape Town, South Africa (2018). Ethics no: N13/03/028*

After adjusting for problems identified in the pilot study, the study design was modified to include a larger sample size, which better controlled for confounding factors described below through matching or adjustment. The neurodevelopmental study that followed was nested in the Mother and Infant Health Study (MIHS), a prospective longitudinal cohort study primarily designed to investigate infectious morbidity in HEU and HUU infants (Slogrove et al., 2017). The MIHS enrolled mother-infant dyads with low-risk obstetric histories within 72 hours after birth from a single community midwife obstetric unit (MOU) to ensure greater socioeconomic homogeneity. The HIV-infected mothers had uncomplicated HIV disease. The cohort included a balanced proportion of language groups to reduce cultural bias, which presumably reflected different child-rearing practices. Infants were tested on the Bayley Scales of Infant Development-third edition (BSID)(Bayley, 2006) and the Alarm Distress Baby Scale (ADBB) (Guedeney & Fermanian, 2001). In this sub-study, we hypothesised that there would be poorer developmental and behavioural outcome in HEU versus HUU infants at 11-14 months.

Chapter 5 *Neurodevelopmental and behavioural outcomes of HIV-exposed uninfected and HIV-unexposed children in Cape Town, South Africa at 2-3 years of age (2019). Ethics no: N13/03/028*

Language development accelerates in the second and third years of life, at which point environmental factors become influential, and milder deficits are more likely to become evident. Neurodevelopmental assessments at 2-3 years are more predictive of childhood intelligence than tests performed in infancy (Girault et al., 2019). Participants initially enrolled in the MIHS infant study were thus recalled at two years, 6 months. Development was reassessed using the BSID, while there-school version of the Strengths and Difficulties questionnaire (SDQ) was used to explore differences in behaviour. The SDQ is a screening test with 25 questions regarding the child's behaviour and emotional wellbeing (Goodman, 1997). We hypothesised that there would be poorer developmental and behavioural outcomes in the HEU compared to HUU infants at 2-3 years of age.

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Chapter 6 *Use of a child development assessment tool in a resource-constrained healthcare setting: a correlational study. Ethics no: N13/03/028*

In this sub-study, we investigated the use of the Molteno Adapted Scale (MAS) screening tool developed to evaluate infants and young pre-school South African children. The MAS has been used by medical practitioners in paediatric developmental clinics in the Western and Eastern Cape for three decades, showing promising results in terms of diagnostic accuracy (Honeth et al., 2018). It is time- and cost-effective, requires limited, easily accessible equipment, and does not necessitate a certified training course or licensing fees. Unlike most childhood development screening tools, the MAS generates developmental age-equivalents for gross motor, fine motor, language and personal/social domains, which are then converted to sub-quotients, by using the chronological age as a denominator and multiplying by 100. Standardised sub-quotients indicate the degree of delay in each domain, which can then be used for plotting the developmental trajectories over time. A General Quotient (GQ) is derived by averaging all four sub-quotients, and a GQ less than 85, generally indicates global developmental delay. The MAS has been compared with the GMDS, but not other comprehensive developmental assessment tools such as the BSID. However, determining diagnostic accuracy of the MAS with the BSID in our cohort was not possible, as too few children (HEU or HUU) had significant developmental delay, limiting this to cross-sectional, correlational analysis. The objective of this exploratory study was to determine the relationship between the MAS and BSID.

Chapter 7 *Value of the Goodenough Drawing test as a research tool to detect developmental delay in South African preschool children. Ethics number: N05/05/092*

The Goodenough Draw-a Person test (DAP) is a commonly used developmental screening tool(Goodenough, 1926). Since the DAP is freely available, easily administered, and requires limited language ability, equipment and administrator training, it is considered a practical tool for resource-constrained settings (Miles, Fulbrook, & Mainwaring-Magi, 2016). Use of this tool may be especially advantageous at five years of age, when timely intervention may improve school readiness and identify children who will require additional support. The DAP has been widely used in the South African research environment, as well as in clinical contexts, as an informal screening tool (Richter, Griesel, & Wortley, 1989; Richter, Mabaso, & Hsiao, 2015). However, the DAP currently lacks recent validation. In this sub-study, we determined the diagnostic accuracy of the DAP to identify developmental delay in 5-year-old pre-school children using the Griffiths Mental Developmental Scales-Extended Revised (GMDS-ER) Eye-Hand coordination sub-quotient (EHQ) as the “gold standard” (Griffiths, 2006). Human figure drawings (HFD) of five-year-old children were analysed

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using the DAP scoring system; participants included HIV-infected (HI), HEU and HUU children enrolled in the CHER trial (Laughton et al., 2018). We hypothesised that the Goodenough DAP test would correlate best with the Eye-Hand sub-quotient (EHQ) of the GMDS-ER, and would provide a suitable developmental screening tool for pre-school children.

Socio--demographic and geographical description of participants of MIHS

Participants of the MIHS were recruited from the Kraaifontein area (Figure 1), a peri-urban settlement situated in the northern sub-district of the city of Cape Town in the Western Cape Province, South Africa. Families reside in a mixture of formal and informal housing, with overcrowding being common, and municipal services limited. Less than 50% of adults complete secondary school, and the unemployment rate in this region exceeds 30%, with high rates of poverty. Eligibility for the MIHS was restricted to mothers from four defined low socio-economic neighbourhoods. These suburbs were situated in the Kraaifontein MOU referral area, which serves as a public primary healthcare obstetric unit for this underserved community.

Figure 1. Map showing location of Kraaifontein in Cape Town, Western Cape, South Africa.

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CHAPTER 2: Neurodevelopmental and behavioural outcome of the HIV-exposed infant and young child in Low- and Middle-income countries: a narrative review

(For Submission to Child: Care, Health and Development)

ABSTRACT

Background: The expanding population of HIV-exposed uninfected (HEU) infants has public health implications for low- and middle-income countries (LMIC). There is little information regarding the longitudinal neurodevelopmental and behavioural outcome of infants and children in the first 3 years of life, a critical period for brain development.

Methods: We conducted a narrative review aimed at providing an overview of how HIV exposure affects cognitive, language, motor, socio-emotional and behavioural outcome of HEU infants and young pre-school children in LMIC. In addition, the influence of risk and protective factors, resilience, and the current use of child development assessment tools (CDAT) are described. We reviewed studies published between January 1992 and August 2019 with predefined inclusion and exclusion criteria, using search engines PubMed, Scopus, and Web of Science.

Results: There were mixed findings on neurodevelopmental outcome in children under three years of age from LMIC, with limited research on behaviour, while heterogeneity of CDAT use complicated study comparisons. However, there is a growing understanding of risk and protective factors, the role of resilience in determining outcome, as well as the development of CDAT tools that include neuropsychological and physiological components, are culture-neutral, and can be applied in global research.

Conclusions: Further longitudinal studies encompassing comprehensive multi-level assessment of neurodevelopment and behavioural outcome are necessary, with incorporation of CDAT which include neuropsychological measures, and allow for cross-country comparison.

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2.1 BACKGROUND

The vast majority (90%) of the estimated 14.8 million children worldwide who are born HIV-exposed but uninfected (HEU) live in low-income and middle-income countries (LMIC) (UNAIDS, 2019). Apart from ante- and post-natal exposure to both HIV and antiretroviral therapy (ART), HEU infants are more likely to be born preterm, and are at risk for poorer growth, with increased morbidity and mortality. In addition, these children may experience a variety of challenges associated with living in an HIV-affected household, including poverty, food insecurity, lack of breastfeeding, as well as compromised maternal physical and mental health (Ramokolo, 2019). These factors have the potential to negatively affect long-term health and growth, as well as cognitive and emotional outcomes in infants (Evans, Jones, & Prendergast, 2016). There is a growing appreciation of the risks and protective factors faced by the HEU infant in LMIC. However, the emphasis has shifted from focusing primarily on the effects of *in-utero* ART and HIV exposure with early innate immune dysfunction, to a wider impact of maternal wellbeing, breastfeeding and socio-economic determinants of child development (Le Roux, Abrams, & Myer, 2016).

The aim of this narrative review was to provide an overview of how HIV exposure influences neurodevelopmental and behavioural outcome of HEU infants and pre-school children in LMIC. In addition, the concept of resilience is discussed, and the current use of child development assessment tools (CDAT) outlined. Toward these goals, we conducted a literature search using the following key words: HIV-exposed uninfected, infant, pre-school child, neurodevelopment, developmental outcome, cognition, behaviour, CDAT, low-income and middle-income countries. We reviewed bibliographies and accessed relevant articles published between January 1992 and August 2019 using the Pubmed, Scopus and Web of Science online electronic databases

2.2 Neurodevelopmental outcome of the HEU infant and child

A significant proportion of children (43%) living in LMIC are at risk of failing to fulfil their neurodevelopmental potential due to the effects of poverty and stunting (Black et al., 2017; Lu, Black, & Richter, 2016). The HIV pandemic has led to additional adversity, including risk of premature birth, low birth weight, impaired immune responses, increased transmission of congenital or acquired infections, and potential effects from ART exposure (Sugandhi et al., 2013). Early reports on neurodevelopmental outcome of HEU children living in LMIC originated from Africa, South America, Thailand and Cambodia, and more recently from India and China(Tables 1 and 2). The cognitive and behavioural outcome of HEU children living in LMIC may differ from high-income countries (HIC). However, comparison between studies is complicated by different

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confounding variables, changing ART regimens and breastfeeding practices (Le Doare, Bland, & Newell, 2012). In a recent meta-analysis, McHenry et al., (2018) reported poorer outcomes of HEU compared to HIV-unexposed, uninfected (HUU) children living in LMIC, while no such differences were found in HIC.

There was initially limited access to combination antiretroviral therapy (cart) in most LMIC, and studies thus focused on ascertaining whether HEU children differed from HIV-infected (HI) children and/or community HUU controls (Tables 1 and 2). In contrast, most HIC initiated effective Vertical Transmission Prevention (VTP) programmes and cart throughout pregnancy at an earlier phase of the pandemic, and multi-site studies were powered to interrogate the *in-utero* effects of ART on HEU cohorts (Williams et al., 2010). Some HIC reported no developmental differences in HEU children versus HUU controls, while others detected subtle language delays, including an association with atazanavir treatment (Caniglia et al., 2016; Rice et al., 2013; Sirois et al., 2013).

An increasing number of studies have emanated from Sub-Saharan Africa (Table 2). Many factors also complicate comparison of neurodevelopmental outcomes across these studies, such as use of heterogeneous comparison groups (HI versus HUU), small sample sizes, varying inclusion criteria, different or non-standardised CDAT measures, changing ART regimens and diverse breastfeeding policies (Le Roux, Abrams, Nguyen, & Myer, 2016). Since the roll-out of WHO Option B+ cart in South Africa, pregnant women receive universal triple-drug ART prophylaxis regardless of initial CD4 count, allowing for extended breastfeeding and lifelong treatment (Western Cape Government (Health), 2014). These policy changes have generated larger, prospective cohort studies to investigate neurodevelopmental outcome in the light of more prolonged ante- and post-natal ART exposure.

South African infants showed an increased risk of cognitive and motor delay at 12 months old, with preterm infants especially vulnerable (Le Roux et al., 2018). Poorer expressive language and motor performance was associated with increased cumulative maternal viral load in pregnancy (Le Roux, Donald, & Kroon, 2019). Wedderburn et al. (2019) found that two-year-old South African HEU participants had delayed receptive and expressive language (Wedderburn et al., 2019). Results from a large prospective cohort study, which followed Ugandan and Malawian HIV-infected (HI), HEU and HUU children up to 60 months of age, however, found no increased developmental risk for HEU children. This cohort also received maternal triple ART exposure during pregnancy and extended breastfeeding (Boivin et al., 2019).

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2.3 Behavioural and emotional outcome of the HEU infant and child

There has been limited research on the emotional and behavioural profile of HEU children during the first three years of life. Studies carried out in LMIC have mainly focused on the older pre-school or school-going child (Malee et al., 2019; Sipsma et al., 2013). A systematic review, which included pre-clinical studies, identified neurobehavioural differences in animals exposed to HIV and ART. However, these findings did not correlate with the mixed results from clinical studies in humans (McHenry et al., 2019). Neuroradiological findings have also varied. Two South African studies have reported differences in fractional isotopy and diffusivity in HEU children (Jankiewicz et al., 2017; Tran et al., 2016). Tran et al., (2016) found variations in white matter connectivity associated with abnormal neurobehavioural scores in HEU newborns. However, a recent Cameroonian study found no behavioural differences between HEU and HUU children, aged 4-7 years, using the Strengths and Difficulties questionnaire (SDQ) (Debeaudrap et al., 2018), and nor did a Botswana study that used the Profile of social emotional development (PSED) (Kacanek et al., 2018).

2.4 Risk and Protective factors in early childhood

Developmental outcome in early childhood is influenced by both risk and protective factors (Walker et al., 2011). Risk factors are defined as “biological and psychosocial hazards that can compromise development”; they include poverty, poor nutrition with intrauterine growth retardation, stunting and micronutrient deficiencies, and exposures to lead and other toxic metals. Additional factors such as lack of cognitive stimulation and learning opportunities, poor caregiver responsiveness and maternal depression, as well as exposure to violence have been associated with sub-optimal development (Walker et al., 2007). A Tanzanian study suggested that impact of risk factors varied between HEU and HUU infants, and found associations between stunting of both mother and HEU infants and delivery-related factors, linked to poorer performance on the Mullen scales at 15 months of age (Blakstad et al., 2018). While studies have largely focused on neurodevelopmental, behaviour, and growth outcomes, the relationship between multiple risk factors has not been fully explored. For example, maternal depression has been shown to affect child behaviour, but also influences parental reports or perception of the child’s behaviour (Familiar et al., 2016). Ideally, assessing maternal mental health at multiple antenatal and post-natal time-points would facilitate earlier treatment of maternal depression and indirectly influence child behaviour (Mebrahtu et al., 2019; Rotheram-Fuller et al., 2018).

There is also limited information on paternal involvement and mental health, which has also been linked with developmental outcome at three years of age (Chan, Nugent, & Bale, 2018;

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Ramchandani, Stein, Evans, & Connor, 2005). Protective factors are less well described, but include early child stimulation and favourable qualities of caregiving and the home environment (Bass et al., 2016; Familiar et al., 2017), as well as breastfeeding (McCrory & Murray, 2013) and higher levels of maternal education (Cockcroft, Amod, & Soellaart, 2008; Magnuson, Sexton, Davis-Kean, & Aletha, 2009).

2.5 The Role of Resilience

The balance between risk and protective factors influences developmental outcomes over the course of the child's lifespan. Resilience is derived from the Latin "resilire" meaning to rebound and has been described as "successful adaptation over time despite adversity". The study of resilience is an evolving field of scientific research (Masten, Garmezy, Gottesman, Rutter, & Sameroff, 2007). Resilience provides a more holistic measurement of neurodevelopment, emotional and behavioural outcome as it integrates both risk and protective factors and has been applied to other aspects of HIV research (Harrison, Li, & Vermund, 2019).

Rotherham-Borus et al., (2019) expanded the definition of childhood resilience to include "adequate attainment of growth, cognitive functioning and behaviour in relation to global standards". On applying these criteria, the authors found similar levels of resilience in a cohort of South African HEU and HUU children, followed longitudinally from birth to five years as part of an intervention trial (Rotheram-Borus et al., 2019). Protective factors included adequate food security and absence of maternal depression, alcohol use, or experience of inter-partner violence. Interestingly the mothers of more resilient children received lower income and were less likely to be either married, live with a partner, or co-habit with more than three adults per household. However, levels of resilience varied widely between neighbourhoods (Rotheram-Borus et al., 2019).

More recently, cost-scaled interventions aimed at improving maternal mental health and supporting maternal-child dyads have been introduced to improve the health, cognitive and emotional outcome of infants and young children (Boivin et al., 2013; Chingono. et al., 2018). The emerging field of infant mental health has emphasised that early detection of developmental, emotional and behavioural problems in younger children can result in effective intervention (Black et al., 2017; McAloon & Lazarou, 2019). Early childhood provides a unique opportunity to detect delays, identify modifiable factors, and institute cost-effective interventions (Black et al., 2017). Supporting development of cognitive potential and emotional resilience will enable children to benefit from formal education and thereby improve their future economic and lifetime opportunities (Heckman, 2006; Richter et al., 2016).However, since universal risk factors affect a significant proportion of

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the population in LMIC, public health, social and educational initiatives should focus on all vulnerable infants and children living in impoverished communities, irrespective of HIV exposure.

2.6 Use of CDAT in infancy and early childhood in HIV-related research in LMIC

A wide range of CDAT have been used in developmental research on HIV-affected infants (Tables 1 & 2).The need for appropriate CDAT is motivated by the fourth Sustainable Development Goal, which has emphasised the importance of early childhood development (United Nations, 2015). CDAT are required for both clinical and research contexts, to measure and compare outcomes, as well as to evaluate benefits of interventional studies (Semrud-Clikeman et al., 2016). While screening tests are designed to be quick and produce a pass/fail result, comprehensive CDAT requires time, training and expertise in working with young children, in order to generate an individual profile of strengths and weakness in selected domains (Sabanathan, Wills, & Gladstone, 2015).

Choice of CDAT may also depend on the specific pathology and population under investigation. For example, follow-up of childhood survivors of cerebral malaria has generated development of customised tools to determine the effects on specific neuropsychological functions in children from a particular socio=cultural setting (Holding et al., 2004). The conventional CDAT may not be sufficiently sensitive to detect more subtle disorders of attention, memory, executive function, language and socio-emotional development, and there have been efforts to develop tools that can interrogate neuropsychological domains in infancy and early childhood. Many of these measures are still laboratory-based and have not been standardised or validated on wider populations; as such they are not widely used in the clinical setting (Brito et al., 2019).

Access to psychologists in LMIC is limited, and the responsibility for detecting developmental delay in infancy and early childhood often rests with healthcare practitioners working in busy paediatric clinics. The South African Road to Health Booklet, a hand-held record of childhood immunisations and health records has a developmental checklist, but this has not been validated (Van der Linde, Swanepoel, & Glascoe, 2015). Developmental paediatricians are generally tasked with comprehensive assessment and diagnosis of infants and pre-school children, including recommendations for specialised educational placement or school deferment of children with severe developmental delay (Rasdien, Redfern, & Springer, 2019).

Aylward (2009) highlighted the practical considerations and pitfalls of developmental assessment. Factors of importance include the dynamics of interchange between the tester, child and caregiver,

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and the lack of true gold standard measures. Most CDAT have psychometric limitations in terms of reliability and validity, and poor predictive value in relation to intelligence testing or future outcome (Aylward, 2009). Since children may be incorrectly classified as having delay when using culturally biased tests, including an appropriate comparison group is advisable when assessing development (Bodeau-Livinec et al., 2019). Performance on a test may deteriorate over time, especially where socioeconomic adversity is present; a control group is useful in this situation so that the decline in performance is not erroneously attributed to an underlying condition (Laughton et al., 2010).

Interpretation of CDAT findings thus requires understanding of test qualities such as the purpose of the tool, its reliability and validity, as well as contextual knowledge (Sabanathan et al., 2015). Research studies involving HEU children in sub-Saharan Africa have used a variety of CDAT which include both direct observation of the child (Bayley, 2006), indirect measures, such as caregiver questionnaires, or a combination (Table 2). Questionnaires administered to caregivers provide reliable data on developmental milestones and behavioural characteristics (Ertem et al., 2008). They are more time- and cost-effective, and require less training to administer, despite requiring adaptation to make them linguistically and culturally appropriate. Measures using direct observation often require imported apparatus, manuals, training and expertise, which may be unfeasible and unaffordable in LMIC (Semrud-Clikeman et al., 2016). Another more feasible and cost-effective way of testing executive function is using tablet-based tasks (Sherr, Hensels, Tomlinson, Skeen, & Macedo, 2018).

Some African countries have developed their own measures, for example the Kilifi Developmental Inventory in Kenya (Abubakar, Holding, Baar, & Newton, 2008), Malawi Development Assessment tool (Gladstone et al., 2010) and Early Childhood Development scale in Tanzania (McCoy et al., 2017). Creation of a tool is time-consuming and costly, as the process requires input from a wide range of experts and widespread testing to establish test properties. Gladstone et al (2010) described the detailed process of using selected Western measures to create a more culturally appropriate tool suitable for use in a low-resource setting (Gladstone et al., 2010). Methodology included face validity, a process by which each test item was critically evaluated and deemed acceptable by local experts. Secondary measures included construct validity, which ensured that an item assessed the skill, or ability it aimed to measure (Gladstone et al., 2010). The MDAT was piloted and found to be statistically sound with respect to sensitivity, specificity, reliability and validity. After further adjustment, it was normed on local children from a rural population. The researchers compiled a manual, list of equipment and training requirements, allowing for more generalised application.

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Most CDAT used in LMIC have been developed in HIC with a different cultural setting, and it is preferable to generate local norms to measure ability and detect children at risk (Cromwell et al., 2014). For example, the BSID motor and cognitive developmental trajectories differ in German and Cameroonian infants, making cross-cultural comparisons difficult (Vierhaus et al., 2011).Certain researchers, have made adaptations to CDAT such as the Bayley (Hanlon et al., 2016) and Ages and Stages Questionnaire (Abessa et al., 2016) to make them more culture fair. Others have relied on well-matched comparison groups to detect differences (Chaudhury et al., 2017; Le Roux et al., 2018).

The heterogeneity of CDAT used in developmental research on HIV-affected infants limits comparisons between different studies (Table 2 & 3). Additionally it complicates assessment of early intervention programmes and their impact on child cognition, language and behaviour (Jeong, Pitchik, & Yousafzai, 2018). This dilemma has prompted a collaborative effort to produce a multidimensional assessment tool that can be applied internationally to measure early child development (Fernandes et al., 2014). The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) is a large prospective longitudinal study, which focuses on typically developing children. The Consortium has developed a test battery or "package" to measure vision, cortical auditory processing, cognition, language, behaviour, motor skills, attention and sleep in two-year-old children. Brazil, India, Kenya, Italy and the United Kingdom have implemented its use in large-scale research. The 53-item tool does not require specialised research staff, and is culturally fair with good psychometric properties. Similar, but less comprehensive tools, such as the Guide for Monitoring Child Development have been developed for use in LMIC to allow for cross-country comparisons (Ertem et al., 2008). Lancaster et al., (2018) have reported on the first version of the "Infant and Young Child Development" tool, comprised of data collated from ten countries. A caregiver report is used to monitor development in the first three years of life, and modalities include gross and fine motor, receptive and expressive language and social-emotional domains.

2.7 CONCLUSIONS

There is increasing awareness that the expanding population of HEU infants could face future challenges, with regard to neurodevelopmental outcome. Research methodology has progressed in countries with the highest HIV prevalence over the past decades, with increased sample sizes and well-matched comparison groups. Ongoing pharmaco-vigilance will be necessary in view of changing ART regimens and increased ART-exposure during pregnancy and prolonged

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breastfeeding. Selection of appropriate CDAT will depend on whether the primary purpose is to detect children at risk, provide a barometer of the quality of early childhood stimulation, or to measure the effects of interventions. Although locally developed CDAT may be more relevant in the clinical context, standardised and validated global tools, which include behavioural and emotional scales, are vital to allow for collaborative research and international comparison. Adaptation and validation of appropriate and cost-effective developmental and behavioural screening tools both for research and clinical purposes should thus be a priority for LMIC.

In conclusion, the evolving research on neurodevelopmental outcome of HEU infants is furthering understanding of the complex interplay between health, psychological and socioeconomic determinants of early childhood development. This knowledge, together with development of appropriate, affordable CDAT measures, aligns with the fourth sustainable development goal outlined in the 2030 Agenda for Sustainable Development at the United Nations General Assembly (United Nations, 2016)

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Table 1. Studies on Neurodevelopmental and Behavioural outcome of HEU infants & pre-school children in Low- & Middle-income countries other than Africa

Author	**Site and study period**	**Age**	**ARV exposure**	**Sample size**	**CDAT Measure**	**Outcome**
Sanmaneechai et al., (2005)	Thailand 2001-2003	3-5 yrs	ZDV	30 HEU 35 HUU	Thai intellectual assessment	Poorer cognition in HEU group
Gomez et al., (2009) (abstract only)	Columbia Study period NS	0 -2 yrs	NS	23 HEU 20 HUU	BSID-2nd edition Denver II	No difference between groups
Kerr et al., (2014)	Thailand & Cambodia 2008-2011	2-15 yrs	WHO Option B	160 HEU 167 HUU	Beery VMI, Purdue Peg, WISC, Binet beadmemory, CBCL	Lower scores on verbal, full scale IQ, Binet bead memory in HEU
Spaulding et al., (2016)	Latin America Brazil,&Caribbean 2002-2009	6 mth	cART	1400 HEU	Neurological and motor clinical examination	No additional neurological conditions in ARV-exposed infants
Rajan, et al,. (2017)	India 2013-2015	6-18 mths	cART	50 HEU 9 HUU	Developmental assessment scale for Indian infants	No difference, affected by wasting & low socioeconomic status
Wu et al., (2018)	China 2010-2013	6-36 mths	cART	250 HEU 250 HUU	BSID-3rd edition	Lower cognitive and adaptive scores in HEU

ART antiretroviral therapy, ARV antiretroviral,Beery VMI Beery test of visual motor integration, BSID-2nd ed. Bayley scales of infant development second edition, BSID-3rd ed.Bayley scales of infant development third edition, cART combination maternal 3-drug antiretroviral therapy, CBCL Child Behaviour checklist, CDAT Child developmental assessment tools, HI HIV-infected, HEU HIV-exposed uninfected, HUU HIV-unexposed uninfected, IQ intelligence quotient, K-ABC Kauffman Assessment Battery for

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Children, NRTI Nucleoside Reverse Transcriptase Inhibitor antiretroviral agents, NS not specified, VTP Vertical HIV-transmission prevention, WHO option A: antenatal CART if CD4 less than 200 cells per µl,WHO Option B: antenatal CART if CD4 less than 350 cells per µl, WHO Option B+:universal antenatal CART irrespective of CD4 count

Table 2. Studies on neurodevelopmental and behavioural outcome of HEU infants and pre-school children in sub-Saharan Africa

Author	Site and study period	Age	ARV exposure	Sample size	CDAT Measure	Outcome
Msellati et al., (1993)	Rwanda 1988-1999	6-24 mths	Nil	20-43 HI 113-133 HEU 156-193 HUU	Selected items from Abbreviated DDST and Illingworth's Development of the Infant and Young Child	No difference HEU vs HUU groups
Boivin et al., (1995)	Zaire Time NS	<2 yrs	Nil	14 HI 20 HEU 16 HUU	DDST < 2 years K-ABC	Poorer global cognitive outcome on K-ABC in HEU versus HUU group
Drotar et al., (1997)	Uganda Time NS	6-24 mths	Nil	79 HI 241 HEU 116 HUU	BSID-2nd ed Fagan test	No difference between HEU and HUU groups
Van Rie et al., (2008)	DRC 2004-5	18-72 mths	Nil	35 HI 35 HEU 90 HUU	BSID-2nd ed, Peabody motor, SON, Rosetti	Poorer motor & expressive language in HEU group
Kandawasvika et al., (2011)	Zimbabwe 2002-4	12 mths	Nil	65 HI 188 HEU 287 HUU	BINS	No difference between HEU and HUU groups
Laughton et al., (2012)	South Africa 2007-2008	10-15 mths	WHO Option A	90 HI 28 HEU 34 HUU	GMDS	No difference between HEU and HUU infants
McDonald et al., (2013)	Tanzania 1995-1998	6, 12, & 18 mths	Nil	32 HI 280 HEU	BSID-2nd ed	Poorer scores if HI, preterm, stunted or wasted
Ngoma et al., (2014)	Zambia 2011-2013	15-36 mths	ART (ZDV/ cART)	97 HEU 103 HUU	Capute CAT and CLAMS	HEU and HUU groups had similar outcome
Brahmbhatt et al.,(2014)	Uganda 2002-2008	0-6 yrs	Nevirapine/ cART	116 HI 105 HEU 108 HUU	Ten Questions (all testing positive) MSEL	HEU poorer receptive language than HUU group
Alcock et al., (2016)	Kenya 2004-2005	8-30 mths	Nil	18 HI 14 HEU 261 HUU	Kilifi CDI	Poorer language in older HEU group
Bass et al., (2016)	Uganda 2012-2014	2-5 yrs	ART WHO Option B+	118 HI 221 HEU	MSEL, color object association test, HOME observation	Association between HOME & MSEL scores

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Familiar et al., (2017)	Uganda 2012-2015	6-12 mths	57 HEU cART Option B+ 18 HEU no cART	57 HEU (cART) 18 HEU (no cART) 140 HUU	MSEL	HEU group lower cognitive scores than HUU HEU infants with better caregiving showed improved outcome
Chaudhury et al., (2017)	Botswana 2010-2012	24 mths	cART n=122 ZDV n=214 CD4 <350	313 HEU 357 HUU	BSID-3rd ed and DMC	No difference between groups
Springer et al., (2018)	South Africa 2013-2014	12 mths	cART Option A	58 HEU 38 HUU	BSID-3rd ed ADBB	No difference HEU infants less vocal on ADBB
Le Roux et al., (2018)	South Africa 2013-2016	12 mths	cART Option B+	215 HEU 306 HUU	BSID-3rd ed	HEU poorer cognitive scores then HUU group
Springer et al., (2019)	South Africa 2015-2016	30-42 mths	cART Option B	32 HEU 27 HUU	BSID-3rd edition SDQ	No difference HEU less conduct problems
Kacanek et al., (2018)	Botswana 2006-2008	24 mths	cART if CD4 <200 cells per mm3	197 HEU (101 triple-NRTI arm) 96 in dual NRTI + PI-exposed)	DMC BSID-3rd edition PSED Ten questions	No difference in performance between groups
Debeaudrap et al., (2018)	Cameroon 2007-2011	1-5yrs	NS	127 HI 101 HEU 110 HUU	KABC- II SDQ, Touwen neurological scale.	HI children poorer cognition & behaviour, HEU and HUU groups similar
Laughton et al., (2018)	South Africa 2007-2013	1-5yrs	cART WHO Option A	96 HI 34 HEU 39 HUU	GMDS-ER CBCL Beery	No difference between HEU and HUU groups
Chigono et al., (2018)	Zimbabwe 2015-2017	0-24 mths	NS	562 HEU	MSEL	High maternal depression scores associated with low infant cognitive scores
Cassidy et al., (2019)	Botswana 2016-2017	24 mths	cART	123 EFV-exposed 367 EFV-unexposed HEU	BSID-3rd edition DMC PSED	EFV-exposed HEU did worse on BSID receptive language, DMC locomotor and fine motor and PSED.
Boivin et al., (2019)	Uganda 2013-2014	12-60 mths	cART	405 HEU 456 HUU	MSEL 12, 24 mths K-ABC 48, 60 mths	No difference between HEU and HUU groups
Wedderburn et al., (2019)	South Africa 2012-2015	6 & 24 mths	cART WHO Option B+	732 HEU 733 HUU	BSID-3rd edition	Poorer receptive and expressive language in HEU group

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Rotherham-Borus et al., (2019)	South Africa 2009-2015	2 wk, 6,18, 36 mths	NS	HI 17 HEU 345 HUU 723	BSID 18mths PPVT CBCL, SDQ 3 and 5 yrs MIP of K-ABC at 5yr	No difference in "resilience" between HEU and HUU groups

ART antiretroviral therapy,ARV antiretroviral, Beery VMI Beery test of visual motor integration, BINS Bayley Infant Neurodevelopmental Screener, BSID-2nd ed Bayley scales of Infant and Toddler Development-second edition, BSID-3rd ed Bayley scales of Infant and Toddler Development-third edition, cART combination maternal 3-drug antiretroviral therapy, CAT (Cognitive Adaptive Test), CDAT Child development assessment tool, CLAMS Clinical Linguistic and Auditory Milestone Scale, CBCL Child Behaviour checklist, DDST Denver Developmental Screening Test, DMC Developmental Milestone Checklist, EFV Efavirenz, GMDS Griffiths Mental Developmental Scales, GMDS-ER Griffiths Mental Developmental Scales-Extended Revised, HI HIV-infected, HEU HIV-exposed uninfected, HUU HIV-unexposed uninfected, HOME Observation for Measurement of the Environment, IQ Intelligence quotient, K-ABC Kauffman Assessment Battery for Children, Kilifi CDI Kilifi Communicative Development Inventory, MSEL Mullen Scales of Early Learning, NRTI Nucleoside Reverse Transcriptase Inhibitor antiretroviral agents, NS not specified, PSED Profile of Social and Emotional Development, SON Snijders-Oomen Nonverbal Intelligence Test. VTP Vertical HIV-transmission prevention, WHO Option A: antenatal CART if CD4 less than 200 cells per µl, · WHO Option B: antenatal CART if CD4 less than 350 cells per µl,, WHO Option B+:universal antenatal CART irrespective of CD4 count.

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CHAPTER 3: Neurodevelopmental status of HIV-exposed but uninfected children: a pilot study. Ethics no: N08/10/289

HEU children are exposed to a variety of risk factors, such as compromised maternal physical and mental health, increased exposure to infections, lack of caregiver consistency, socio-economic disadvantage, lack of breastfeeding, and exposure to ART regimens both *in-utero* and post-natally. Thus, in addition to their innate immune deficits, infants living in an HIV-affected household could experience poorer neurodevelopmental outcomes (Gray et al., 2007). In 2009, the Western Cape provincial policy for Prevention of Mother-to-Child Transmission (PMTCT) was somewhat limited. As such, only pregnant women with a CD4 count less than 200 cells per μl, or HIV WHO Stage III or IV, qualified for cART, while those with a CD4 count more than 200 cells per μl qualified for maternal short-course zidovudine with a single dose nevirapine at delivery and all infants received short-course zidovudine (South African National Department of Health ; South African National AIDS Council, 2010).

In the pilot phase of our research, we drew data from a larger study, which sought to assess the risk of infectious morbidity and mortality in HEU infants (Slogrove et al., 2012). Mothers living with and without HIV, and their HIV-negative infants, were recruited within 72 hours of delivery at the post-natal ward of Tygerberg Academic Hospital, Cape Town, from March to June 2009. Mother-infant dyads were enrolled in the neurodevelopmental study at the 18 months visit and assessed using the Griffiths Mental Development scales (Griffiths, 1996) from 2011-2012.

The participants in the neurodevelopmental study included 17 to 19-month-old toddlers. The study group included 21 HEU participants, while the control group comprised 17 HUU participants delivered contemporaneously and matched for socioeconomic status. The control group allowed for future adjustment of potential confounding variables. Use of a standardized measure such as the GMDS was motivated by its history of application in the South African context (Griffiths, 1996).However, a limitation was that the HEU participants were predominantly isiXhosa speakers, while the control group spoke Afrikaans. Thus, cultural differences may have accounted for the lower scores of the HEU toddlers on the personal/social scale.

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ARTICLE

Neurodevelopmental status of HIV-exposed but uninfected children: A pilot study

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Introduction. HIV affects children both directly and indirectly, with evidence of increased infectious mortality and morbidity in the HIV-exposed but uninfected (HEU) infant. There is little published research on neurodevelopmental outcome of HEU infants in Africa. Following the introduction of successful prevention of mother-to-child transmission programmes, it has become important to determine whether differences exist between HEU infants and infants born to HIV-negative mothers in order to guide current management policies of this rapidly growing group of infants.

Objectives. To compare the developmental outcome of infants exposed to HIV *in utero* who remained uninfected (HEU) with that of infants unexposed to HIV *in utero* (HUU).

Methodology. This was a prospective, blinded, hospital-based study. Infants aged between 17 and 19 months were assessed on the Griffiths Mental Developmental Scales (GMDS). Birth history, previous hospitalisation, maternal and infant characteristics, antiretroviral exposure, anthropometric measurements and abnormal clinical findings were documented.

Results. Of the original 55 infants enrolled at 2 weeks of age, 37 (17 HEU and 20 HUU) underwent neurological and developmental assessment. There were no significant differences between the groups with regard to the GMDS general quotient or other subscales, apart from the Personal/social subscale, where the HEU group performed significantly more poorly than the HUU participants (p=0.026). This difference is probably a result of cultural differences between the groups, as 76% of HEU and only 15% of HUU participants were of Xhosa origin.

Discussion. There was no difference in neurodevelopmental outcome at 18 months between the HEU and HUU groups.

S Afr J CH 2012;6(2):51-55.

Successful prevention of mother-to-child transmission (PMTCT) programmes have resulted in a decrease in vertical transmission of HIV to below 5%.[1] In South Africa, with an antenatal HIV prevalence rate of around 30%, about a quarter of infants born are therefore classified as HIV exposed but uninfected (HEU). HIV affects children both directly and indirectly, and there is evidence of increased infectious mortality and morbidity in the HEU infant.[2] There remains uncertainty regarding possible mechanisms of increased susceptibility and also the preventive measures to reduce these effects. Potential factors include increased exposure to infections and immune abnormalities in the infant, socio-economic difficulties, poor maternal health (including mental health), lack of parental care, reduced breastfeeding and unsuitable feeding practices.[3] Conflicting data have been published about toxicity to the fetus of antiretroviral drugs (ARVs) and their effects on neurodevelopment.[4-6] All these factors could potentially affect child development.

Of the published research on HEU children in Africa, only a few studies have high methodological quality using control groups and systematic validated measures of cognitive function.[7] Msellati *et al.* in Rwanda demonstrated no difference in neurodevelopmental outcome between HEU and HIV-unexposed children (HUU), i.e. infants born to HIV-uninfected mothers.[8] A Ugandan study also showed no significant difference between a group of HEU and HUU infants.[9,10] On the other hand, Boivin *et al.* demonstrated deficits in cognitive performance in HEU children in Zaire compared with HUU controls,[11] while Van Rie *et al.* found that HEU preschool children in the Democratic Republic of the Congo had poorer motor development and expressive language than HIV-unexposed controls.[12] The authors argued that socio-economic differences between these groups rather than the inherent consequences of *in utero* HIV exposure may have accounted for the poorer outcome.

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In South Africa the availability of ARVs and PMTCT, while decreasing the number of HIV-infected infants, has significantly increased the number of HEU infants born to HIV-infected mothers.[1] It is important to determine whether any neurodevelopmental differences exist between HEU and HUU children, in order to facilitate the development and implementation of appropriate interventions for this growing population of infants.

Aims and objectives

The primary objective was to compare the neurodevelopmental outcome of infants who were exposed to HIV *in utero* but were uninfected (HEU) with that of infants born to HIV-uninfected mothers (HUU). A secondary objective was to identify markers for poor neurodevelopmental outcome in either group.

Methods

Recruitment

Participants were recruited from the postnatal maternity wards of Tygerberg Hospital, Western Cape, for a pilot study of the innate immune abnormalities in HEU infants. Tygerberg Hospital is one of two tertiary academic hospitals servicing the city and surrounds of Cape Town, Western Cape province, South Africa. It serves as the teaching hospital for Stellenbosch University. Patients accessing care are generally from lower socio-economic communities and are predominantly Afrikaans- or Xhosa-speaking. Participants were recruited consecutively over a 16-week period from March to June 2009. Mothers' HIV infection status was confirmed on presentation in labour using standard HIV testing algorithms.[13]

The study protocol was approved by the Human Research Ethics Committee, Faculty of Health Sciences, Stellenbosch University (N08/10/289).

Inclusion and exclusion criteria

All infants who tested HIV negative (HIV-DNA-PCR) at 2, 6 and 12 weeks of age were included. Participants had to be between 17 and 19 months of age and physically healthy on the day of neurodevelopmental assessment. HIV-infected infants were excluded from the study.

Data collection

Information regarding pregnancy, birth history, weight gain, previous illnesses and hospitalisation, maternal characteristics and family history was obtained from the caregiver, hospital medical records and the child's Road-to-Health card (immunisation record). Head circumference, weight and length were plotted on charts from the Centers for Disease Control and Prevention (USA), and a developmental and neurological examination was performed.

Instruments

The Griffiths Mental Developmental Scales (GMDS) 0 - 2 years[14] were administered. There are 5 subscales: Locomotor, Personal/social, Hearing and speech, Eye and hand co-ordination, and Performance. The GMDS have been adapted for South African children. Standard instructions and questions are available in English, Afrikaans and Xhosa. Although this tool has been widely used in South Africa,[15-17] it has yet to be validated and standardised on South African children. The mother or a primary caregiver was present during the assessment, which was carried out in the child's home language by one of two developmental paediatricians. An interpreter, also a trained GMDS administrator, helped the paediatricians to complete the scales with Xhosa-speaking patients. The paediatricians initially assessed a participant together and reached consensus on discrepant pass or fail test items, until it was felt that scoring was of a similar standard. The testers were blinded to the child's HIV exposure status.

Data analysis

Statistica (Release version) 10 (Statsoft, Inc Tulsa, OK, USA) was used for analysis. Categorical data were analysed using either Fisher's two-tailed analysis or Pearson's chi-square analysis. The differences in numerical data (i.e. gestational age, birth weight, maternal age, weight, length, head circumference, chronological age and hospitalisation) among the two groups were analysed using *t*-tests. A Mann-Whitney U-test was used to determine differences in the GMDS scores.

Results

Twenty-five HIV-infected and 28 HIV-uninfected mothers were recruited from the postnatal wards at Tygerberg Hospital and their infants (27 HEU and 28 HUU) were enrolled 2 weeks after delivery. Of the original 55 infants enrolled, 39 presented for the visit at 18 months. Fifteen infants (6 HUU and 9 HEU) were lost to follow-up and 1 infant (HUU) died before 12 months. Thirty-seven of the remaining 39 infants underwent neurodevelopmental assessment, as one parent declined consent and one missed the appointment.

Among the 37 participants, there were 17 children who were HEU and 20 who were HUU. There was no significant difference between the groups with regard to gender, gestation, birth weight, mode of delivery or maternal age and education (Table 1). However, the HUU participants were predominantly Afrikaans language speakers (85%) while the HEU participants were predominantly Xhosa (76%).

There was no significant difference between HEU and HUU participants with regard to the general quotient and 4 of the 5 GMDS subscales, although both HEU and HUU group means were lower than the standardised mean (Table 2). However, the HEU group performed significantly more poorly than the HUU participants on the Personal/social subscale of the GMDS (Fig. 1). Specific items on the Personal/social scale which differentiated the groups included:

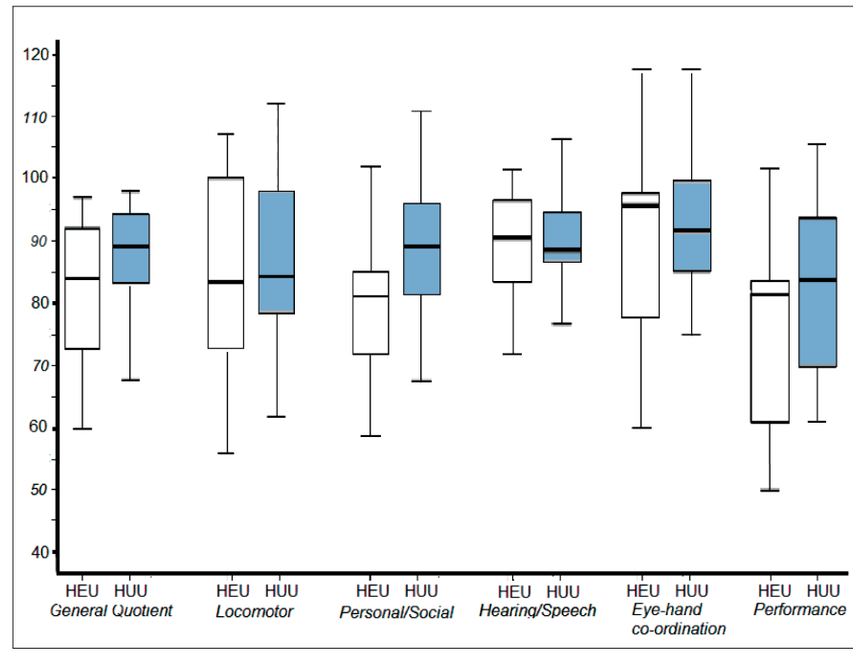

Fig. 1. Mean general quotients and subquotients obtained on the Griffiths Mental Development Scales: comparison of HIV-exposed but uninfected (HEU) and HIV-unexposed and uninfected (HUU) infants.

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- Item 42: 'shows shoes on request' – correctly indicated by 85% of the HUU but only 47% of HEU participants
- Item 43: 'mother reports that child uses spoon himself but spills some' – passed by 85% of the HUU versus 59% of HEU participants
- Item 45: 'shows one part of a doll's body on request, e.g. hands, hair, feet, eyes, nose' – passed by 65% of HUU versus 41% of HEU participants.

Five of the HEU and 2 of the HUU infants required at least one hospital admission for acute infection during their first 18 months of life, while 3 of the 5 HEU infants had two hospital admissions (Table 3). However there was no statistically significant difference between the groups with regard to the number of infants with one or more hospitalisations (p=0.21). An unexpected finding was the anthropometric differences between the groups. More children in the HUU group were stunted (Fig. 2). Two HUU participants had height-for-age z-scores (HAZ) scores more than 2 standard deviations (SD) below the mean, and 5 HUU participants had HAZ scores that fell between 1 and 2 SD below the mean. Only 1 HEU participant had a HAZ score between 1 and 2 SD below the mean, and none was greater than 2 SD. There were no infants in either group with weight-for-length z-scores (WLZ) more than 2 SD below the mean at 18 months. Although there was no statistically significant difference in head circumference between groups (0.21), 3 of the HEU infants had head circumferences above the 97th centile and 3 of the HUU infants had head circumferences below the 3rd centile.

The groups differed significantly in feeding patterns. All but 1 of the HEU infants were formula-fed, while all HUU infants were breastfed for a median of 12 weeks.

A significantly greater percentage of mothers in the HUU group (45%) versus the HEU group (11%) admitted to smoking during pregnancy (p=0.036).

Discussion

There was no significant difference in the General quotients of HEU and HUU participants, which correlates with findings of previous studies in Africa.[8-10] However, the Personal/social subquotient was significantly lower in the HEU group. It is difficult to ascertain whether the lower mean Personal/social score was due to the biological and environmental exposures associated with having an HIV-positive mother or to a

Table 1. Maternal and infant characteristics: comparison of HIV-exposed but uninfected (HEU) with HIV-unexposed uninfected (HUU) infants

Demographics	HEU (n=17)	HUU (n=20)	p-value
Gender, male (n (%))	6 (35)	10 (50)	0.093
Gestation (wks) (n)			
<37	4	4	0.65
≥37	13	16	
Birth weight (g) (median (range))	2 980 (1 900 - 3 820)	3 068 (2 080 - 3 600)	0.78
Mode of delivery (n (%))			
Vertex delivery	16 (94)	19 (95)	0.362
Breech delivery	0	1 (5)	
Caesarean section	1 (6)	0	
Maternal age at delivery (yrs) (median (range))	27 (19 - 41)	28 (19 - 44)	0.51
Maternal education (final grade attained in formal schooling) (n (%))			
≤7	3 (17)	3 (15)	0.745
8 - 10	8 (47)	11 (55)	
>10	6 (35)	6 (30)	
Language (n (%))			
Afrikaans	4 (23)	17 (85)	0.026
Xhosa	11 (64)	3 (15)	
Mixed Xhosa/Eng/French	2 (11)		

Table 2. Mean quotients and subquotients on the Griffiths Mental Development Scales: comparison of HIV-exposed but uninfected (HEU) with HIV-unexposed (HUU) infants

Griffiths quotients	Group	Mean	Median	Minimum	Maximum	SD	p-value
General quotient	HEU	83.05	84	60	97	11.31	0.190
	HUU	87.45	89	68	98	8.65	
Locomotor	HEU	82.76	83	56	107	16.33	0.433
	HUU	86.75	84	62	112	14.25	
Personal/social	HEU	79.35	81	59	102	11.20	0.026
	HUU	88.45	89	68	111	11.41	
Hearing and language	HEU	89.11	91	72	102	9.37	0.968
	HUU	89.25	89	64	107	10.70	
Eye-hand co-ordination	HEU	89.52	96	60	118	18.16	0.451
	HUU	93.25	92	75	118	11.26	
Performance	HEU	76	82	50	102	13.71	0.139
	HUU	83.4	84	61	106	16.01	

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Table 3. Possible confounders: comparison of HIV-exposed but uninfected (HEU) with HIV-unexposed (HUU) infants

Variable	HEU (*n*=17)	HUU (*n*=20)	*p*-value
Low birth weight (<2 500 g) (*n* (%))	2 (11)	1 (5)	
Head circumference (cm) (mean)	46.92 Macrocephaly (*n*=3)	46.09 cm Microcephaly (*n*=2)	0.21
Weight for age (mean *z*-scores)	0.2773	-0.3985	0.016
Length for age (mean *z*-scores)	0.2272	-0.6266	0.045
Weight for length (mean *z*-scores)	0.6105	-0.1419	0.040
Physical and neurological findings	No major neurological or physical abnormalities	Achilles tendon contractures (*n*=1) Fetal alcohol spectrum disorder (*n*=1) Strabismus (*n*=1) Serous otitis media (*n*=1)	

SD = standard deviation.

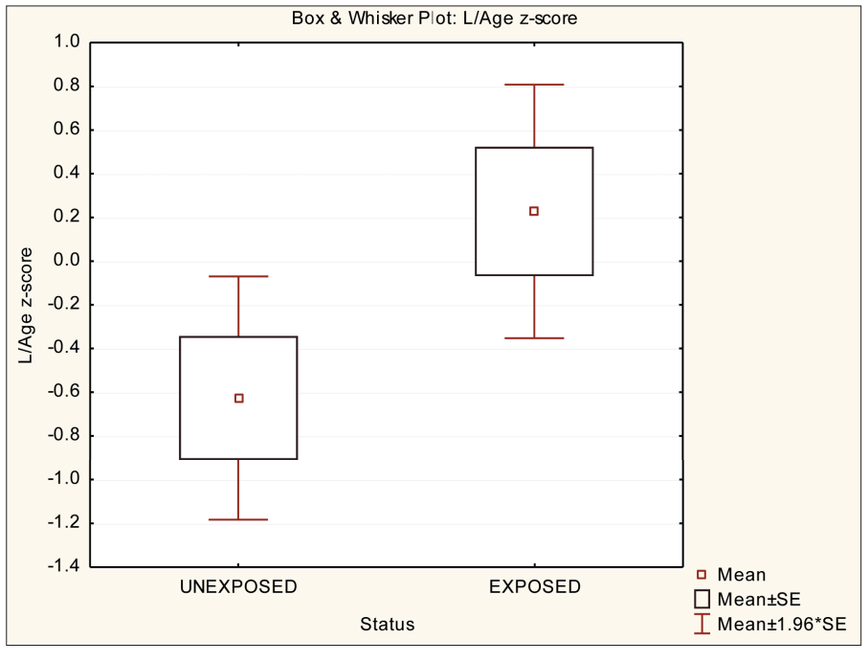

Fig. 2. Comparison of length-for-age z-scores between HIV-unexposed uninfected (HUU) and HIV-exposed but uninfected (HEU) infants.

confounding effect of cultural differences between the groups which manifested as different child-rearing practices. For example, items in the GMDS such as spoon feeding and exposure to dolls are not culturally universal activities. The HUU participants were predominantly Afrikaans speaking, while the HEU participants were largely Xhosa speaking. When Personal/social subquotients were grouped primarily by home language and not by HIV exposure, the difference in scores between the Afrikaans and Xhosa groups was even more significant (p=0.015). The influence of cultural differences has been supported by Cockcroft *et al*., who found that black South African infants aged between 13 and 16 months performed significantly more poorly on the Personal/social scale compared with a British sample.[15] Luiz also postulated that this subscale was the most culturally biased.[18]

Infant nutrition, specifically stunting, may also adversely affect development. Increased stunting among the HUU participants was an unexpected finding. Stunting has been found to be associated with poor neurodevelopmental outcome.[19] It could be postulated that stunting was a confounder that adversely affected the HUU developmental scores, thus minimising the difference between the HUU and HEU groups. A significantly greater percentage of mothers in the HUU group admitted to smoking during pregnancy, and 3 of the mothers, all HIV uninfected, admitted to drinking alcohol. The HUU group may therefore have had other risk factors that could potentially have lowered their developmental scores.

All but 1 of the HEU participants had been exposed to ARVs, either as a result of PMTCT prophylaxis or combination ARV therapy given to their mothers, but no neurological abnormalities attributable to ARVs were evident at 18 months.

The strengths of the GMDS are that the tool has been extensively used on this age group in South Africa with Xhosa and Afrikaans translations, and it does appear to be reliable in picking up differences between groups.[15-17]

Limitations

Limitations of the study include the number of children lost to follow-up from the original cohort. By the 18-month time point when development was assessed, a large number of infants had been lost from the study as a result of relocating or mothers returning to work. Secondly, the small sample size precluded multivariable analysis to adjust for the effects of confounding factors. In particular this meant that any effect of the cultural imbalance between the HEU and HUU groups could not be adequately adjusted for. Finally, the effects of ARVs on neurodevelopmental outcomes could not be ascertained as all but 1 of the HEU children had been exposed to ARVs at some point in time.

Conclusion

There was no difference in performance on the GMDS between HEU and HUU infants, except for the Personal/social scale, where the HEU participants did significantly worse. This was probably accounted for by cultural variations between the groups.

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Recommendations

Studies with a larger sample size attempting to control for confounding factors through matching or adjustment are recommended. Evaluating children's development at 12 months of age may reduce attrition. It would be beneficial to review items on the Personal/social subscale for cultural bias.

Acknowledgements. This work was supported in part by National Institute of Allergy and Infectious Diseases, NIH, Grant number: N01 AI50023, the Martha Piper Fund, and the Peter Wall Institute for Advanced Studies. ME was supported in part through the National Health Laboratory Service Research Trust (grant number TY94171), the National Health Laboratory Service (K Fund numbers KNC97 and KNC103), the Poliomyelitis Research Foundation (grant numbers 10/02, 10/31 and 11/37), and the Harry Crossley Foundation, 2009 - 2011 (grant numbers 5415 and 5762). MT is supported by grants from the National Institute of Alcoholism and Alcohol Abuse (USA), the National Institute on Drug Abuse (USA), and the National Research Foundation (South Africa). The authors would like to thank Staff Nurse S Sylvester and Ms N R Khethelo for their practical and logistical contributions.

Author contributions. PS contributed to protocol design, carried out the interviews and neurodevelopmental assessments, contributed to the understanding of the results and drafted the initial article as well as revisions. BL contributed to the conceptualisation of the project, protocol design, carried out the interviews and neurodevelopmental assessments, contributed to the understanding of the results and assisted in the write-up and revision of the article. MT contributed to the understanding of the results and assisted in the write-up and revision of the article. JH provided data analysis support. ME was the supervisor, contributed to the conceptualisation of the project and assisted in the revision of the article. We gratefully acknowledge the data provided by co-workers Amy Slogrove, Shalena Naidoo, Kevin Ho and Gareth Mercer.

There is evidence of increased infectious mortality and morbidity in the HIV-exposed but uninfected infant.

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Chapter 4: Neurodevelopmental outcome of HIV-exposed but uninfected infants in the Mother and Infant Health study, Cape Town, South Africa. Ethics number: N13/03/028

The Mother and Infant Health Study (MIHS) commenced in June 2012, with the primary aim of comparing infectious morbidity and mortality of HEU infants with an HUU group from a similar cultural and socio-economic background. Longitudinal follow-up and a rich prospective data set made this a suitable cohort for evaluating the neurodevelopmental and behavioural outcome of HEU infants. Certain adjustments were made to the study design, as a result of confounders identified in the pilot study, whereby the HEU participants spoke predominantly isiXhosa, while the control group spoke Afrikaans. Cases and controls were thus frequency-matched for home language in order to improve homogeneity with regards to maternal social characteristics, cultural background and child-rearing practices. Participant attrition had been identified as a limitation of the pilot study; thus, infants were recalled and assessed at an earlier time-point (twelve months) in an effort to improve retention. The assessors were blinded to the HIV-exposure status of the participants.

Maternally-indicated cART expanded (2009-2013) and pregnant South African women on the MIHS with a CD4 count less than less than 350 cells per µl, or HIV WHO Stage III or IV, qualified for lifelong cART. In comparison, those with CD4 count less than 350 cells per µl, with WHO Stage 1 or II disease received a mono- or dual-agent prophylactic ART regimen referred to as VTP. South African infants may potentially have received *in-utero* or post-natal exposure to nucleoside/nucleotide reverse transcriptase inhibitors, including zidovudine, tenofovir, lamivudine, emtracitibine, the non-nucleoside/nucleotide reverse transcriptase inhibitors, efavirenz and nevirapine, and the protease inhibitor lopinavir/ritonavir.MIHS inclusion criteria included infants delivered>34 weeks gestation with no peri-natal complications following low-risk pregnancies; mothers with pre-eclampsia, eclampsia or multiple pregnancy were excluded, as well as HIV-infected mothers on third-line cART.

The Bayley Scales of Infant Development-3rd edition (BSID) was selected, as this tool differentiates between receptive and expressive language domains and has a cognitive scale. We also included the Alarm Distress Baby Scale (ADBB) to assess the quantity of infant vocalization and behavioural features of social withdrawal (Guedeney, Matthey, & Puura, 2013).Potential confounders such as demographic characteristics, symptoms of postpartum depression (CES-D), caregiver consistency, as well as language-promoting activities and influence of day-care were analysed and adjusted for where appropriate. Although the two groups were similar with regards to neurodevelopmental outcome, subtle behavioural differences were found with regards to vocalisation.

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Tropical Medicine and International Health doi:10.1111/tmi.13006

VOLUME 23 NO 1 PP 69–78 JANUARY 2018

Neurodevelopmental outcome of HIV-exposed but uninfected infants in the Mother and Infants Health Study, Cape Town, South Africa

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Abstract

OBJECTIVES To compare neurodevelopmental outcomes of HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) infants in a peri-urban South African population. HEU infants living in Africa face unique biological and environmental risks, but uncertainty remains regarding their neurodevelopmental outcome. This is partly due to lack of well-matched HUU comparison groups needed to adjust for confounding factors.

METHODS This was a prospective cohort study of infants enrolled at birth from a low-risk midwife obstetric facility. At 12 months of age, HEU and HUU infant growth and neurodevelopmental outcomes were compared. Growth was evaluated as WHO weight-for-age, length-for-age, weight-for-length and head-circumference-for-age Z-scores. Neurodevelopmental outcomes were evaluated using the Bayley scales of Infant Development III (BSID) and Alarm Distress Baby Scale (ADBB).

RESULTS Fifty-eight HEU and 38 HUU infants were evaluated at 11–14 months of age. Performance on the BSID did not differ in any of the domains between HEU and HUU infants. The cognitive, language and motor scores were within the average range (US standardised norms). Seven (12%) HEU and 1 (2.6%) HUU infant showed social withdrawal on the ADBB ($P = 0.10$), while 15 (26%) HEU and 4 (11%) HUU infants showed decreased vocalisation ($P = 0.06$). There were no growth differences. Three HEU and one HUU infant had minor neurological signs, while eight HEU and two HUU infants had macrocephaly.

CONCLUSIONS Although findings on the early neurodevelopmental outcome of HEU infants are reassuring, minor differences in vocalisation and on neurological examination indicate a need for reassessment at a later age.

keywords HIV-exposed uninfected infants, neurodevelopmental outcome, infant growth, South Africa, low- and middle-income countries

Introduction

HIV-exposed but uninfected (HEU) infants face biological and environmental risk factors that could potentially affect cognitive development [1–4]. Neurodevelopmental outcome of this vulnerable group in low- and middle-income countries remains uncertain [5–7]. Sher, reviewing studies prior to 2009, found that research methodologies differed and studies generally lacked HIV-unexposed uninfected (HUU) child comparison groups [8]. The few African studies with HUU comparison groups have shown mixed findings. In Zaire, cognitive delay was observed in HEU *vs*. HUU children [9]; in the Democratic Republic of Congo motor, expressive language delays were observed [10], and in Zambia, differences in scholastic performance were reported [11]. However, numerous other studies in Africa have found no differences in cognitive, motor and language development between HEU and HUU children [12–16].

In South Africa, the antenatal HIV prevalence is one of the highest in the world (29.5% in 2011) [17]. Prevention

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of mother-to-child transmission (PMTCT) programmes have successfully reduced vertical transmission rates to less than 5% [18], resulting in an estimated 290 000 HEU newborns annually in South Africa [19]. Early detection of neurodevelopmental delays and targeted intervention during the pre-school years improves long-term developmental outcome in all children irrespective of HIV exposure [20]. South African policymakers require information about the neurodevelopmental status of the large population of HEU infants and children to provide future surveillance and support.

The HUU comparison group is crucial as there are many additional factors that can affect neurodevelopmental outcome including maternal education, mental health, alcohol or recreational drug use in pregnancy and poverty [21]. Most developmental tools are not validated locally or contextually appropriate for African infants, so comparison with USA standardised norms may be insufficient. This study therefore aimed to compare cognitive, motor and language development of HEU and HUU South African infants.

Methods

This prospective cohort study was nested in the Mother Infant Health Study (MIHS), a longitudinal study with the primary objective of comparing risk for infectious morbidity in HEU and HUU infants [22]. From July 2012 to June 2013, HIV-infected and HIV-uninfected women were enrolled within 72 h of delivery from a single, community, low-risk, midwife obstetric unit serving a peri-urban community on the outskirts of Cape Town, South Africa. HIV-infected and HIV-uninfected mothers were frequency matched on race–ethnicity to reduce heterogeneity in the primary language and maternal social characteristics between HEU and HUU infants which were identified as confounders to neurodevelopmental outcome in a preceding pilot study [23].

Maternal HIV infection status was confirmed on presentation in labour using standard South African national HIV testing algorithms and confirmed again 2 weeks postnatally [24]. The HIV-infected mothers received routine PMTCT interventions during the study according to the Western Cape Provincial guidelines at the time (WHO Option A) [25]. This included combination antiretroviral therapy (cART) for all pregnant women with CD4 < 350 cells/μl or WHO stage 3 or 4 disease, or zidovudine (ZDV) monotherapy if criteria for cART were not met. Infant eligibility criteria included birthweight >2000 g and ≥34 weeks' gestation. Only confirmed HIV-uninfected infants aged 12 ± 2 months were included in the neurodevelopmental assessment. All infants underwent HIV testing (HIV-ELISA and HIV DNA-PCR if HIV-ELISA was positive) to exclude HIV infection at the assessment visit. Neurodevelopmental assessments were rescheduled if infants were physically unwell on the day.

The assessments took place at the Tygerberg Hospital (TBH) paediatric outpatient department. Each mother–infant pair was allocated a study number to anonymise data. A research assistant took consent and administered the Centre for Epidemiological Studies Depression Scale (CES-D) [26] to the primary caregiver in their language of choice. One of two developmental paediatricians blinded to the HIV-exposure status assessed the infant using Bayley Scales of Infant and Toddler Development III (BSID III) [27] followed by a full neurological examination. The hearing was screened with a high-frequency rattle, and if there were concerns, infants were referred for audiological evaluation. The paediatricians initially assessed five infants together using the BSID III and reached consensus on discrepant pass or fail items. The principal investigator (PS) then assessed a further 86 infants, while the second assessor (HS) assessed five infants independently. An interpreter assisted the paediatricians in completing the scales with Xhosa-speaking participants. At least 30 min of each assessment was videotaped to allow for review of the behavioural features. Infant anthropometry and baseline maternal, socioeconomic and infant feeding data collected at study visits prior to the 12-month neurodevelopmental assessment were accessed from the MIHS database.

The BSID III is an internationally recognised standardised, norm-referenced tool that has been used in South Africa but not adapted or standardised for South African children [28]. Infants were tested using the cognitive, language and motor scales. Children with developmental delay (any BSID III composite score below 80) were referred to the TBH neurodevelopmental service.

The Alarm Distress Baby Scale (ADBB) is a screening tool that detects social withdrawal by observing an infant's behaviour with a stranger while in the presence of the mother [29]. It has previously been used in South African research [30]. The principal investigator obtained distance-training accreditation using videotaped examples and performed all of the ADBB assessments. The assessor rates behaviours including infant's facial expressivity, eye contact, vocalisation, activity and ability to form a relationship with an observer to generate a total ADBB score. A threshold score of 5 has shown optimal sensitivity and specificity to detect infants at risk [29]. A vocal score of above zero indicates reduced vocalisation and rates the quantity of vocalisation ranging from brief spontaneous vocalisation (score 1) to a complete silence (score 4). Videotaping each

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assessment allowed for review of the ADBB scoring. Two accredited scorers reviewed 15 of the more difficult assessments with the principal investigator for final consensus. Infants rated as having social withdrawal were rebooked over a fortnight to confirm behavioural features. The CES-D was used to screen the primary caregiver's mental health [26]. It is a 20-item self-rating scale previously used in South Africa with a threshold of 16 indicating significant depressive symptomatology. Primary caregivers with significant depressive symptomatology were referred to the community psychiatric outpatient service and those who reported thoughts of self-harm were referred to the TBH emergency psychiatric service.

The sample size for comparison between the two groups was calculated using information from interim analysis of Bayley scores. A sample size of at least 50 HEU and 50 HUU infants was deemed necessary to show a clinically meaningful 5-point difference in the composite scores. Expected mean general quotients were estimated to be in the region of 100 with a standard deviation of 15 [27]. US norms classify scores between 70 and 85 as moderately impaired and <70 as severe, and thus, BSID III composite scores below 85 were classified as 'poorer neurodevelopmental outcome' [28]. World Health Organization (WHO) child growth standards of head circumference, weight and length of infants were converted into standardised Z-score anthropometric values utilising WHOAnthro (WHO 2011) and included weight for age (WAZ), length for age (HAZ), weight for length (WHZ) and head circumference for age (HCZ). Definitions included the following: underweight (WAZ < −2 Z-score), stunted (HAZ < −2 Z-score) wasted (WHZ < −2 Z-score), macrocephaly (HCZ > +2 Z-score) and microcephaly HCZ < −2 Z-score). Categorical data were analysed using chi-square analysis or Fisher's exact test. Numeric data were analysed using a t-test or Wilcoxon rank-sum test. A *P*-value less than 0.05 was considered significant. Stata version 13.1 (StataCorp, Texas, USA) was used for analysis.

Ethics approval was granted (N13/03/028) for the neurodevelopmental substudy of the Mother and Infant Health Study (S12/0/009) by Human Research Ethics committees of Stellenbosch University and the University of British Columbia. Caregivers gave separate consent for participation in the neurodevelopmental study and maternal mental health questionnaire and received verbal feedback and a report.

Results

Of the 176 mother–infant pairs enrolled at 2 weeks of age, 103 (58.5%) returned for the 12-month visit and 96 (54.5%) infants underwent neurodevelopmental assessments, 58 HEU and 38 HUU infants (Figure 1). Significantly more HIV-infected than HIV-uninfected mothers were retained ($P = 0.03$); a higher proportion of those retained had completed secondary education ($P = 0.04$), while their infants had a lower mean birthweight ($P = 0.05$). There were no other major differences between mother–infant pairs retained in the study and those that were not, with regard to baseline maternal data (age, ethnicity, home language, primiparity, pregnancy ARV regime and delivery CD4 count) and infant characteristics (gestational age, length and low birthweight) (Table S5).

Ninety-four (98%) infants were accompanied by their biological mother and two (2%) by maternal grandmothers, one of whom was the primary caregiver as the mother resided in another province and the other the daytime caregiver while the mother worked. All infants lived with their biological mother except the one HEU infant who was in the grandmother's care. Mothers of HEU infants were older, less educated and fewer reported having planned their pregnancy than mothers of HUU infants (Table 1). The mean gestation at booking was 21.8 weeks for both HEU (SD 6.2) and HUU (SD 6.8) groups ($P = 0.99$).

Two mothers, one HIV-infected and one HIV-uninfected, were treated antenatally for tuberculosis, and one HIV-uninfected mother was treated for syphilis. Two HIV-infected mothers admitted to using illicit drugs during pregnancy. Twenty-nine (50%) of the HEU infants were exposed *in utero* to combination antiretroviral therapy (cART) and the remaining 50% to ZDV monotherapy (24). Ninety-four mothers and one grandmother who was the primary caregiver completed the CES-D questionnaire, while one mother (HUU group) declined. Scores indicated depressive symptomatology in more than half of mothers, with no difference between HIV-infected and HIV-uninfected participants (HIV-infected 30/58 (52%) *vs*. HIV-uninfected 20/37 (54%)) (Table 1).

All infants had uncomplicated perinatal histories, and maternal mean body mass index (BMI) at 2 weeks postpartum did not differ ($P = 0.85$) in the two groups. There was a significant difference in the proportion of infants breastfeeding at 2 weeks (39% HEU *vs*. 100% HUU infants) ($P < 0.001$) and at 6 months (12% HEU *vs*. 87% HUU infants) ($P < 0.001$) but no group difference in 12-month anthropometry (Table 2). However, four (6.7%) HEU and six (15.7%) HUU infants were stunted, two (3.4%) HEU infants were stunted and underweight, and one (1.7%) HEU infant was underweight, stunted and wasted.

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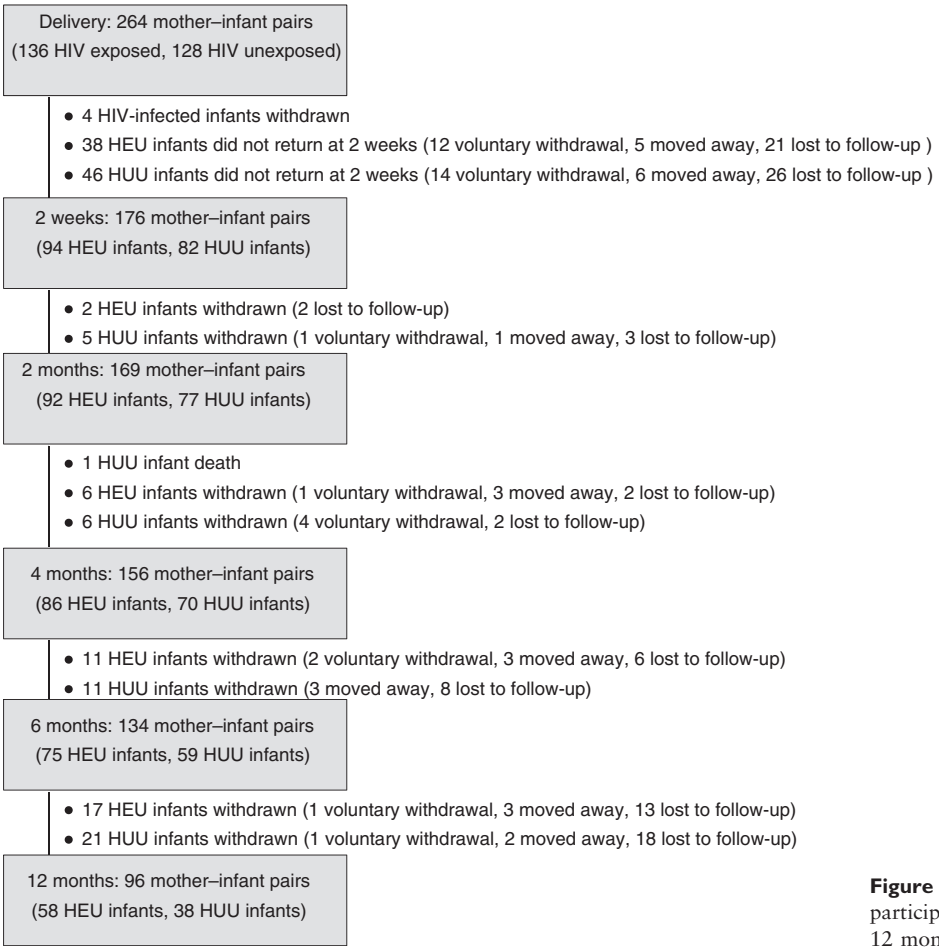

Figure 1 Disposition of study participants between enrolment and 12 months of age.

Fourteen (24%) of the HEU infants and seven (18%) of the HUU infants required hospitalisation in the first year of life with four (6.9%) HEU infants and two (5.2%) HUU infants requiring two admissions and one HEU infant requiring three admissions. No complications related to hospitalisation resulted in neurological compromise.

The infant requiring three hospitalisations had congenital macrocephaly and global developmental delay and presented with torticollis and history of a head injury but no loss of consciousness. The torticollis resolved and neuroimaging of brain and spine was normal. The infant was exposed to efavirenz from the first trimester of pregnancy.

Eight HEU (13.8%) and two HUU (5.5%) infants had macrocephaly at the 12-month visit ($P = 0.19$), whereas none were microcephalic. Three of the eight macrocephalic HEU infants had been exposed antenatally to cART including two infants to tenofovir disoproxil fumarate (TDF), lamivudine (3TC) and efavirenz and one infant to TDF, 3TC and lopinavir/ritonavir. Four (6%) HEU infants had abnormal neurological signs including generalised hypotonia ($N = 1$), unilateral dystonia ($N = 1$), convergent squint ($N = 1$) and congenital unilateral ptosis ($N = 1$). One HUU infant had generalised hypotonia.

There were no significant differences in the cognitive, language (receptive and expressive) or motor (gross motor and fine motor) composite scores between the HEU and HUU infants (Table 3).

The group mean (standard deviation (SD)) language composite scores were 91.75 (11.3), which was lower than the cognitive (100.46 (10.23)) and motor scores (96.5 (9.42)), but still within the average range. Cognitive and motor composite scores for all HEU and HUU infants were within two standard deviations of the mean (≥70), but one HUU infant had a language composite score in the severely impaired range (<70) despite normal

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Table 1 Maternal, infant and socio-economic characteristics compared between HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) infants

Characteristic	HEU (N = 58)	HUU (N = 38)	P-value
Maternal characteristics			
Age at delivery (in years) – mean (SD)	27.8 (5.15)	24.8 (4.8)	0.005
Ethnicity			
African† (%)	51 (87.9%)	34 (89.5%)	0.54
Mixed ancestry	7 (12.1%)	4 (10.5%)	
Marital status (%)			
Never married	40 (69.0%)	26 (68.4%)	0.69
Married	16 (27.6%)	12 (31.6%)	
Widowed/Divorced/separated	2 (3.4%)	0 (0%)	
Highest level of education (%)			
Primary school education only	5 (8.6%)	0 (0%)	0.02
Attended Secondary school	35 (60.3%)	17 (44.7%)	
Completed secondary education	18 (31.0%)	21 (55.3%)	
Primiparous (%)	8 (13.8%)	11 (29.0%)	0.07
Planned pregnancy (%)	11 (19.0%)	14 (36.8%)	0.05
Any tobacco use during pregnancy (%)	9 (15.5%)	1 (2.6%)	0.08
Any alcohol use during pregnancy (%)	11 (19.0%)	4 (10.5%)	0.39
Depressive symptoms	30/58	20/37	0.68
CES-D score ≥16 n/N (%)	(51.7%)	(54.0%)	
Infant characteristics			
Male	28 (48.3%)	16 (42.1%)	0.55
Gestational age in weeks mean (SD)	38.5 (1.56)	39.0 (1.64)	0.16
Birthweight in grams – mean (SD) (95% CI)	3068 (392) (2965–3172)	3157 (449) (3010–3304)	0.31
Low birthweight <2500 g	5 (8.6%)	1 (2.6%)	0.40
Breastfeeding: at age 2 weeks	23 (39.6%)	38 (100%)	<0.001
Still breastfeeding at age 6 months	7 (12.1%)	25 (65.8%)	<0.001
Socio-economic characteristics			
Mother's mean (SD) monthly income at 6 months postpartum (ZAR)	1055.8 (992.3)	1068.3 (1024.5)	0.98
Receiving Child Support Grant for study infant	34 (63.0%)	23 (67.6%)	0.65
Type of Housing: Stand-alone house	21 (36.2%)	17 (44.7%)	0.32
Informal stand-alone	23 (39.7%)	8 (21%)	
Other (apartment)	14 (24.1%)	13 (34.3%)	

†African includes infants of Xhosa-speaking South African (n = 76), Ndebele-speaking South Africans (n = 2) and Zimbabwean (n = 7) descent; CES-D, Centre for Epidemiological Studies Depression Scale; HEU, HIV exposed uninfected; HUU, HIV unexposed uninfected; SD, standard deviation.

hearing. Five HEU infants demonstrated cognitive scores <85 *vs.* no HUU infants (P = 0.15). A similar proportion of HEU (6.9%) *vs.* HUU (5.2%) demonstrated poorer neurodevelopmental outcome on motor domain (score <85) (P = 0.74); however, a higher proportion of HEU infants compared to HUU infants had 'poorer neurodevelopmental outcome' (<85) on the language domain; 28% HEU *vs.* 18% HUU (P = 0.23).

There was no significant difference between the groups with regard to total ADBB scores (Table 3). Seven (12.1%) HEU infants and one (2.6%) HUU infant were classified as 'socially withdrawn' (Fisher exact=0.14). Seven (87%) of the eight socially withdrawn infants were female (Fisher exact P = 0.07). Fifteen (25.9%) HEU *vs.* four (10.5%) HUU infants showed decreased vocalisation on the ADBB vocal subscale (Fisher exact P = 0.07); however, there was no sex difference in these 19 infants with decreased vocalisation (Fisher exact P = 1.00). The 'socially withdrawn' infants scored lower on the BSID III language subscale (P < 0.001). The seven 'socially withdrawn' HEU infants had a mean language quotient of 81.1 (range 79–91), and the single HUU infant's quotient was 77. The 19 infants with decreased vocalisation on ADBB subscale also had decreased BSID III receptive (P < 0.01), expressive (P < 0.01) and composite language quotients (mean 80.3 P < 0.01); the mean composite

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Table 2 Infant sociodemographic and anthropometric characteristics at age 12 months compared between HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) infants

Characteristic	HEU	HUU	*P*-value
Sociodemographic characteristics	*N* = 58	*N* = 38	
Age at assessment in days – mean (SD)	364.3 (11.8)	365.1 (8.7)	0.60
Daycare attendance – *N* (%)	12 (20.7%)	3 (8.3%)	0.11
Living with mother – *N* (%)	57 (98%)	38 (100%)	
Anthropometric characteristics at age 12 months	*N* = 58	*N* = 38	
Head circumference Z-score mean (SD)	0.56 (1.23)	0.41 (1.03)*	0.55
Weight-for-age Z-score mean (SD)	0.12 (1.31)	0.28 (1.07)*	0.53
Length- for-age Z-score mean (SD)	−0.75 (0.95)	−0.59 (1.24)**	0.46
Weight-for-length Z-score mean (SD)	0.62 (1.39)	0.74 (0.93)**	0.65

HEU, HIV exposed uninfected; HUU, HIV unexposed uninfected; SD, standard deviation.
Data missing *Two participants **Three participants.

Table 3 Neurodevelopmental outcomes at 12 months of age in HIV-exposed uninfected (HEU) and HIV unexposed uninfected (HUU) infants according to the Bayley Scales of Infant and Toddler Development 3rd edition (BSID III) and the infant social withdrawal scale (ADBB)

	HEU (*N* = 58)	HUU (*N* = 38)	*P*-value
BSID III			
Composite scores – mean (SD)			
Cognitive	99.9 (7.8)	101.3 (11.6)	0.51
Motor	95.6 (9.1)	97.8 (9.8)	0.26
Language score	90.4 (9.4)	92.5 (11.0)	0.31
Scaled scores – mean (SD)			
Gross motor	9.0 (2.5)	9.6 (2.5)	0.17
Fine motor	9.5 (1.5)	9.6 (1.2)	0.86
Receptive language	8.1 (2.0)	8.2 (1.9)	0.72
Expressive language	8.7 (1.9)	9.2 (2.2)	0.28
ADBB			
Increased social withdrawal – *N* (%)	7 (12.1%)	1 (2.6%)	0.10
Decreased vocalisation – *N* (%)	15 (25.9%)	4 (10.5%)	0.06

ADBB, Alarm Distress Baby Scale; BSID III, Bayley Scales of Infant and Toddler Development 3rd edition; SD, standard deviation.

language score of the 15 HEU infants with decreased vocalisation on ADBB was 81.9 (range 71–91) and that of the four HUU infants was 75.5 (range 59–89).

A high proportion of the caregivers (52.6%) scored above the CES-D threshold for depressive symptomatology; but there was no difference between HEU and HUU groups ($P = 0.55$). There was also no association between elevated CES-D score and poorer outcome on the BSID III language subscale ($P = 0.26$) or ADBB social withdrawal (Fisher exact $P = 0.29$) or vocal subscale (Fisher exact $P = 0.80$). However, the mother of the sole HUU infant with social withdrawal had the second highest CES-D score of all participants.

Accordingly, there was no association between poorer outcome on the BSID and maternal CD4 count < 350 cells/μl at delivery ($P = 0.53$), but four mothers (57%) of the seven HEU infants with social withdrawal (ADBB) had CD4 counts <350 cells/µl.

HEU infants born to mothers on cART had significantly poorer fine motor scaled scores than those on ZDV monotherapy ($P = 0.04$) although there were no significant differences in other domains of BSID and ADBB (Table 4). Stunting at 12 months was associated with social withdrawal ($P = 0.05$), but not reduced vocalisation on the ADBB ($P = 0.43$). There was no association between stunting and poorer outcome on the BSID cognitive ($P = 0.36$), language ($P = 0.66$) or motor ($P = 0.44$) composite scores and receptive ($P = 0.34$), expressive ($P = 0.32$), fine (0.42) or gross motor ($P = 0.5$) scaled scores. The numbers of underweight and wasted infants were too small for further comparisons.

Discussion

There was no difference in Bayley composite scores between HEU and HUU infants. This finding concurs with other African studies on children younger than 3 years [12–16]. Alimenti (Canada) reported no difference after adjusting for illicit drug exposure by the mothers of HEU infants [31].

The mean BSID III language scores of both groups, although still in the 'average' range, were lower than the cognitive and motor scores. A similar developmental

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Table 4 Neurodevelopmental outcome according to antenatal antiretroviral exposure

Antenatal ARV regime	cART *N* = 29	Zidovudine monotherapy *N* = 29	None (HUU) *N* = 38	*P*-value
BSID III Composite score – mean (SD)				
Cognitive	99.1 (12.2)	100.7 (11.2)	101.3 (7.8)	0.52
Language	89.9 (10.4)	90.9 (8.7)	92.5 (11.0)	0.56
Motor	93.6 (9.5)	97.6 (8.5)	97.8 (9.8)	0.14
BSID III Scaled scores – mean (SD)				
Receptive language	7.9 (1.8)	8.3 (2.3)	8.2 (1.9)	0.54
Expressive language	8.9 (2.0)	8.6 (2.1)	9.2 (2.2)	0.49
Fine motor	9.1 (1.2)	10.0 (1.7)	9.6 (1.3)	0.04
Gross motor	8.8 (2.5)	9.2 (1.7)	9.6 (2.5)	0.31
ABBB social withdrawal (%)	3 (10.3)	4 (13.8)	1 (2.6)	0.11
ABBB reduced vocalisation (%)	6 (20.7)	9 (31)	4 (10.5)	0.19

profile was described in a US study involving HEU infants from a lower socio-economic group [32]. Language quotients may also have been influenced by cultural factors such as unfamiliarity with the pictures and nature of objects used in the BSID III. Although studies have reported language deficits or late language emergence in HEU *vs*. HUU children [7, 10, 33], our cohort showed no difference. However, language delay in HEU infants may not be evident as early as 12 months of age [34].

Seven HEU infants (12%) and one (2.6%) HUU infant reached the ADBB threshold for social withdrawal behaviour. Puura reported a prevalence of 2.7% of social withdrawal in a study of 363 infants attending a well-baby clinic in Finland [35], while Guedeney reported 13% in a non-clinical community sample [36]. An earlier study on South African HIV-infected mother–infant dyads classified 31% of infants as socially withdrawn using the modified-ADBB; however, their study cohort included mothers with advanced HIV [37].

A higher proportion of HEU than HUU infants had abnormal vocalisation scores on the ADBB. Both HEU and HUU infants with decreased vocalisation also performed poorly on the BSID language subscales, suggesting subtle developmental language or emotional differences in these infants. A lower level of maternal education was not a confounder in this group. Previous studies have not explored the relationship between the ADBB vocal subscale and developmental outcomes. Molteno *et al.* found that infant emotional withdrawal on ADBB was a significant predictor of IQ at 9 years in children with foetal alcohol syndrome but did not report on individual subscales [30].

Although there was no significant group difference between caregiver CES-D scores, a high proportion of mothers scored above the threshold for psychiatric referral. South African studies have previously documented high prevalence rates of postnatal depression in mothers from lower socio-economic groups [38–41] as have other African countries [42, 43].

Parsons found an association between postnatal depression and adverse child developmental outcome in low- and middle-income countries [44], whereas we found no significant association between an elevated maternal CES-D score and abnormal infant ADBB ($P = 0.29$). However, the CES-D was administered at a single time-point and the sample size was small. Previous studies have associated prolonged depression with compromised infant development [44, 45].

HEU infants born to mothers on cART had lower fine motor scores (Table 4). There was no difference in other domains between cART-exposed and unexposed HEU infants, which concurs with previous findings regarding antenatal cART exposure [46, 47]. However, subgroups were small. Moreover, treatment with cART was also a marker of vulnerable maternal immunological health at the time of this study and we did not adjust for this in the analysis. This group of HEU mothers discontinued breastfeeding much earlier than would typically be the case in more resource-constrained sub-Saharan African settings, resulting in less exposure to cART or ZDV from breastfeeding but potentially increased the risk of infection.

The association of stunting and social withdrawal concurs with other sub-Saharan African studies relating growth measures to neurodevelopmental outcomes in young HIV-affected children [21]. However, macrocephaly in 13.8% of HEU infants was an unexplained finding not previously documented in research literature. Two of these children had language delay (composite scores 71 and 74) and were exposed antenatally to

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efavirenz suggesting a need for further investigation. No other studies have reported similar findings [32,47] including drug event registries [48, 49].

A limitation of this study was the small sample size due to the high attrition rate, which is common in populations faced with socio-economic adversity [50]. In addition, seven of the eight infants assessed as socially withdrawn on the ADBB did not attend follow-up assessments to confirm the ADBB findings. Transient factors such as illness, anaemia or hunger may result in an elevated ADBB score, and follow-up is recommended for clinical confirmation. The ADBB tool cannot be used in isolation to diagnose infant social withdrawal [35]. Another limiting factor is that not all children attended an audiological evaluation to rule out hearing loss as a cause for decreased vocalisation and delayed BSID language scores. Although groups were matched socio-economically, there was no evaluation of the home environment to ascertain differences in the level of stimulation. There is also selection bias in that initial recruitment by MIHS would have excluded high-risk pregnancies and preterm delivery, which are known risk factors associated with maternal HIV infection. However, the main strength of this study is the well-matched control group with adjustment for confounders and use of comprehensive neurodevelopmental assessment tools.

In conclusion, in this low-risk group of HEU and HUU infants from a single community, there was no difference in neurodevelopmental outcome at 12 months of age. These findings are encouraging; however, language delay in particular may only emerge on longitudinal follow-up as environmental factors become more influential on child development. Therefore, it will be important to determine whether neurological and behavioural differences detected in the small subgroup of HEU infants have long-term sequelae.

Acknowledgements

We thank the mothers, fathers and infants who generously donated their time to the MIHS study and without whose participation the study would not have been possible. We gratefully acknowledge the expert assistance provided by the staff at KIDCRU, Department of Paediatrics and Child Health, Tygerberg Academic Hospital, Stellenbosch University, Cape Town, South Africa and the Vaccine Evaluation Center, British Columbia Children's Hospital, University of British Columbia, Vancouver, Canada. We would like to thank R/N Marchalaine Hendricks, Mr Carlos Moffat, Staff Nurse S. Sylvester, for their practical and logistical contributions. We greatly acknowledge the data provided by co-workers Moleen Zunza, Gareth Mercer, Emma Kalk, advice and training from Professor Antoine Guedeney regarding the use of ADBB, and the review of videos for ADBB assessments by Dr Anusha Lachman, and Professor Kaija Puura. We would like to acknowledge Professor Rhoderick Machekano, Professor Martin Kidd and Maxwell Chirehwe for statistical analysis and advice on sample size calculation. This work was supported by the HOPE Cape Town Trust (PBO (SA) No 93/00/24/843 - 053-417NPO (SA)) 2013 – 2015, Harry Crossley Foundation 2013–2015 (SU-PT-14/10-000106) and South African Medical Research Council. This work was supported by a Major Thematic Grant from the Peter Wall Institute for Advanced Studies, University of British Columbia [grant number F0906208] and the Canadian Institutes of Health Research Canada-Hope programme [grant number CH1-106949]. Dr. Slogrove was supported by research fellowships from the Canadian Institutes of Health Research Canada-Hope Programme, The Canadian HIV Trials Network International Fellowship and the South African National Health Scholarship Programme. Dr. Bettinger is a Michael Smith Foundation for Health Research Scholar.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S5. Differences between MIHS participants retained versus those lost: 12 months visit

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Chapter 5: Neurodevelopmental and behavioural outcomes of HIV-exposed uninfected and HIV-unexposed children at 2-3 years of age in Cape Town, South Africa. Ethics no: N13/03/028

Longitudinal neurodevelopmental follow-up of infants is necessary to detect milder deficits not evident at a younger age(Laughton et al., 2010).Furthermore, the BSID findings at two years of age are more predictive of childhood intelligence than in infancy (Girault et al., 2019). Adult caregivers can influence a child's cognitive ability by language-promoting activities such as book-sharing (Kalb & Van Ours, 2014), while universal risk factors such as stunting and poverty are associated with poorer developmental and behavioural outcome (Sudfeld, Mccoy, Danaei, Fink, & Ezzati, 2015; Walker, Wachs, Grantham-Mcgregor, Black, Nelson, Huff, et al., 2011).

Previous studies on HEU children detected later emergence of language deficits(Smith, Puka, Sehra, Read, & Bitnun, 2017).Our cohort however showed no significant differences in language scores at 11-14 months, although there were subtle behavioural differences found on the ADBB, including decreased vocalization in HEU infants, which warranted further follow-up. The behaviour of very young HEU children has not been systematically studied. This is important, since early detection of emotional difficulties creates the opportunity to improve child mental health and social adjustment, thereby alleviating maternal stress (Taylor & Biglan, 1998).

Our study also highlighted the difficulties in interpreting results evident from developmental assessments in children from a different cultural and socio-economic context, hence the importance of selecting inappropriate comparison group for longitudinal follow=up (Bodeau-Livinec et al., 2019).Unfortunately, high attrition rates were a major study limitation, and the majority of infants found to be "at risk "of social withdrawal at the 12-month visit were lost to follow-up and did not attend the visit at year 2. The finding that more behavioural problems were reported in HUU children does raise the possibility that caregivers of these children who returned for this follow-up visit may have already harboured concerns, leading to a selection bias.

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AIDS Care

Psychological and Socio-medical Aspects of AIDS/HIV

ISSN: 0954-0121 (Print) 1360-0451 (Online) Journal homepage: https://www.tandfonline.com/loi/caic20

Neurodevelopmental and behavioural outcomes of HIV-exposed uninfected and HIV-unexposed children at 2–3 years of age in Cape Town, South Africa

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To cite this article: P. E. Springer, A. L. Slogrove, M. Kidd, E. Kalk, J. A. Bettinger, M. M. Esser, M. F. Cotton, M. Zunza, C. D. Molteno & M. Kruger (2019): Neurodevelopmental and behavioural outcomes of HIV-exposed uninfected and HIV-unexposed children at 2–3 years of age in Cape Town, South Africa, AIDS Care, DOI: 10.1080/09540121.2019.1637506

To link to this article: https://doi.org/10.1080/09540121.2019.1637506

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AIDS CARE
https://doi.org/10.1080/09540121.2019.1637506

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Neurodevelopmental and behavioural outcomes of HIV-exposed uninfected and HIV-unexposed children at 2–3 years of age in Cape Town, South Africa

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ABSTRACT

Successful vertical HIV transmission prevention programmes (VTP) have resulted in an expanding population of HIV-exposed uninfected (HEU) infants whose growth, health and neurodevelopmental outcomes could have consequences for future resource allocation. We compared neurodevelopmental and behavioural outcomes in a prospective cohort of 2–3 year old HEU and HIV-unexposed uninfected (HU) children.

Women living with and without HIV and their infants were enrolled within three days of birth from a low-risk midwife obstetric unit in Cape Town, South Africa during 2012 and 2013, under WHO Option A VTP guidelines. HIV-uninfected children aged 30–42 months were assessed using the Bayley scales of Infant Development-Third edition (BSID) and Strengths and Difficulties questionnaire (SDQ).

Thirty-two HEU and 27 HU children (mean birth weight 3048g vs 3096g) were assessed. HEU children performed as well as HU children on BSID cognitive, language and motor domains. Mean scores fell within the low average range. Mothers of HEU children reported fewer conduct problems but stunting was associated with increased total difficulties on the SDQ.

HEU and HU children's performance on the BSID was similar. In this low-risk cohort, HIV exposure did not confer additional risk. Stunting was associated with increased behavioural problems irrespective of HIV exposure.

ARTICLE HISTORY
Received 25 January 2019
Accepted 29 May 2019

KEYWORDS
neurodevelopment; behaviour; HIV-exposed uninfected pre-school child

Introduction

There is increased recognition of the need to understand and improve the long-term neurodevelopmental outcome of HIV-uninfected children born to women living with HIV, particularly in low and middle-income countries (Evans, Jones, & Prendergast, 2016). In South Africa, the HIV vertical transmission rate has decreased to below 5% (Goga et al., 2015), but the high antenatal HIV prevalence has resulted in an expanding population of HIV-exposed uninfected (HEU) children with implications for their health, educational and social wellbeing (UNAIDS, 2018).

Evidence regarding neurodevelopmental outcome in HEU children remains conflicting. Studies from high-income countries found language delay and impairment in HEU toddlers and children respectively (Caniglia et al., 2016; Rice et al., 2013; Sirois et al., 2013). A meta-analysis reported poorer cognitive and motor performance in six of twelve cohorts of young HEU versus HIV- unexposed (HU) children tested on the Bayley Scales of Infant and Toddler Development, and lower cognitive and motor scores in HEU infants exposed to antiretroviral drugs (ARV). However, the six studies assessed as high quality, all in the United States, showed no difference in outcome between HEU and HU children (McHenry et al., 2018). Findings in Africa are mixed; a recent study described poorer cognitive and motor development in South African HEU infants (Le Roux et al., 2018) while poorer language outcomes were found in Kenyan toddlers (Alcock, Abubakar, Newton, & Holding, 2016) and children in the Democratic Republic of Congo (Van Rie, Mupuala, & Dow, 2008). Others

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found no difference between young HEU and HU children (Chaudhury et al., 2017; Ngoma et al., 2014) and no adverse effects from ARV exposure (Chaudhury et al., 2018). However methodologies vary with regards to inclusion criteria e.g., preterm infants, use of well matched control groups, and choice of child development assessment tools, while changing ARV regimes and other confounders may also influence findings.

There is limited information on behavioural outcomes in young HEU children. Most research has focused on school-going children and is confounded by social and educational factors (Kandawasvika, Gumbo, & Kuona, 2016; Sharp et al., 2014; Sherr, Skeen, Hensels, Tomlinson, & Macedo, 2016; Sherr et al., 2017; Sipsma et al., 2013). Detection of problems at a younger age provides an opportunity for earlier intervention (Holtz, Fox, & Meurer, 2015). Encouragingly, the South African government has prioritised investment in the first 1000 days (from conception to 2 years of age), adopting strategies to address modifiable factors, potentially enabling children to fulfil their cognitive and socio-emotional potential (Western Cape Government Department of Health, 2017).

We previously reported similar outcomes on Bayley Scales of Infant and Toddler Development-Third edition (BSID) in HEU and HU infants with subtle language and behavioural differences at 11–14 months (Springer et al., 2018). However significant deficits may only emerge at a later age (Smith, Puka, Sehra, Read, & Bitnun, 2017). Here we present the follow-up findings of a prospective cohort study comparing the neurodevelopmental and behavioural profile of HEU and HU children at age two to three years old. Secondary outcomes of interest included comparison of BSID scores (developmental trajectory) at one and three years of age and identification of factors associated with adverse outcomes.

Methods

This neurodevelopmental study was nested in the Mother Infant Health Study (MIHS), primarily designed to compare infectious morbidity in HEU and HU infants. Study methods were described previously (Slogrove et al., 2017). Women living with and without HIV and their infants were enrolled within 72 hours of delivery at a low-risk midwife obstetric unit. All shared similar cultural and socioeconomic characteristics. Inclusion criteria were newborns weighing more than 2000 g, ≥34 weeks gestation with no perinatal complications.

Participants

Women from the MIHS cohort with children aged between 30 and 42 months were invited for a neurodevelopmental and behavioural assessment at Tygerberg Academic Hospital. A developmental paediatrician and an experienced tester performed the assessments blinded to the children's HIV-exposure status. They initially assessed children together, in order to reach consensus on scoring. A behavioural screening questionnaire was read to the caregiver in her preferred language (English, Afrikaans or isiXhosa) assisted by a translator, allowing time for clarification. Thereafter, the assessor documented her responses. Physical examination and anthropometry were performed after completion of developmental assessments. Appointments were rescheduled if the child was physically unwell or tired.

At the time, the vertical transmission of HIV prevention guidelines of the Western Cape (Option A) recommended that pregnant women living with HIV with a CD4 count ≤ 350/μl or WHO stage 3 or 4 disease received triple drug antiretroviral therapy (ART); the remainder received zidovudine (ZDV) monotherapy from 14 weeks gestation and single-dose nevirapine (NVP) at delivery, while newborns received NVP and ZDV for one week (South African National Department of Health; South African National AIDS Council, 2010).

Both MIHS and neurodevelopmental studies were approved by Stellenbosch University's Human Research Ethics Committee (N13/03/028 and S12/0/009) and the Children's and Women's Research Ethics Board at the University of British Columbia (H12-01181-A010).

Measures

Development was assessed using the cognitive, language and motor scales of the BSID (Bayley, 2006) with no adaptations to test materials. The BSID was administered in the child's home language using a translator. The United States BSID composite score norms classify developmental delay as moderate (70-85) and severe (<70). For this study, BSID composite scores below 85 (>1 standard deviation below the mean) were classified as "poorer neurodevelopmental outcome". Children with significant delays were referred to the appropriate developmental service.

Behaviour was assessed by direct interview using the pre-school version of the Strengths and Difficulties Questionnaire (SDQ) with Afrikaans and isiXhosa translations (Goodman, 1997). The instrument has 25 questions divided into five subscales: emotional symptoms, hyperactivity, conduct and peer relationship problems, and prosocial behaviour. The first four subscales combine to form internalising and externalising scores, and a summative Total Difficulties Score (TDS). The cut-off scores for the SDQ TDS and subscales have not been

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validated for South African children, thus statistical analysis was limited to group comparison (Hoosen, Davids, de Vries, & Shung-King, 2018). Decisions regarding referral for formal evaluation were made in consultation with the caregiver.

Weight, height and head circumference were converted into standardised z-score anthropometric values utilising WHOAnthro (WHO, 2010) giving weight-for-age (WAZ), height-for-age (HAZ), weight-for-height (WHZ) and head circumference-for-age (HCZ) Z-scores. Children were further classified as underweight (WAZ < −2 Z), stunted (HAZ< −2 Z) and/or wasted (WHZ < −2 Z), macrocephalic (HCZ > 2Z) or microcephalic (HCZ < −2Z).

Baseline maternal sociodemographic information, maternal education, gestation, antenatal exposures, Centre for Epidemiological Depression (CES-D) scores at 12 months postpartum, newborn anthropometry, duration of breastfeeding, placental pathology, previous hospitalisation, and caregiver consistency were obtained from the MIHS database, direct interview and the child's immunisation record. Macroscopic and microscopic features of placentae were available on 46 participants (78%) (Kalk et al., 2017). Caregiver consistency indicated that the child had not been separated from their biological mother since birth. Mothers were also questioned regarding book-reading to their children.

Statistical analysis

Statistica 13 (TIBCO Software Inc.) was used for analysis. Cross tabulation with Chi-square test was used to compare categorical variables between groups (HEU vs HU). Effect size was reported using Cohen's d. For continuous measurements, one-way ANOVA was used for group comparison. When comparing neurodevelopmental scores at 12 and 30 months, mixed model ANOVA was performed with participants as random effect, and time, group and time*group interaction as fixed effects. Post-hoc testing was done using Fisher-LSD and Games-Howell testing where homogeneity of variants did not apply. Associations between poorer neurodevelopmental outcome and risk factors, including maternal education, antenatal exposures, placental pathology, breastfeeding and anthropometry, were assessed using a mixture of correlations and one-way ANCOVA.

Results

Of the original 176 mother-infant dyads (94 HEU and 82 HU) in the MIHS on whom baseline data were available, 96 (58 HEU and 38 HU) infants had neurodevelopmental assessments at age 12 months (Springer et al., 2018) and 59 children (32 HEU and 27 HU), were assessed at age 30–42 months. The proportion of HEU and HU infants either retained or not retained for neurodevelopmental assessment had similar baseline characteristics except for lower median birth weight in those with neurodevelopmental assessments compared to those not retained (3070 g vs 3199 g, $p = 0.03$). Of the 59 participants in the neurodevelopmental study, 29 HEU and 24 HU children had previous BSID evaluations at age 12 months.

Maternal and child characteristics are shown in Tables 1 and 2. In total, 58 children were accompanied by their biological mothers and one by the grandmother. Mothers of HEU children were older, attained a lower grade of schooling, and were less likely to have planned their pregnancy or breastfed than mothers of HU children (Table 1). Only one mother of an HEU child reported illicit antenatal drug use. Thirteen (40.6%) HEU children were exposed in utero to combined antiretroviral therapy (cART), and 19 (59.4%) to zidovudine.

All except one HU child were primarily cared for by their mothers and caregiver consistency amongst the two groups was similar (HEU 81% vs. HU 89%, $p = 0.41$). Mothers read books to six (18.7%) HEU and four (14.8%) HU children, however only eight (four HEU and four HU) children were read to more than once a week. Eight (25%) HEU and three (11%) HU children required hospitalisation after one year of age ($p = 0.52$), without reported neurological sequelae. The HU group had lower WHZ ($p = 0.04$), but none were underweight. However, two HEU (6%) and four HU (14.8%) children were stunted.

Four HEU children had macrocephaly (12.5%), absent at birth, but documented in three of the children at both 12 months and 30–42 months. Two macrocephalic children had moderate language delay, one with *in utero* ZDV exposure, and the other with ART exposure; the latter had normal neuroimaging and tested negative for glutaric aciduria (Govender, Mitha, & Mubaiwa, 2017). No child had microcephaly.

Results of the neurodevelopmental and behavioural assessments are shown in Table 3. All 59 children completed BSID assessments. There was no significant difference between HEU and HU infants for cognitive, language, or motor domains after adjustment for stunting and maternal education. No child had severe delay in any BSID domain. HEU children with *in utero* ART exposure performed as well as those with single ARV exposure (data not shown).

All caregivers completed the SDQ. Mothers of HEU children reported fewer behavioural problems. However after adjustment for stunting and maternal education, only conduct problems (Cohen's $d = 0.54$, $p = 0.02$,)

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Table 1. Maternal and perinatal characteristics of HIV-exposed uninfected and HIV-unexposed children at the 2 year follow-up visit of the MIHS cohort.

Characteristic	HIV exposed uninfected ($n = 32$)	HIV unexposed ($n = 27$)	p-value
Maternal age at delivery (years) mean (SD)	28.2 (5.2)	25.3 (5.2)	0.04
Maternal home language N (%)			
Afrikaans	3 (9.4)	4 (14.8)	0.54
isiXhosa	26 (81.2)	21 (77.8)	
Other African language	3 (9.4)	2 (7.4)	
Ethnicity N (%)			
Black African	29 (90.6)	23 (85.2)	0.55
Mixed ancestry	3 (9.4)	4 (14.8)	
Maternal marital status N (%)			
Married	8 (25.0)	8 (29.6)	0.86
Never married	21 (65.6)	19 (70.4)	
Widowed/divorced/ separated	3 (9.4)	0 (0.0)	
Maternal education			
Years of education – mean (SD)	10.3 (1.7)	11.1 (1.3)	0.04
≥Grade 12 *N* (%)	11 (34.7)	14 (51.8)	
Grades 10–11 *N* (%)	12 (37.4)	11 (40.7)	
Grades 8–9 *N* (%)	7 (21.8)	1 (3.4)	
≤Grade 7 *N* (%)	2 (6.3)	1 (3.4)	
Primiparous *N* (%)	5 (15.5)	7 (25.9)	0.33
Planned pregnancy *N* (%)	6 (18.8)	11 (42.3)	0.04
Gestation in weeks at first antenatal visit – mean (SD)	21.9 (6.8)	21.4 (6.8)	0.81
Tobacco use during pregnancy *N* (%)	4 (12.5)	1 (3.7)	0.21
Alcohol use in pregnancy *N* (%)	8 (25.0)	4 (14.8)	0.33
Maternal CD4 percentile at birth – mean (SD) (*N*)	28.4 (8.2) ($N = 29$)	38.8 (8.0) ($N = 27$)	<0.01
Infant gender, male *N* (%)	19 (59.4)	13 (48.2)	0.39
Gestation at delivery in weeks – mean (SD)	38.7 (1.5)	39.0 (1.6)	0.49
Late preterm (36–37 weeks) *N* (%)	2 (6.2)	2 (7.4)	
Low birth weight < 2500 g *N* (%)	3 (9.4)	1 (3.7)	0.38
Birth weight (g) – mean (SD)	3048 (380)	3096 (445)	0.65
Birth length (cm) – mean (SD)	48.8 (3.2)	48.5 (4.0)	0.78
Breastfeeding duration in months – mean (SD)	5.5 (4.7)	13.7 (8.8)	<0.01
Breastfeeding at age 2 weeks *N* (%)	13 (40.6)	27 (100)	<0.01
Still breastfeeding at 6 months *N* (%)	3 (9.3)	18 (66.7)	<0.01
Type of Housing *N* (%)		$N = 26$*	
Formal Housing	16 (50)	15 (59.2)	0.56
Informal Housing	16 (50)	11 (42.7)	
Subsequent pregnancy *N* (%)	6 (19)	4 (14.8)	0.74
Maternal employment *N* (%)	15 (46.9)	11 (40.8)	0.64
Regular contact with father (*N*)	12 (37.5%)**	13 (48%)***	0.24

MIHS = Mother Infant Health Study; SD = standard deviation.
*One value missing; **two fathers demised; ***one father demised.

Table 2. Sociodemographic and anthropometric characteristics of HIV-exposed uninfected and HIV-unexposed children at 2–3 years of age in the MIHS cohort.

Characteristic	HIV-exposed uninfected $N = 32$	HIV-unexposed $N = 27$	P value
Age at assessment in months – mean (SD)	36 (2.6)	35 (2.6)	0.15
Gender (male) *N* (%)	19 (59.4)	13 (48.2)	0.39
Currently living with mother *N* (%)	32 (100.0)	26 (96.3)	0.46
Temporary change in primary caregiver *N* (%)	6 (18.8)	3 (11.1)	0.49
Daycare attendance *N* (%)	8 (25.0)	14 (51.8)	0.64
Head circumference-for-age z-score – mean (SD)	0.39 (1.38)	0.07 (0.87)	0.31
Weight-for-age z-score – mean (SD)	0.36* (0.87)	0.09 (0.69)	0.19
Height-for-age z- score – mean (SD)	−0.90 (0.85)	−0.83 (0.95)	0.77
Weight-for-height z-score – mean (SD)	1.26* (0.98)	0.77 (0.77)	0.04

MIHS = Mother Infant Health Study SD = standard deviation.
Missing Data *One participant value missing.

Table 3. Neurodevelopmental outcomes of HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HU) children according to the Bayley Scales of Infant and Toddler Development 3rd edition (BSID) and the Strengths and Difficulties Questionnaire pre-school version (SDQ).

Assessment	HIV exposed uninfected ($N = 32$)	HIV unexposed ($N = 27$)	P value	Cohen's D effect size (CI)
BSID Domain Composite scores-mean (SD)				
Cognitive	87.5 (5.2)	88.5 (7.2)	0.61	0.16 (−0.36, 0.68)
Motor	93.9 (7.9)	94.5* (7.8)	0.73	0.08 (−0.45, 0.61)
Language	89.9 (6.6)	90.5 (8.0)	0.82	0.09 (−0.44, 0.61)
Scaled scores-mean (SD)				
Fine Motor	9.4 (1.7)	9.4 (1.6)	0.90	0.04 (−0.48, 0.57)
Gross Motor	8.6 (1.7)	8.6* (1.3)	0.73	0.06 (−0.47, 0.59)
Receptive Language	8.1 (1.4)	8.2 (1.5)	0.97	0.06 (−0.46, 0.59)
Expressive Language	8.4 (1.3)	8.5 (1.5)	0.65	0.1 (−0.42, 0.63)
SDQ scores-mean(SD)				
Total difficulties	13.4 (5.0)	15.8 (5.3)	0.05	0.47 (−0.07, 1.00)
Externalising problems	8.4 (3.7)	10.4 (4.0)	0.04	0.51 (−0.02, 1.04)
Internalising problems	5.1 (2.9)	5.4 (2.7)	0.49	0.14 (−0.39, 0.66)
Conduct problems	3.2 (1.8)	4.3 (2.3)	0.02	0.54 (0.01, 1.07)
Hyperactivity	5.2 (2.6)	6.1 (2.6)	0.20	0.35 (−0.18, 0.88)
Emotional problems	3.5 (1.8)	3.0 (2.0)	0.26	0.27 (−0.26, 0.80)
Peer problems	2.0 (1.4)	2.0 (1.6)	0.99	0.05 (−0.57, 0.48)
Prosocial behaviour	7.2 (1.7)	7.0 (2.2)	0.54	0.09 (−0.62, 0.43)

BSID Bayley Scales of Infant and Toddler Development- Third edition CI Confidence interval SD Standard deviation SDQ Strengths and difficulties questionnaire (pre-school version).
*=one value missing.

remained significantly higher in the HU participants while externalising difficulties showed a trend towards significance in HU children (Cohen's $d = 0.51$, $p = 0.05$). When applying British SDQ cut-off scores, there were twelve children (20.3%), (six HEU and six HU), with "very high" TDS, eleven children (18.6%), (two HEU and nine HU) with "very high" conduct scores

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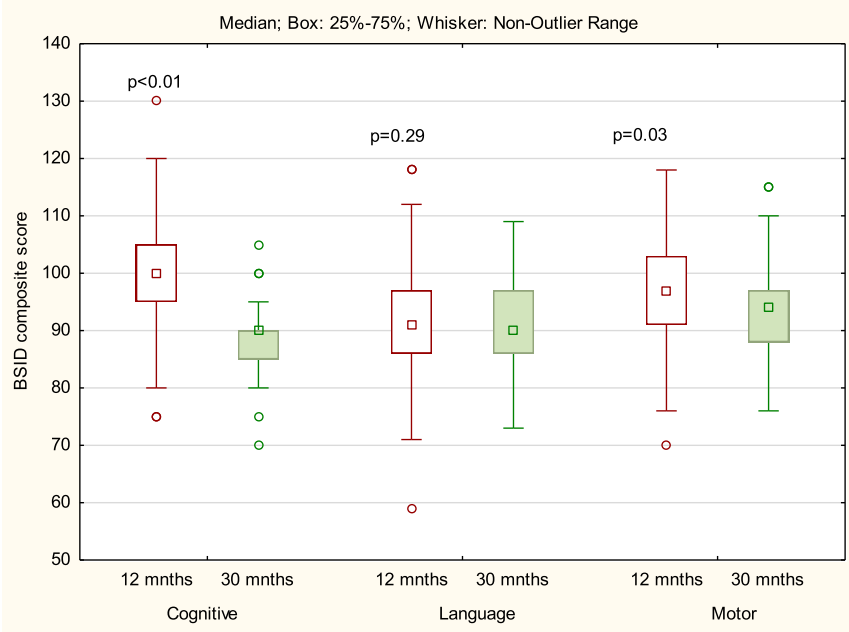

Figure 1. Comparison of Bayley composite scores of MIHS cohort at 12 months ($n = 96$) and 30 months ($n = 59$) visits. *Fifty three children had assessments at both 12 and 30 month visits.

and thirteen (22%), (six HEU and seven HU) with "very high" hyperactivity scores.

Stunted children (two HEU and four HU) had lower BSID motor scores (mean 88.0, SD 6.8) than those with normal height (93.8, SD 7.6; $p = 0.05$) and a trend towards lower fine motor scores (8.3 (SD 1.0) versus 9.5 (SD 1.6); $p = 0.08$). Stunting was also associated with higher SDQ TDS (17.8, SD 1.3) versus that of non-stunted children (14.1, SD 5.4; $p < 0.01$).

Higher level of maternal education was significantly associated with improved motor (Pearson's $r = 0.4$, $p < 0.01$), less strongly with cognitive ($r = 0.25$, $p = 0.06$) but not language domains ($r = 0.15$, $p = 0.27$). Antenatal alcohol and tobacco exposure were not associated with poorer outcome on the BSID or SDQ in either group. Mothers who had experienced depressive symptomatology at 12 months postpartum (CES-D. > 15) did not report higher child SDQ scores ($p = 0.18$) and this did not differ by group. Breastfeeding did not confer an advantage on behavioural outcomes in either group.

Serial BSID assessments of children tested at twelve months and 30–42 months ($n = 53$) showed significant decline in cognitive scores ($p < 0.001$) with similar decreases in HEU and HU groups (Figure 1). There was a statistical but not clinically significant decline in motor scores for the combined cohort ($p = 0.03$). Cognitive scores increased in only three (5.6%) HEU children at the second assessment, language scores increased in eight (27.5%) HEU and six (25%) HU children, and motor scores increased in ten HEU (34%) and six (25%) HU children.

Neither low placental weight nor pathological lesions (acute and chronic chorioamnionitis, chronic villitis, placental insufficiency and subacute fetal hypoxia) were associated with poorer neurodevelopmental or behavioural outcomes; a finding that persisted when stratified by HIV-exposure status.

Discussion

We demonstrated similar outcomes for low-risk HEU and HU children on the BSID. No child in our cohort had severe developmental delay, however this may be attributed to excluding all infants with preterm or perinatal complications. The high proportion of HEU children with macrocephaly observed at age 12 months was sustained at age 30–42 months (Springer et al., 2018). The neurodevelopmental findings are in keeping with observations from recent studies conducted in Zambia and Botswana (Chaudhury et al., 2017; Ngoma et al., 2014). Our HEU cohort resembled that from Botswana in terms of maternal ARV regimen and low rate of breastfeeding. In contrast, a multicentre study of older Thai and Cambodian children found slightly lower verbal, full scale IQ and Binet Bead memory scores in HEU children although the clinical significance of this finding was uncertain (Kerr et al., 2014).

This cohort had a lower prevalence of stunting than the national average of 27% (Said-Mohamed, Micklesfield, Pettifor, & Norris, 2015). Four of the six stunted children (three HU and one HEU) were breastfed for a

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duration of four to six months while the other two HEU infants received formula feeds. Other potential causes for short stature were not investigated. However stunting was associated with lower BSID motor scores similar to other African studies; and was more prevalent in the HU group (Casale, Desmond, & Richter, 2014; McDonald et al., 2013).

Socioeconomic disadvantage leading to lack of educational opportunities is an independent risk factor for poor performance on neurodevelopmental assessments and may have accounted for the "low average" BSID composite scores of the cohort (Burchinal, Roberts, Hooper, & Zeisel, 2000), potentially overriding or masking the effects of other factors. Interpretation of the significance of these generally low-average scores is limited, by the lack of validated South African BSID norms for two to three year olds. A Malawian study argued that US BSID norms cannot be applied to categorise neurodevelopmental delay in other cultural contexts where child-rearing practices differ (Cromwell et al., 2014). This underlines the importance of comparing HEU with HU participants from a similar background, in the absence of local norms, as in our cohort.

Ballot et al reported declining BSID language scores between 9 and 19 months and low average cognitive scores in South African infants from a lower socioeconomic group. (Ballot et al., 2017). Our cohort's language quotients although similarly low, did not decrease over time, however there was a significant decline in their cognitive scores. This may partly be attributed to certain test items. Colour discrimination is an essential knowledge requirement of the BSID cognitive scales at 30 months, and tasks involving identification and naming of colours depend on early childhood education (Bonnier, 2008). Book-reading has also been associated with improved cognitive and language outcomes in young children (Raikes et al., 2006). Since only eight (13.5%) mothers read to their child more than once a week, it is unsurprising that we did not see this effect of book-reading. Early childhood education and book-reading are both areas that policymakers could target to improve cognitive outcomes in young children.

Mothers of HEU children reported fewer behavioural difficulties than the HU group. Reasons for this were unclear. Mothers with HIV are in a care system that may also give them access to psychosocial support which could indirectly assist parenting and coping strategies. Similar findings were described in a Thai cohort although differences did not reach statistical significance (Sanmaneechai, Puthanakit, Louthrenoo, & Sirisanthana, 2005) while Kerr found no difference in behavioural outcome in older Thai and Cambodian HEU and HU children (mean age 7.3 years) (Kerr et al., 2014). Smith reported poorer adaptive and socialisation skills in young HEU children, but suggested that cultural differences might be a confounding factor (Smith et al., 2017). We did not fully explore risk and protective factors; our cohort generally had high SDQ externalising behaviour scores possibly related to family stressors and socioeconomic adversity (Holtz et al., 2015; Hunt & Tomlinson, 2018).

Amongst other factors, breastfeeding can improve neurodevelopment although the lack of a dose-response effect suggests additional confounders (McCrory & Murray, 2013). This advantage was not evident in our cohort, but given that breastfeeding was not universally recommended to HIV positive mothers during our study, we were not fully able to interrogate this (Zunza et al., 2018). Furthermore, there was no association between placental pathology and neurodevelopmental delay as found previously (Hodyl et al., 2017). Likewise depressive symptomatology at 12 months postpartum was not associated with poorer behavioural outcome at 3 years. However, maternal mental health should be evaluated at multiple antenatal and postnatal time-points to determine duration and severity of depression (Rotheram-Fuller et al., 2018).

Strengths of the study included contemporaneous HEU and HU participant groups, which partially adjusted for confounders and enabled between-group comparisons. All children lived with their biological mothers and caregiver consistency was similar in both groups.

Limitations included small sample size with lower statistical power. Attrition was high throughout the MIHS study. There were similar numbers of HEU and HU in the non-retained group; the lower infant birth weight of participants tested at 2–3 years of age compared with the non-retained group was not clinically significant. Previous studies have reported high attrition in young HEU participants due to mothers returning to employment (Sidze et al., 2015; Williams et al., 2008), but our participants were lost to follow up, so the reason for attrition is not known. We did not investigate other aspects of the home environment (e.g., quality of caregiving) that have also been shown to improve early neurodevelopmental outcome (Bass et al., 2016) and SDQ scores reflected only the mothers' perceptions. Finally, interpretation of results of assessments without contextually relevant and validated tools can be challenging in different cultural environments.

In conclusion, the developmental and behavioural outcome of pre-school HEU children was equivalent to that of a well-matched HU control group from a similar socio-economic background while HEU children were reported to exhibit fewer conduct problems. Thus in

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this cohort of term HEU children born to women with low-risk pregnancies and without advanced maternal HIV disease, HIV-exposure did not confer additional risk. Stunting was nevertheless associated with increased behavioural problems, regardless of HIV exposure.

Future recommendations include additional developmental surveillance for both HEU and HU children living in impoverished circumstances (Bonnier, 2008; Slogrove et al., 2018). Recent initiatives such as the "First 1000 days Campaign" involving partnership between the Western Cape Social Development and Health departments could provide caregiver education, counselling and support to optimise children's cognitive and emotional development as suggested by the WHO Nurturing Care Framework (Western Cape Government Department of Health, 2017) (WHO, 2018).

Acknowledgements

We thank the mothers, fathers and infants who generously donated their time to the MIHS. We thank SRN Ronel Barnard for her assistance with the assessments and data entry, and SRN Marchalaine Hendricks, Mr Aviwe Cweya, Staff Nurse S. Sylvester and Mr Carlos Moffat for their practical and logistical contributions. We acknowledge the study assistance provided by the staff at FAMCRU, Paediatrics and Child Health, Tygerberg Academic Hospital, Stellenbosch University and the Vaccine Evaluation Center, BC Children's Hospital, University of British Columbia, Vancouver, Canada.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by HOPE Cape Town Trust (PBO (SA) No93/00/24/843-053-417NPO(SA) 2013-2016, South African Medical Research Council, the Harry Crossley Foundation, South Africa, National Institute of Health Major Thematic Grant from the Peter Wall Institute for Advanced Studies, University of British Columbia [grant number F0906208] and the Canadian Institutes of Health Research Canada-Hope Programme [grant number CH1-106949] Dr Slogrove receives salary support from the Fogarty International centre of the National Institute of Health under award number 1K43TW010683 and the CIPHER Grantee Programme of the International AIDS Society (2017/518-SLO). Dr Bettinger is a Michael Smith Foundation for Health Research Scholar. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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CHAPTER 6: Use of a child development assessment tool in a resource-constrained healthcare setting: a correlational study

(For Submission to: South African Journal of Psychology)

ABSTRACT

The Molteno Adapted Scale (MAS) is a developmental screening tool for children up to five years of age, used by medical practitioners in the Western Cape province of South Africa. It generates sub-quotients for language, personal/social, fine and gross motor domains. The general quotient is calculated as the average of all four sub-quotients, with a score <85 indicating risk for global developmental delay. In this study, our objective was to explore the relationship between the MAS and Bayley Scales of Infant and Toddler Development-3rd edition (BSID) identified as a comprehensive assessment reference measure. We determined Pearson correlation coefficients for the MAS and BSID across similar domains in one-year-olds (n=90) and two-to-three-year-old children (n=53). The Bland Altman analysis was used to detect bias between MAS and the BSID language, gross motor and fine motor scores. This largely normative cohort was enrolled in a longitudinal neurodevelopmental sub-study of the Mother and Infant Health Study, which compared children who were HIV-exposed uninfected with an HIV-unexposed group. Correlation was generally moderate to high between MAS and BSID domains, but was low between MAS and BSID fine motor domains in one-year-olds. Discordance between the MAS and BSID language and motor scores was greatest at the upper- and lower-performance ranges. Thus, although correlations appeared promising, future studies are necessary to standardise the operational procedures of the MAS and validate it across a wider age range, including children with varying degrees of delay.

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1. INTRODUCTION

There is a need for child development assessment tools (CDAT) in low- and middle-income countries (LMIC) to screen and comprehensively assess children for developmental delay in both clinical and research contexts (Sabanathan, Wills, & Gladstone, 2015). Since access to psychologists is limited in LMIC settings (Berger, 2013), healthcare professionals including general and specialist clinicians are best positioned to detect developmental delay in infancy and early childhood. In South Africa, developmental and community paediatricians are often tasked with referring children for specialised intervention and educational placement. In these situations, it is vital not to wrongly classify children as intellectually disabled (Luiz, Foxcroft, &Tukulu, 2009).

The Molteno Adapted Scale (MAS) is a developmental screening tool for young children (aged six weeks to five years) (Appendix I). It was conceptualised by Professor Christopher Molteno, a developmental paediatrician at the Red Cross War Memorial Children's Hospital in Cape Town, South Africa (Molteno, 1987) and details of its origins have been described previously (Honeth et al; 2018). The tool was designed for use by developmental and community medical practitioners working in public health clinics with resource constraints. It is time- and cost-effective, requiring limited equipment that is locally accessible and does not require a certified training course or licensing fees, thus a useful tool for resource-constrained settings. Unlike most screening tools, the MAS generates a general quotient (GQ) and developmental sub-quotients in the gross motor, fine motor, language and personal/social domains, thus quantifying delay in specific areas. Change in quotients over time can be used to track longitudinal developmental trajectories. A recent study comparing the MAS with the Griffiths Mental Development Scales-Extended-revised (GMDS-ER), showed adequate diagnostic accuracy to justify its continuing use in South African toddlers (Honeth et al., 2018). MAS GQ scores less than 83 (versus 85) were identified as the optimal cut-off, below which children were deemed "at risk" for global developmental delay.

The first and second editions of the Bayley Scales have been used in international research, including South Africa (Richter, & Grieve, 1991) and the second edition was found to be predictive of "at-risk" status for late school entry in South African children (Richter et al., 2015). The latest version, viz. the Bayley Scales of Infant and Toddler Development-3rd edition (BSID), was standardized on a population that included children with learning difficulties (Bayley, 2006). This comprehensive developmental diagnostic tool includes cognitive, language and motor scores, has been applied globally as a gold standard in relation to evaluating screening tests, and was previously used in this manner to assess three screeners in a low-income region of Columbia (Rubio-Codina, Araujo,

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Attanasio, & Mu, 2016).

In the South African setting, the Mother and Infant Health Study (MIHS) cohort included few children with significant global developmental delay (MAS GQ<85), so we were unable to test the diagnostic accuracy of the MAS and establish its validity as a screening tool for global developmental delay. In the present correlational study we thus explored the relationships between the MAS and BSID in a predominantly normative population sample which included infants (11-14 months) and young children (2-3 years) from socio-economically disadvantaged communities.

2. MATERIALS AND METHODS

2.1.Study design and selection of participants

Data collected from the neurodevelopmental sub-study of the MIHS were extracted for more comprehensive statistical analysis (Springer et al., 2018). Inclusion criteria for this cohort study included birth weight more than 2000g, gestation more than 34 weeks with no peri-natal complications or congenital neurological conditions (Slogrove et al., 2017).

2.2.Assessment measures

Participants were tested on both the BSID and MAS at two time-points, i.e. aged 11-14 months, and again at 30-42 months of age. The MAS and BSID were administered on the same day, but an effort was made to alternate the sequence of the assessments, and testing was discontinued if the child was tired or uncooperative. Two developmental paediatricians (PS and HS) initially completed five assessments together to establish consensus on administration and scoring. One hundred and thirty eight (97%)of the total BSID and MAS assessments were performed by the first tester (PS), while five (3%) of the “one year” BSID and MAS assessments were done by the second tester (HS).

The MAS is a developmental screening tool, with items originally derived from the Griffiths Mental Development Scales (Griffiths, 1970) and other developmental screening tools. It encompasses an age range from six weeks to five years, and includes gross motor, fine motor, language (communication) and personal/social subscales. A developmental age equivalent is obtained from the assessment sheet (appendix1) and subscale sub-quotients are estimated by dividing the developmental age on each subscale by the chronological age, expressed as a percentage i.e. standard score. The MAS General quotient (GQ) is calculated by averaging the four sub-quotients. A MAS GQ less than 85 indicates “risk for global developmental delay”; developmental delay in any general or sub-quotient is further classified as mild (GQ<70) moderate (GQ 30-50) and severe (GQ<30).

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The BSID is a comprehensive tool, which provides discrete cognitive, language and motor composite scores (Bayley, 2006). It also produces separate scaled scores to discriminate between receptive and expressive language, as well as fine and gross motor delay. However, unlike the MAS and GMDS, it does not generate a combined General quotient (GQ). The US norms classify a child with a BSID composite score less than 85 as "at risk for" developmental delay, while a score below 70 is classified as severe delay.

2.3.**Statistical analyses**

Data were analysed using SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Continuous data were described using mean and standard deviation (SD) if symmetrically distributed; otherwise the median and inter-quartile range were used. Performing both parametric and non-parametric tests yielded results that were similar, hence for consistency, the decision was taken to use Pearson correlation analysis. Thus the linear associations between the MAS (including GQ, gross and fine motor as well as language sub-quotients) and comparable domains on the BSID (including cognitive and language composite scores, gross and fine motor sliding scores) were explored using Pearson correlation coefficient. However, there was no comparable domain for correlation with the MAS personal/social subscale as we did not use the BSID adaptive scale. We considered r>0.6 as strong, 0.3-0.6 as moderate and <0.3 as weak degrees of correlation. Bland Altman analysis was used in order to detect bias between scales when comparing similar BSID and MAS domains i.e. gross motor, fine motor and language domain scores (Giavarina, 2015).

3. RESULTS

Ninety participants (n=90) aged one year (time-point one) and 53 participants (n=53) two to three years of age (time-point two) completed both BSID and MAS assessments. The remaining children had incomplete assessments due to time constraints or participant fatigue. Results at the two time-points are shown in Table 1. There were three (3%) children with a MAS GQ below 85 at the one-year visit and nine (17%) children with an MAS GQ less than 85 at the two to three-year visit i.e. in the "at risk" category for global developmental delay. There were varying numbers of specific delays indicating "at risk" i.e. MAS gross motor, fine motor, language and personal/social scores <85. The BSID scores showed a similar profile with only one language composite score of less than 70, indicating severe language delay. However there were varying percentages of children with BSID language, motor and cognitive composites ranging from 70 to 85 (Figure 1).

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Table 1. Performance on the Bayley Scales of Infant and Toddler Development-3rd edition and Molteno Adapted Scales at 11-14 months (n=90) and 30-42 months (n=53)

Assessment	11-14mths	30-42 mths
Results of Bayley Scales Infant and Toddler Development-3rd edition		
Cognitive Subscale		
Composite score , mean (SD)	100.5 (10.2)	88.3 (6.2)
Language Subscale		
Composite score, mean (SD)	91.2 (10.1)	90.4 (7.4)
Motor Subscale		
Fine motor, scaled score (SD)	9.6 (1.4)	9.5 (1.7)
Gross motor, scaled score (SD)	9.2 (2.3)	8.6 (1.7)*
Composite score, mean (SD)	96.5 (1.4)	94.5 (8.2)*
Results of Molteno Assessment Scales		
Gross motor sub-quotient (SD)	93.7 (6.8)	96.0 (8.9)
Fine motor sub-quotient (SD)	93.6 (9.3)	88.2 (13.3)
Language sub-quotient (SD)	94.1 (10.1)	90.7 (13.6)
Personal/social sub-quotient (SD)	99.4 (6.4)	91.2 (5.1)
General quotient (GQ) (SD)	95.2 (5.7)	92.2 (8.3)

* One value missing

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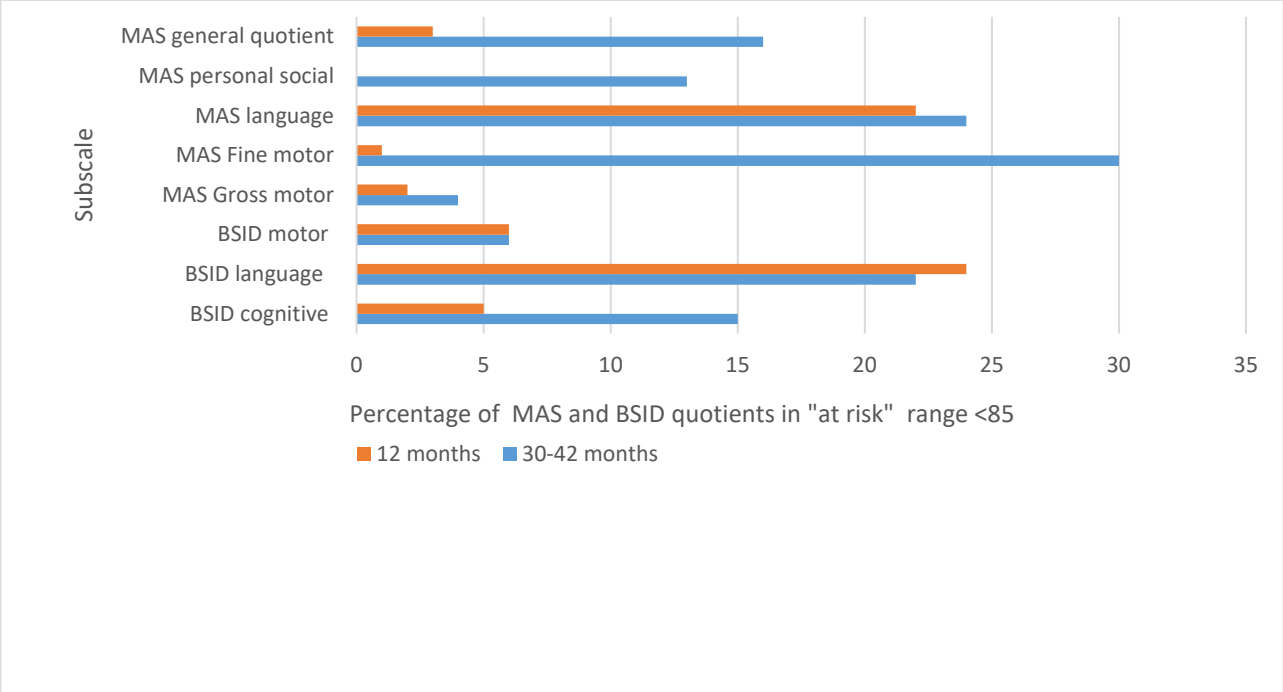

Figure 1. Percentage of Molteno Adapted Scale (MAS) and Bayley scales of infant and toddler development-3rd edition (BSID) quotients in "at-risk" range (<85) at 12 months (n=90) and 30-42 month (n=53) follow-up visits.

The linear relationships between individual domains of the MAS and BSID are described in Table 2. In brief, correlations between MAS and BSID scores on similar domains were moderate, except for the fine motor domain, where BSID scaled scores and MAS sub-quotients showed low correlation at 11-14 months. In contrast, at the 2-3 year visit, there was high correlation between MAS fine motor and both BSID fine motor and cognitive scores. Correlation between the MAS gross motor and BSID gross motor scaled score at 11-14 months was also high. The mean difference between the MAS and BSID language, gross motor, and fine motor scores are shown in Figures 2. The MAS language scores were significantly lower than the BSID language scores at one year ($p=0.029$), MAS gross motor scores were significantly higher than the BSID gross motor scores at 2-3 years ($p<0.001$), and MAS fine motor scores were lower than fine motor scores on the BSID at 2-3 years ($p<0.001$). However at both time-points, the mean differences between the MAS and BSID language, gross and fine motor scores were less than six in all domains.

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While correlations of the MAS and BSID language, gross and fine motor domains were predominantly moderate at both time-points, the Bland-Altman plots showed bias. Discordance between scores on MAS and BSID increased in both upper- and lower-performance scores. This is of particular relevance to children with lower scores in the "at-risk" range i.e. MAS or BSID score <85 (Figure 2) i.e. certain children scoring in the range "at-risk" (<85) for language development on the BSID may have scored above this cut-off on the MAS. The bias appeared less in the two year olds, although there were fewer participants in this age group (n=53).

Table 2. Pearson correlation between Molteno Adapted Scale general and sub-quotient scores and Bayley Scales of Infant and Toddler Development-3rd edition composite and scaled scores

Sub-quotient comparisons		**Time point 1 (11-14 months)**			**Time point 2 (30-42 months)**		
MAS	BSID	r	p	CI	r	p	CI
Gross motor	Gross motor-AS	0.75	<0.001	[0.61,0.90]	0.44*	<0.001	[0.18,0.69]
Fine motor	Fine motor-AS	0.23	0.030	[0.20,0.44]	0.66	<0.001	[0.45,0.87]
Language	Language-cs	0.54	<0.001	[0.30,0.68]	0.58	<0.001	[0.35,0.81]
Fine motor	Cognitive-cs	0.48	<0.001	[0.29,0.64]	0.70	<0.001	[0.45,0.87]
Language	Cognitive-cs	0.46	<0.001	[0.26,0.62]	0.46	<0.001	[0.21,0.71]
GQ	Cognitive-cs	0.56	<0.001	[0.35,0.73]	0.62	<0.001	[0.40,0.84]
GQ	Language-cs	0.51	<0.001	[0.35,0.73]	0.56	<0.001	[0.32,0.79]
GQ	Motor-cs	0.53	<0.001	[0.35,0.72]	0.58	<0.001	[0.35,0.81]

* = One value missing; BSID= Bayley scales of infant and toddler development 3rd edition; CI= confidence interval; GQ= General Quotient; cs=Composite Score; MAS= Molteno Adapted Scale, r= Pearson correlation coefficient rho-value.

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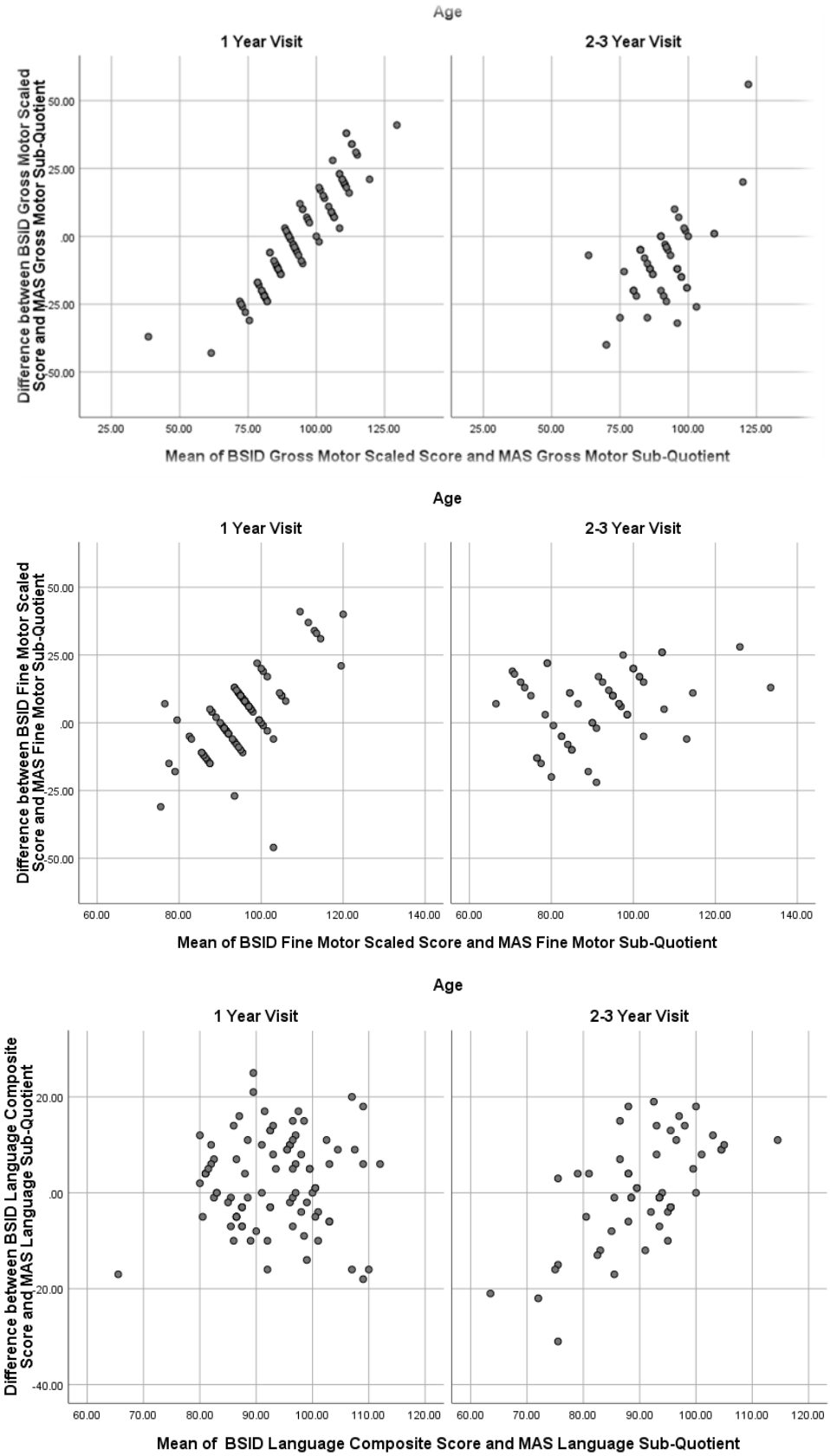

Figure 2. Bland-Altman scatterplots showing mean differences between BSID & MAS scores versus mean MAS & BSID scores when comparing gross, fine motor and language domains at one-year and 2-3 year visits.

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4. DISCUSSION

In the present study, we explored the correlation between similar BSID and MAS domains in a normative sample of South African children across two periods critical to early development. Importantly, despite generally moderate to strong correlations between domains, discrepancy between these assessment tools was elevated across both the lower and upper ends of the performance range. The lower range is important when screening for delay; as such, our findings call into question the ability of the MAS to accurately classify children as "at-risk for developmental delay "when using the BSID as reference measure. The poor correlation between the fine motor domains on both developmental assessment tools at the first time-point was an unexpected finding. This may be explained by a paucity of items in the MAS fine motor subscale at one year, unlike the BSID, which tests broader aspects of fine motor and visuo-perceptual ability and is more discriminatory. It is important not to miss or over-identify children as having delays when screening their development. Aylward (2009) questioned the value of a composite score (average of the sub-quotients) such as a GQ to define developmental delay. The author also cautioned against estimating developmental quotients, which use ratios of mental age to chronological age, as they may not be psychometrically valid; as such, use of standard deviation cut-offs is recommended as an alternative (Aylward, 2009). The MAS may thus have limitations as a screening tool.

The latest third edition of the Bayley Scales of Infant Development (BSID) was standardized on a US population that included children with learning difficulties (Bayley, 2006). This cohort was more representative of the population; however, the distinction between cognitive and language domains meant that the structure of the test differed from the Bayley Scales of Infant Development-second edition (BSID-II), which generated mental developmental and psychomotor developmental index scores. The US norms classify developmental delay as "moderate" or "at risk" (70-85) and "severe" (<70). Concerns have been raised over the BSID under-identifying children with delay (Anderson & Burnett, 2017). Children tested on both second and third versions scored higher on the BSID (third edition), and led to some researchers questioning the current cut-off scores for "at risk" and "severe" developmental delay (Johnson, Moore, & Marlow, 2014). Therefore, there may potentially be limitations in using the BSID as a reference measure in this context.

Measures such as the BSID developed in Western countries may disadvantage African childrenwho find the apparatus and tasks unfamiliar (Kammerer, Isquith, & Lundy, 2013) or have a different developmental trajectory (Vierhaus et al, 2011). This has prompted creation of locally developed culturally-fair tools such as the Malawi Developmental Assessment tool (Lancaster et al., 2010) and

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the Kilifi Developmental inventory (Abubakar, Obiero, Lewa, & Kenga, 2016). These tools have not yet been validated on South African children, which precluded their use as a reference measure for this study. Thus, when using the MAS, a number of children at risk for developmental delay could be missed, a potential limitation of the tool. Overall, we found moderate correlation between comparable developmental domains of the MAS and BSID using a normative sample from a lower socioeconomic community, which is reassuring, since the BSID is a globally recognised tool.

5. CONCLUSIONS

In summary, there was moderate correlation between the BSID motor, language and cognitive scales and the MAS GQ, gross motor and language subscales, but poor correlation with the fine motor domain at one year of age. The Bland Altman analysis revealed bias at the lower and higher range of developmental scores. This could potentially affect classification of children in the lower range who are “at risk for delay” if a cut-off score of <85 is applied. The small sample size at the second time-point may have limited the generalisability of findings.

We thus recommend further development of the MAS, including standardisation and validation on a wider age range of children with varying degrees of delay, in order to ascertain norms as well as floor and ceiling effects. Although the MAS remains a useful tool for detection of specific or global developmental delay in a paediatric outpatient clinic, administration does require standardised training of assessors in administration and scoring of the test. A manual should specify dimensions for the apparatus, including form boards, pegman, building blocks and stairs as well as procedural instructions such as the number of permitted trials and criteria for “pass or fail”. The language evaluation also requires adaptation and standardisation to ensure it is culture-fair. Consultation with language practitioners with translation into all official South African languages will improve and broaden the applicability of the MAS to other provinces.

In conclusion, in this exploratory analysis, the MAS showed moderate correlation with the BSID cognitive, language and motor composite scores, but increased discordance at upper and lower performance ranges. The MAS thus requires further validation on children aged five years and under, with varying degrees of development delay, before it can be endorsed for wider clinical and research purposes. At this stage, its use is best restricted to medical or allied healthcare practitioners who regularly assess children with developmental problems.

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MOLTENO ADAPTED SCALE (Appendix 1)

GROSS MOTOR

Mths			
1		1	Lifts head when prone
2		2	Supported sitting - head vertical
3	⌜	3	Supine - symmetrical
	⌞	4	Prone elbow support
4		5	Pull to sit - no head lag
5		6	Rolls from prone to supine
6	⌜	7	Rolls from supine to prone
	⌞	8	Prone - extended arm support
7		9	Sits alone = 1 minute
8	⌜	10	Prone - pivots in circle using arms
	⌞	11	Sits alone = 1 minute
9	⌜	12	Pulls to stand
	⌞	13	Crawls
10		14	Sitting - can recover toy behind him
11	⌜	15	Creeps - like a bear
	⎸	16	Cruies around furniture
	⌞	17	Stands at furniture - lifts one foot at a time
12	⌜	18	Walks with one hand held
	⌞	19	Walks alone - 10 steps (high guard)
15	⌜	20	Walks - reciprocal arm movements
	⌞	21	Walks backwards
18	⌜	22	Throws a ball
	⌞	23	Kicks a ball
21		24	Climbs on and off adults sized chair without help
24	⌜	25	Jumps off step - two feet together
	⌞	26	Stands on one (either) leg - briefly
30		27	Pedals tricycle
36		28	Up stairs one foot per step, down two feet per step
42		29	Hops on one (either) foot 3 - 5 times
48		30	Stands on one leg - 10 secs.
54	⌜	31	Hops on one leg - 20 times
	⌞	32	Catches ball 2/3
60		33	Hops on each foot - 20 times

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66		34	Walks along straight line (10 paces)
72	⌜	35	Sits up without help of hands
	⌞	36	Walks backwards along straight line (10)

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PERSONAL-SOCIAL

Mths			
		1	Watches mother when feeding
1	⌈	2	Sucks well
	⌊		
		3	Smiles at mother
2	⌈	4	Enjoys bath
	⌊		
		5	Excited when sees bottle
3	⌈	6	Obvious pleasure at being handled
	⌊		
		7	Tries to hold bottle
4	⌈	8	Friendly towards strangers
	⌊		
5		9	Holds bottle
		10	Chews solids
6	⌈	11	Smiles, pats mirror image
	⌊		
7		12	Drinks from a cup
8		13	Plays peek-a-boo (Waar's hy)
		14	Holds and eats biscuit
9	⌈		
	⌊	15	Stranger anxiety
		16	Pulls off hat
10	⌈	17	Pushes arm into sleeve
	⌊	18	Deliberate casting
11		19	Finger feeds
12		20	Holds spoon
		21	Uses spoon - spills most
15	⌈	22	Pulls off socks
	⌊	23	Domestic mimicry
		24	Uses spoon - spills very little
18	⌈	25	Pulls up pants
	⌊	26	Indicates wet/dry nappy
21		27	Handles cup very well

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	⎡	28	Sits on parent's knee and looks at books
	⎣		
		29	Clean and dry by day
24	⎡	30	Jealous of other children
	⎣		
		31	Parallel play
30	⎡	32	Washes and dries hands
	⎣		
		33	Dresses - needs help with buttons
36	⎡	34	Dry at night
	⎣		
42		35	Manages buttons
		36	Dresses with supervision
48	⎡	37	Likes to dress up
	⎢	38	Play - group of 2 - 3
	⎣		
60		39	Play - group of 4 - 5
72		40	Co-operative play - leadership and division of labour

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FINE MOTOR

Mths		
	1	Follows to midline
2	2	Hand to mouth as a voluntary act
	3	Follows past midline
3	4	Fingers one hand with other when lying quietly
	5	Follows through 180°
4	6	Four - part sequence - reach, grasp, retrieve mouth
5	7	Crumples paper
	8	Grasps ring
6	9	Grasps ring, mouth and transfer
	10	Shakes waves and bangs object
7	11	Retains only one cube in hand at a time
8	12	Grasps ring by the string
	13	Retains one cube in each hand
9	14	Mouthing exploratory (not obligatory)
	15	Removes pegman from car
10	16	Clicks two cubes together
	17	Throws objects
11	18	Thumb (index finger) opposition
	19	Holds care and “explores” with index finger
12	20	Replaces pegman
	21	Simple formboard - replaces large circle
	22	Retains three cubes
15	23	Retains four cubes
	24	Simple formboard - replaces both circle
	25	Two cube tower
18	26	Three - four cube tower
	27	Completes simple formboard with reversal (trial and error)

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21	28	Three pieces formboard - two shapes in
	29	Simple formboard with reversal
24	30	Three pieces formboard - replaces three shapes
	31	Six cubes tower and train
30	32	Three piece formboard with reversal (trial and error)
	33	Train with chimney
36	34	Three piece formboard - with reversal (no trial and error)
	35	Copies O
	36	Nine cube tower and bridge
42	37	Coloured formboard five out of five
	38	Copies +
48	39	Coloured formboard five out of five
	40	Gate
54	41	Copies □
60	42	Steps (six cubes)
	43	Copies Δ
66	44	Copies ◊
72	45	Steps (ten cubes)
	46	Copies

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LANGUAGE (COMMUNICATION)

Mths		
1	1	Startles to sounds
	2	Throaty sounds
	3	Cries when hungry
2	4	Vowel sounds
3	5	Coos, chuckles, squeals
4	6	Initiates vocalisation
	7	Giggles and laughs
5	8	Combines sounds eg. ah-goo
6	9	Object permanence - looks after dropped object
	10	Makes “m” sound
7	11	Response when called
	12	Shouts for attention
8	13	Combines syllables, eg. ba-ba, ma-ma
9	14	Waves bye-bye
	15	Babbles tunefully
	16	Says mama, dada
10	17	Object permanence find cube under cover
	18	Shakes head for no
	19	One word with meaning
11	20	Two - three words with meaning
	21	Imitates one or two words
12	22	Where is daddy - looks at father
	23	Reacts with expression
15	24	Definition by use
	25	Uses five words
18	26	Points to one picture
	27	Points to one body part

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		28 Two-word utterance
21	⌜	29 Points to three body parts
	⌞	30 Names six familiar objects
	⌜	31 Points to five body parts
24	|	32 Uses pronounce - I, you, me
	⌞	33 Combines three words
30		34 Names eightpicture cards
	⌜	35 Names ten picture cards
36	⌞	36 Digit repetition (3)
42		37 Names twelve picture cards
	⌜	38 Knows name age and sex
48	⌞	39 Sentence repetition
54		40 Comprehends cold, tired, hungry
	⌜	41 Opposites:woman and man,big and small, hot and cold.
60	⌞	42 Knows address, birthday
66		43 Word definition (5)

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CHAPTER 7: Value of the Goodenough Drawing Test as a research tool to detect developmental delay in South African preschool children

Children will attempt to draw a person from as young as 3 years old, and their drawings become more detailed over time. Francis Goodenough, having observed this phenomenon, created a scoring system that measured mental maturity (Goodenough, 1926). Human figure drawing (HFD) requires cognitive, motor, perceptual, attentional and motivational abilities, and evolves over the course of well-defined developmental stages(Chappell & Steitz, 1993).HFD has been incorporated into child development assessment tools (CDAT) or included as part of a test-battery for both cognitive and psychological assessment. Its use has advantages in resource-constrained settings as it is time-efficient, does not require elaborate equipment, and transcends language barriers (Miles, Fulbrook, & Mainwaring-Magi, 2016).

However, application of the Goodenough "Draw-a-Person test" as a screening tool remains controversial, since construct validity and psychometric properties are lacking (Kamphaus & Pleiss, 1991). Psychological, social and emotional interpretations of the HFD have proven unreliable, especially when used as a measure of intelligence (Imuta, Scarf, Pharo, & Hayne, 2013). More recently, researchers have investigated the construct validity, underlying abilities assessed and the predictive value of the HFD(Arden, Trzaskowski, Garfield, & Plomin, 2014; Rehrig & Stromswold, 2018). Its use as an informal screening tool by paediatricians continues, and there has been a resurgence of interest in its research application. A study analysing the HFD of 7752 pairs of twins born from 1994 to 1996 found greater similarity at 4 years of age in the HFD of the identical (monozygotic) versus non-identical (dizygotic) twins. These findings suggested that genetic differences exert greater influence on childhood drawings than family-environmental differences (Arden et al., 2014). Genovese (2018) found that children's drawings became more detailed over the period from 1902-1968, making them appear more advanced for their age; improvement in performance scores over time is a phenomenon known as the Flynn effect, and has been found in other cognitive assessments (Genovese, 2018).

Despite widespread use of the HFD in African research studies, the Goodenough "Draw-a-Person test" and its iterations lacks recent standardization and validation, and there is evidence that its usefulness may be age-dependent. A comparison of drawings of 415 urban African children with historical samples from 1938 and 1950 found that 5 to 8-year-olds showed no change in performance, but this did not apply to children older than 8 years (Richter, Griesel, & Wortley, 1989).

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We planned to interrogate the diagnostic accuracy of the HFD as a screening tool for 5-year-old HIV-infected children from a lower socio-economic neighbourhood in Cape Town, South Africa. Children enrolled in the CHER study (Laughton et al., 2012) were assessed at 5 years on the Griffiths Mental Developmental Scale-extended revised version (GMDS-ER) which includes a HFD in the eye-hand co-ordination scale(Laughton et al., 2018). Two medical officers with no prior experience of the Goodenough drawing test, as well as a developmental paediatrician scored the drawings independently using the original test manual (Goodenough, 1926). Inter-rater reliability was estimated by comparing their scores. Each Goodenough drawing test score was converted to a quotient (DAP) by expressing the developmental age as a percentage of the chronological age in order to obtain a standardardised score. This method of analysis, first described by Ireton (Ireton, Quast, & Gantsher, 1971), was used in a previous South African study (Zeegers et al., 2009). We estimated the diagnostic accuracy of the DAP as a screening tool using the GMDS-ER Eye-hand sub-quotient as the reference standard.

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South African Journal of Psychology 1–11 © The Author(s) 2019
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DOI: 10.1177/0081246319850683 journals.sagepub.com/home/sap
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Article

Value of the Goodenough Drawing Test as a research tool to detect developmental delay in South African preschool children

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Abstract

There is a need for simple, cost-effective research tools to detect developmental delay in preschool children in low- and middle-income countries where insufficient resources are often a barrier to detection and management. The Goodenough Draw-a-Person test is freely available, easily administered, and requires limited language ability and equipment; it is thus potentially useful in resource-constrained settings. We aimed to determine the diagnostic accuracy of the Draw-a-Person test to identify developmental delay in 5-year-old preschool children using the Griffiths Mental Developmental Scales-Extended Revised eye-hand coordination subquotient as the gold standard. This was a cross-sectional analysis of drawings by South African preschool children from low-income families, whose Griffiths Mental Developmental Scales-Extended Revised assessments included a human figure drawing. Draw-a-Person test quotients were estimated independently by a developmental paediatrician and two medical officers to calculate inter-rater agreement. The paediatrician's scores were used to determine the diagnostic accuracy of the Draw-a-Person test quotient (<85) to predict developmental delay with the eye-hand coordination subquotient (<75). A total of 125 children were included, with a mean age of 60.8 months (range 59–66 months) of which 48.8% were boys. The mean Draw-a-Person test score was 94 (standard deviation 15) with 28 Draw-a-Person test scores below 85. Applying the Draw-a-Person test cut-off of 85, sensitivity

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of the Draw-a-Person test to the eye-hand coordination subquotient was 80% and specificity 89%. The area under the receiver operator characteristic curve was 0.87 (95% confidence interval [0.78–0.96]). The Goodenough Draw-a-Person test could thus be a useful research tool for detecting fine motor and visuoperceptual delay in South African preschool children.

Keywords
Developmental delay, draw-a-person, fine motor delay, human figure drawing, preschool child, research tool

There is a need for simple, cost-effective tools to detect developmental delay in preschool children in Low- and Middle-income countries (LMIC) in both research and clinical contexts (Sabanathan, Wills, & Gladstone, 2015). In such resource-constrained settings, imported equipment and copyrighted assessment booklets are often unaffordable, parents generally have limited funds for transport or time off work to attend more comprehensive assessments, and clinics have long waiting times. Human figure drawing (HFD) has a long history both as an informal developmental screening tool and in standardised test batteries such as the Griffiths Mental Developmental Scales (GMDS) (Luiz, Foxcroft, & Tukulu, 2004). It was itemised in the Eye and Hand coordination subscale of the Extended Revised GMDS (GMDS-ER) and is retained in the most recent version version (Griffiths III) (Stroud, Foxcroft, & Green Bloomfield, 2016). Further applications of the HFD have included assessment of mental maturity and as a projective instrument to assess emotional and personality traits (Koppitz, 1968). Koppitz also validated a simplified scoring system as a developmental screening tool for children 6 years and older (Koppitz, 1968).

There is a resurgence of interest in using the HFD for research. A recent study of over 4000 pairs of twins reported that HFD at 4 years old correlated significantly with heritable factors and intelligence at both 4 and 14 years of age (Arden, Trzaskowski, Garfield, & Plomin, 2015). Tükel, Eliasson, Bőhm and Smedler (2018) found that the HFD was influenced by visual perception and visuomotor control and could be used to screen for developmental delay in Swedish preschool children.

Frances Goodenough originally developed the 'Draw-a-Man' (Draw-A-Person/DAP) scoring system in 1926 and found it correlated well with concurrent standard intelligence quotient (IQ) tests (Goodenough, 1926). Subsequent iterations of the test were widely used in South African research (Hunkin, 1950; Oates, 1938; Reynolds & Hickman, 2004; Sherr et al., 2017): DAP scores obtained from the McCarthy scales (McCarthy, 1972) for under 8-year-olds were comparable with historical samples and demonstrated validity both as 'a measure of intellectual functioning' and school performance in African children (Richter, Griesel, & Wortley, 1989). Venter and Bham (2003) found that the Goodenough-Harris DAP (Harris, 1963) predicted academic achievement in first-grade African pupils. Burger applied the international norms of the DAP:IQ version (Reynolds & Hickman, 2004) and found them appropriate for 5–7-year-olds, suggesting that it might be a suitable screening tool to detect mild to moderate global developmental delay in South African children (Burger, 2008).

The DAP scoring system was refined by Ireton, Quast, and Gantsher (1971) to produce an age-equivalent standardised score called the 'Index of Psychological Function' (IPF). Children aged 4–10 years with an IPF below 85 had significant risk of a developmental disorder or delay. In this way, the Goodenough DAP was used to screen for developmental delay in a cohort of HIV-infected (HIV+) South African children (Zeegers et al., 2009).

The Goodenough DAP is easy to administer and transcends language barriers. The instructions are simple, and can be conveyed to the child by a translator, an advantage where language

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difficulties are present. The tool is self-explanatory and without formal training or certification requirements. In a review of 48 standardised instruments, the DAP fulfilled six 'usability' criteria, that is, (1) rapid test administration, (2) scoring time, (3) low level of assessor qualification, (4) minimal training required and being the only test available (5) free of charge, and (6) not requiring expensive equipment or manuals. All of these are important considerations for LMIC. However, it fell short on psychometric properties including recent standardisation, validity, and reliability (Miles, Fulbrook, & Mainwaring-Magi, 2016).

Questions remain regarding the construct validity of the Goodenough DAP test (Kamphaus & Pleiss, 1991). Richter, Mabaso, and Hsiao (2015) also found that the DAP administered at age 7 years had insufficient predictive power to identify learners requiring intervention to prevent grade repetition, and it underestimated abilities in children above 8 years of age (Richter et al., 1989).

Controversy regarding use of DAP (and other versions of HFD) largely relates to its inaccuracy in predicting intelligence, as it does not detect children with above average or borderline IQ (Imuta, Scarf, Pharo, & Hayne, 2013). Imuta et al. (2013) assessed 100, 5-year-old children, and reported that none of the five children with a DAP:IQ standard score below 80 showed borderline functioning on the Wechsler Preschool Scale of Intelligence (WPSI), and neither of the two children with borderline functioning on the WPSI were delayed on the DAP:IQ test. However, no participants in their cohort had intellectual disability (IQ $<$ 70).

The DAP has not been validated for South African preschoolers. Diagnostic accuracy (i.e. sensitivity, specificity, and positive and negative predictive values measured against a gold standard) must be established before its use can be recommended. Validation of its potential value in research could affirm or guide its use as a clinical tool. Because of this uncertainty, we aimed to explore the potential value of HFD as a research tool in South Africa. Moreover, the study was justified in order to determine the construct and predictive validity of the DAP for a specific age group. Our hypothesis was that the Goodenough DAP would correlate best with the eye-hand quotient (EHQ) of the GMDS-ER, which was selected as the gold standard.

The objectives were to determine (1) whether the DAP correlated best with the EHQ versus other GMDS-ER quotients and (2) the diagnostic accuracy of Goodenough DAP in detecting developmental delay in South African preschool children.

Method

This was a cross-sectional neurodevelopmental sub-study linked to the Children with HIV Early Antiretroviral Therapy (CHER) trial (Cotton et al., 2013). The primary aim of the CHER study was to evaluate different antiretroviral regimens over time in children from Cape Town and Soweto.

Participants

The participants were enrolled in two prospective interlinking studies during 2005–2006 at the Children's Infectious Diseases Clinical Research Unit (KID-CRU) (Laughton et al., 2012; Madhi et al., 2010). HIV+ children enrolled in the CHER study at the Cape Town site and a control group of HIV-exposed uninfected (HEU) and HIV-unexposed (HU) children from a concurrent vaccine trial (Madhi et al., 2010) were recruited for a longitudinal neurodevelopmental sub-study. The neurodevelopmental study inclusion criteria were birth weight greater than 2000 g, and no dysmorphism or central nervous system insults such as foetal alcohol syndrome, perinatal asphyxia, or metabolic abnormalities. HIV+ children were enrolled in the CHER study before 12 weeks of age with a normal neurological examination at that time. A total of 128 participants from the neurodevelopmental sub-study with Griffiths assessments that included HFDs at 5 years of age were

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Table 1. Characteristics of study participants ($n = 125$).

Characteristic	Mean *SD* or *n* (%)
Age (months)	60.8 (*SD* = 1.2)
Sex	
Male (%)	61 (48.8%)
Female (%)	64 (51.2%)
HIV status	76 HIV+ (60.8%)
	21 HEU (16.8%)
	28 HU (22.4%)
No preschool attendance	28 (22.4%)
Crèche	61 (48.8%)
Preschool (structured programme)	33 (26.4%)
Missing	3 (2.4%)
Abnormality on neurological exam	5 (4%)
Spastic Diplegia	

HIV+: HIV positive; HEU: HIV-exposed uninfected; HU: HIV-unexposed.

Table 2. Correlation between Draw-a-person test and Griffiths mental developmental-extended revised subscale quotients.

Griffiths Subscale: function assessed	Pearson's *r* coefficient	95% CI
Locomotor: gross motor skills	0.141	[–0.039, 0.311]
Personal/social: proficiency in activities of daily living and ability to interact with other children	0.243	[0.068, 0.404]
Language: receptive and expressive language	0.416	[0.256, 0.553]
Eye-hand: fine motor skills, manual dexterity and visual perception	0.685	[0.577, 0.769]
Performance: manipulation skills including speed and precision	0.388	[0.226, 0.529]
Practical Reasoning: ability to solve practical problems, simple maths, moral and sequential issues	0.455	[0.301, 0.586]
General Quotient: average of 6 subscale quotients shown above	0.570	[0.435, 0.680]

eligible for the study. Three drawings were excluded as they consisted of illegible scribbles. Mean age was 60.8 months ranging from 59 to 66 months, and 48.8% were boys (Table 1). The majority (76%) were attending a daycare or preschool facility.

Instruments

The GMDS-ER is a comprehensive paediatric developmental assessment tool from the United Kingdom (UK), which has been adapted and used extensively in South Africa (Luiz et al., 2006). Training and certification are required to administer the tests. It is a criterion and norm-referenced tool that assesses various developmental domains in children from 2 to 8 years of age based on six subscales detailed in Table 2. The raw scores are converted to *z*-scores, percentiles, and age-equivalents derived from UK normative data. A subscale quotient is estimated by dividing the age-equivalent by the chronological age expressed as a percentage. The general quotient (GQ) is calculated by averaging all six subscale quotients.

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Developmental delay is defined as a score more than two standard deviations (−2 *SD*) below the expected mean (Davies et al., 2011). Thus, a general or subquotient score below 70 indicates definite developmental impairment by British norms. However, there is no universally accepted definition of delay, with uncertainty as to which cut-off score is most relevant in the South African context. The referral criteria vary, and are set by therapists based on local experience. For this analysis, the conservative EHQ threshold of 75 (as opposed to 70) was set as the score requiring referral for further diagnostic evaluation, to allow for the imprecision of subquotient determination.

The human figure in the Goodenough DAP instrument is scored against 51 specified characteristics and applies a quantitative scoring system to the drawing (Goodenough, 1926). This is expressed as a mental age and converted to a standardised score or quotient. It therefore provides a non-verbal measure of mental development for children 3–10 years old. A standard score below 85 was taken to represent significant delay requiring referral (Ireton et al., 1971).

Procedure

All children were tested with the GMDS-ER at 5 years of age by one of two developmental paediatricians (B.L. and H.S.) assisted by a Griffiths-trained translator (L.R.K.). The GMDS-ER Eye and Hand Coordination Subscale (EHQ) includes an HFD which is scored differently to the DAP. Participants were tested individually in the presence of their caregiver, who sat in the background but was requested not to help or make comments. The children were instructed in their home language to draw a person with a pencil in the Griffiths (1970) record book using the standardised administration instructions outlined in the manual. They sat in a quiet room and the assessor encouraged them 'to draw the best possible person' but did not offer assistance and applied no time limit. Vision was assessed using a Snellen's picture chart and tiny cake decorations. Participants were excluded if any item on the EHQ was missing.

Copies of each drawing were placed in three separate files with no identifying information apart from a participant code. Drawings were then scored independently according to the Goodenough DAP scoring system (Goodenough, 1926) by a third developmental paediatrician (P.S.) and two medical officers (E.K. and H.E.). The assessors did not collaborate and were blinded to GMDS-ER findings and to the HI and HIV-exposure status of the children. The medical officers had no experience with the Goodenough DAP scoring system prior to the study and used the DAP instruction sheet for scoring. The DAP scores together with the de-identified GMDS-ER data were converted into quotients and entered into an Excel database.

Ethical considerations

The study was approved by the Stellenbosch University Health Research Committee (N05/05/092). Informed consent was obtained in person from the child's legal guardian in their preferred language according to Good Clinical Practice guidelines. Parents remained with their children for reassurance during the assessments and only children who remained cooperative were tested. Children with developmental problems were referred with parental consent to relevant services. Clinical files were stored at the study site. No identifying data were accessed during the analysis and data were stored on a password-protected database.

Data analysis

Data were analysed using Stata version 14 (StataCorp LP, College StationTX). Continuous data were described using mean and standard deviation (*SD*) if symmetrically distributed; otherwise the median and interquartile range (IQR). Pearson's correlation analysis of all the GMDS-ER

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subscales was used to assess the relationship between continuous variables, and the associated confidence interval (CI) was derived using Fisher's tranformation. CIs which show the likely degree of correlation in the population were calculated rather than p is values, which only test whether the correlation is significantly different from zero. If the 95% CI provided does not include a zero, the correlation is significantly different from zero at the 5% level of significance.

Intraclass correlations (ICCs) between the DAP and the EHQ and GQ were also calculated. The correlation coefficients were used to determine strength of the relationship between variables. Cohen (1992) suggested that effect sizes could be categorised as small ($r=0.10$), medium ($r=0.30$), and large ($r=0.50$). We used two-way random effects ICC to measure the inter-rater agreement between DAP values by the three scoring clinicians. Sensitivity and specificity and 95% CI and positive and negative predictive values were calculated for DAP quotient less than 85 versus EHQ using an EHQ threshold of 75.

Optimal cut-off points for DAP versus the EHQ as gold standard were explored using receiver operating characteristic (ROC) curves. The area under the ROC curve and its significance were examined using a non-parametric assumption. Various thresholds were tested to identify the optimal values.

Results

Participant characteristics

A total of 128 drawings were available. Three consisted of illegible scribbles and were excluded and these children all had EHQs below 75 (i.e., 62, 72, and 58.3), confirming definite developmental delay. The DAP scores was calculated on the remaining 125 drawings. GMDS-ER EHQ scores were available for all 125, and GQ scores for 123 participants.

Correlation between DAP and GMDS-ER quotients

The median DAP score was 94 (IQR:85–103) and 28 children (22%) had a DAP score below 85, that is, meeting our definition for developmental delay. There were no differences in median DAP score between the HIV+, HEU, and HU groups ($p=.25$). The median EHQ of the cohort was 83.3 (IQR 76.9–88.8), while median GQ was 82.8 (IQR 77.5–88.1). Most participants (93%) had numerically higher DAP than EHQ and GQ quotients. The correlation between DAP and EHQ was strong (Pearson's $r=0.69$ 95% CI=[0.58–0.77]), less so for GQ, $r=0.57$ 95% CI=[0.44–0.68], and moderate for other GMDS-ER subscale quotients (Table 2). HIV status had no significant effect on these correlations ($p=.22$**).**

Inter-rater agreement

Agreement on overall DAP scoring between the developmental paediatrician and medical officers was fair (ICC=0.73, 95% CI=[0.43–0.86]. The medical officers tended to give higher scores than the developmental paediatrician. For participants with DAP less than 85 the ICC was 0.66, 95% CI=[0.56–0.81], whereas amongst those with DAP$\geqslant$85, ICC was 0.58, 95% CI=[0.18–0.78].

Diagnostic accuracy

Using a DAP threshold of 85 as specified by Ireton to indicate developmental delay we generated optimal sensitivity and specificity for an EHQ below 75. The threshold of 85 was tested using the experienced scorer (P.S.). Sensitivity of the DAP:EHQ was 80% and specificity 89%. In all, 19

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Table 3. Diagnostic properties of the Goodenough Draw-a-Person score <85 when predicting scores <75 on Griffiths eye-hand coordination subscale.

	Mean	Range	*p* value
Sensitivity	80%	59–93%	<.01
Specificity	89%	81–94%	<.01
Positive likelihood ratio	7.27	4.03–13.1	<.01
Negative likelihood ratio	0.22	0.10–0.49	<.01
Positive predictive value	64.5%	45.4–80.8%	<.01
Negative predictive value	94.7%	88–98.3%	<.01
Disease prevalence	20%	13–28.1%	<.01
ROC	0.845	0.749–0.931	<.01

ROC: receiver operator characteristic curve.

(68%) of the 28 participants with developmental delay on the DAP were also delayed on EHQ, while 91 of 97 (93.8%) participants scoring above 85 on the DAP were not delayed on the EHQ (Table 3). Thus, when comparing the DAP with the GMDS-ER there was concordance between the two tests in classifying participants as delayed versus non-delayed in 110 (92.8%) participants, that is, giving positive and negative predictive values of 64.5% and 94.7% (Tables 3).

There were six false negative results using the DAP threshold of 85 i.e., DAP greater than/equal to 85 but EHQ less than 75 (range 69.9–74.8). Two of these children had a borderline DAP score of 85. Only one child with DAP ⩾ 85 had an EHQ less than 70 (definite developmental delay). This child also had severe language delay (language subquotient 56.9), an EHQ of 69.9, and GQ of 70.7 but a DAP score of 102.

We identified optimal cut-off points for DAP versus the EHQ gold standard using ROC curves. Various thresholds were tested to identify the optimal values. Using the area under the ROC curve the variable DAP threshold of 85.6 was the best predictor for EHQ < 75 (ROC = .87; p =< .001) versus the DAP threshold of 85 (ROC = .84, p < .001) (Table 3).

Diagnostic accuracy was initially also estimated for the DAP versus GQ, however, the low prevalence of global developmental delay (3%) in the cohort precluded the diagnostic accuracy analysis of DAP/GQ, as it undermined positive predictive value determinations.

Discussion

We assessed the diagnostic accuracy of the Goodenough DAP instrument as a research tool, to detect developmental delay, against the gold standard GMDS-ER assessment in 125, 5-year-old South African children from low-income families. The correlation between the DAP and the EHQ (eye-hand coordination quotient) was the strongest according to Cohen's criteria (Cohen, 1992), and less so for the GMDS-ER GQ. Burger, who tested 30 children with a wider age range using the DAP:IQ version, found a strong correlation with GMDS-ERGQ (r = .76) (Burger, 2008). However although the DAP:IQ has better psychometric properties than the Goodenough DAP (Miles et al., 2016), it requires longer administration time and the need to import and pay for manuals, often unfeasible in LMIC.

The DAP threshold score of 85 yielded optimal sensitivity and specificity and a high negative predictive value for the EHQ, demonstrating its value to screen for delayed eye-hand coordination. By identifying children with a DAP score <85 we would have detected 76% of those with significant developmental delay as indicated by an EHQ < 75. Of the remaining 34%, only one had severe delay, that is, EHQ < 70.

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Inter-rater agreement was good when identifying DAP scores < 85 but less so on higher scores. The three assessors interpreted certain descriptors differently, for example, 'Firm lines without overlapping at junctions'. These disparities in scoring require further analysis.

The mean Griffiths GQ and EHQ of our cohort were significantly below average, that is, more than one *SD* below the standardised UK norms (Griffiths, 1970). Similar findings were reported by Lowick, Sawry, and Meyers (2012), who compared neurodevelopment of 31 HIV+ South African children (mean EHQ 77.2) with 30 'apparently healthy' children (mean EHQ 82.8). Allan (1992) reported that lower socio-economic status adversely affected performance, with South African children from a higher socio-economic bracket performing better. Our cohort were all of lower socio-economic status, some with additional risks for cognitive delay, that is, HIV infection (50%), and exposure (20%), and would thus require developmental surveillance (Potterton, Hilburn, & Strehlau, 2015).

The South African Road to Health Book (RTHB) is a caregiver-held document in which the child's routine immunisations, growth parameters, and unscheduled clinic visits are recorded. It includes a developmental milestone checklist to be completed by primary healthcare nurse practitioners (Western Cape Government Department of Health, 2011). In the 2011 version, it listed 'Ability to draw a stick person' as the only developmental criterion for fine motor development at 5–6 years, however, there were no accompanying administration or scoring guidelines. It would, however, be impractical to use the Goodenough DAP in this setting, as the scoring system is time-consuming and requires standardised instruction sheets and training.

The DAP is currently used in developmental assessment clinics in South Africa as an informal component of a more comprehensive assessment. However, the DAP may have additional clinical applications, for example, for doctors working in busy community-based paediatric clinics. Children with a DAP below 85 could be referred to an occupational therapist for further assessment and therapy. Validation of the DAP as a research tool could thus inform its clinical use. Children with mild versus severe delay comprise 85% of those with developmental delay and intellectual disability and have the potential to make significant gains with early intervention (Sadock, Sadock, Ruiz, & Kaplan, 2009).

A recent study involving 345 American preschoolers found that while the DAP:IQ scores were not a valid measure of cognitive ability, they were useful to screen for fine motor delay in at-risk children (Rehrig & Stromswold, 2018). Likewise, Tükel et al. (2018) also reported that the HFD was influenced largely by visual perception and visuomotor control at 5.5 years in a group of Swedish children. These latter two studies concur with our findings.

The strengths of our study are as follows: first the DAP scores were calculated by independent assessors blinded to the child's GMDS-ER results as well as their HIV infection or exposure status. Second, although the age-band of the cohort was narrow, it represents an age at which children require school readiness testing and would benefit from intervention prior to school entry. In addition, this cohort was representative of children needing developmental surveillance, that is, HIV+, HEU, and HU children from LMICs. Children from economically disadvantaged environments with developmental impairment who receive therapeutic input prior to school entry show improved scholastic achievement (Heckman, 2006). Finally, children scoring below the cut-off point (DAP less than 85) had mild to moderate (vs severe) developmental delay on the GMDS-ER, a group often undetected at an earlier age.

The study was, however, limited by the low prevalence of global developmental delay in the sample (3%). Paediatric HIV clinics have previously reported higher prevalence of global delay (55%) which probably relates to much later antiretroviral therapy initiation than in the CHER cohort (Potterton et al., 2015). Also, our cohort included HEU and HU children not expected to

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have severe developmental problems. Second, the findings are not generalisable to all South African preschool children as this cohort had a narrow age range. Finally, the inclusion of the HFD task in the GMDS-ER, even though the scoring method differs from the DAP, could have confounded the diagnostic assessments.

Conclusion

Our findings support using the DAP as a research tool to detect fine motor and visuoperceptual delay in 5-year-old children. It could complement a more comprehensive assessment including verbal and non-verbal tasks. In addition there are clinical contexts where the DAP may be useful, that is, for medical practitioners in resource-constrained outpatient settings. Children with DAP scores $\leqslant 85$ or those unable to draw a person could be referred to an occupational therapist for assessment and intervention where indicated. However, we recommend that future studies should initially focus on a full standardisation of the DAP to include a broader cross-section of South African society with a wider age range. One could then evaluate the ability of the DAP to predict later scholastic performance in reading, writing, and mathematics.

Acknowledgements

The authors acknowledge Dr Henriette Saunders and Ms Lungiswa Khethelo for their assistance with the Griffiths assessments, Dr Hesti van Huyssteen for her assistance with the scoring of the human figure drawings and Ms Tonya Esterhuizen for her statistical support.

Funding

The author(s) declared receipt of the following financial support for the research, authorship, and/or publication of this article: Support for the CHER study, which provided the infrastructure for the neurodevelopmental substudy, was provided by the US National Institute of Allergy and Infectious Diseases through the CIPRA network, Grant U19 AI53217; the Departments of Health of the Western Cape and Gauteng, South Africa; and GlaxoSmithKline. Additional support was provided with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, United States Department of Health and Human Services, under Contract No. HHSN272200800014C. Permission to conduct the neurodevelopmental sub-study on this cohort was granted by Avy Violari, Shabir Madhi, Mark Cotton and the CHER steering committee. Neurodevelopmental assessments from were funded through grants from the Harry Crossley Foundation and the South African Medical Research Council (MRC), the National Research Foundation of South Africa and CIPRA-SA.

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CHAPTER 8: Conclusions and Recommendations

From converging lines of evidence, our study showed that HEU infants delivered at a midwife obstetric unit managing low-risk deliveries had similar developmental outcomes compared to their HUU counterparts. A lack of early childhood stimulation and learning opportunities provides possible explanations for the poorer performance of both groups on the BSID cognitive domain at the two-year follow-up visit.Caregivers of the two to three-year-old HEU children reported fewer behavioural and emotional difficulties in their children compared to the control group. This unexpected finding could be related to innate or environmental factors: the HIV-infe**c**ted mothers, already in a supportive care system, may have also received additional psychosocial support during their regular follow-up at ART clinics. However, selection bias is also a possibility, given the high study attrition rate. Stunting was an important risk factor for motor delay and behavioural problems in our study, independent of HI exposure, and may serve as a proxy for other health and social determinants of early childhood development.

The strength of our research lies in its prospective design, the inclusion of a contemporaneous, comparison group (HUU infants) from a similar community, and the assessment of important neurodevelopmental and behavioural outcomes in HEU children across different stages of early life, using comprehensive measures. Moreover, the wealth of ante- and post-natal data collected allowed us to interrogate the associations of poorer developmental and behavioural outcomes with multiple risk factors. Several important limitations are however also acknowledged. The neurodevelopment findings, although reassuring, must be interpreted with caution, as the study excluded low birth weight and preterm infants, factors associated with maternal HIV-disease, and potential mediators for increased developmental risk. Secondly, it was difficult to separate the effects of HIV exposure from other biopsychosocial determinants of development. In addition, high rates of attrition and relatively small sample size contributed to decreased statistical power. Several major confounders, including maternal depression and childhood resilience, were not comprehensively assessed. Hearing and vision were not formally tested, although children with suspected deficits were referred for further evaluation. Importantly, the predictive value of CDAT and behavioural screening tools are limited in infancy and to a lesser extent in early childhood (Girault et al., 2019).

Although poorer performance on developmental tests, as evident in our study, may reflect fewer learning opportunities rather than cognitive potential, the sub-optimal developmental trajectory over time indicates that children remain at a disadvantage at school entry. To date, compromised neurodevelopmental outcome in the early pre-school years has been linked to lack of school-readiness

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and poor scholastic progress, both limiting economic progress and perpetuating intergenerational poverty (Richter et al., 2015).This is particularly relevant in South Africa where children experience poor educational outcomes and a recent study showed only 52% of children had completed twelve years of formal schooling (Weybright, Caldwell, Wegner, & Smith, 2017)

Critical appraisal and use of appropriate developmental and behavioural screening tools both for research and clinical purposes should be prioritised in LMIC. Cost-effective and time-efficient CDAT, such as the Molteno Adapted Scale and Draw-a-Person test could be applied in resource-limited healthcare settings, but require further standardisation and validation. Future research studies should also include more refined neuropsychological tests for children under five years old, as developmental tests such as the BSID are not specifically designed to detect memory, executive function and attention domain-specific deficits (Brito et al., 2019). Neurobehavioural measures such as the General Movements test can be used from the neonatal period to detect differences, including potential effects of ART(Coelho, Tricarico, Celsi, & Crovella, 2017).

Determination of the effects of HIV exposure and ART on early childhood development will ultimately require integration of pre-clinical, clinical, neuropsychological and functional neuroradiological findings, as recommended in a recent systematic review (McHenry et al., 2019). The significance of differences detected in pre-clinical and neuro-radiological studies of HEU participants, may only become evident over time, as in other developmental and psychiatric disorders. Multi-disciplinary longitudinal cohort studies into adolescence will increase the understanding of both mechanism and effects of neuropathological changes caused by HIV, associated systemic inflammation and increased antiretroviral (ARV) exposure on the developing brain. Since early developmental surveillance provides an opportunity for timeous intervention, guidelines are needed for monitoring child development, optimising maternal wellbeing and supporting families with parenting programmes (Boivin et al., 2014).

The World Health Organisation and UNICEF have thus developed initiatives such as Care for Child Development (CCD) based on the scientific evidence on child development which are aimed at promoting caregiving and enhancing psychosocial development in early childhood (Lucas, Richter,& Daelmans, 2017). The United Nations Global Strategy for Women's, Children's and Adolescents' Health has incorporated early child development in the Sustainable Development Goals and the expanding population of HEU children in South Africa has made this a national priority (UN, 2015). The mandate for government and non-governmental organisations to focus on the "First Thousand Days", encourages collaboration between health, education and social welfare sectors (Western Cape

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Government Department of Health, 2017). It is crucial to determine the surveillance, intervention and support needed in order to achieve the outcomes prioritised in the National Development Plan 2030(National Planning Commission, 2010). The Nurturing Care framework will be best positioned to address the plight of children at risk for developmental delays and disability, by scaling up existing health and social programmes, to address modifiable risk factors such as stunting and lack of early childhood stimulation(Britto et al., 2017).

In conclusion, future neurodevelopmental research involving HEU infants should focus on high-risk groups, such as preterm and low birth weight infants, stunted children, or in instances of compromised maternal physical and mental well-being and socioeconomic adversity. Secondly, ongoing pharmacovigilance is essential in the face of changing ART regimens and more prolonged ARV exposure. Finally, evaluating cognitive and behavioural outcome of young children, including effects of early intervention programmes, will require adoption of contextually appropriate CDAT which allow for global comparisons.

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ADDENDUM

Acknowledgements

This thesis could not have been completed without the guidance, support and encouragement of many people to whom I offer my gratitude and appreciation.

Professor Mariana Kruger, my promoter, who assisted me throughout the studies, granting access to funding and clinical support. Thank you for all your input, support and encouragement.

Professor Christopher Molteno, my co-promoter, an eminent researcher in the field of developmental paediatrics.

The Steering Committee of the Mother and Infant Health Study including Professor Monika Esser, Professor Mark Cotton and Professor Julie Bettinger from the University of British Columbia.

Dr Barbara Laughton my colleague and friend who has mentored me in neurodevelopmental research and generously shared her knowledge, data and ideas over the years.

Dr Amy Slogrove whose knowledge and passion for the MIHS helped me with the conceptualisation, planning, implementation and write-up of the neurodevelopmental studies.

Dr Emma Kalk for data on placental pathology and her contributions to the neurodevelopmental and Goodenough Draw-a-person study.

Professor Rhoderick Machanik, Professor Martin Kidd, Dr Maxwell Tawanda Chirehwa and Mrs Tonya Esterhuizen, who performed the statistical analyses.

Dr Moleen Zunza for the data on infant feeding and statistical input.

Dr Gareth Mercer for sharing his information on the fathers in the MIHS.

Professor Mark Cotton for his logistic support, advice, encouragement and assistance with writing.

Mrs Ronel Barnard for her assistance with the developmental assessments and data entry.

Dr Henriëtte Saunders for her assistance with infant developmental assessments.

Marchalaine Hendricks, Shariefa Sylvester, and the FAMCRU team who assisted with the study.

Carlos Moffat and Aviwe Cweya for their expert assistance with translation.

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Lungiswa Rosie Khetelo and Sonya Cotton for their advice on the translation of assessment tools.

Dr Hilmar Klaus Luckhoff for his editing, writing suggestions and formatting of the thesis.

Ms Nikki Armstrong for designing the book cover.

Ms Anita Fourie for administrative support, formatting and collation of the thesis

Professor Johan Schoeman, a respected mentor who taught me the foundations of research.

Most of all; the infants and their parents to whom this study is dedicated.

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LIST OF ABBREVIATIONS

ADBB Alarm Distress Baby Scale

ARV Antiretroviral

ART Antiretroviral therapy

BSID Bayley scales of infant Development-3rd edition

BSIDII Bayley scales of infant Development-2nd edition

cART Combination antiretroviral therapy

CDAT Child development assessment tools

CES-DCentre for Epidemiological Depression scale

CI Confidence Interval

DAP Draw-a-Person quotient

ECD Early childhood development

EHQ Eye-hand sub-quotient

GMDS-ER Griffiths mental development scales-extended revised

GQ General quotient

HAART Highly active antiretroviral therapy

HEU HIVexposed uninfected

HFD Human figure drawing

HI HIV-infected

HIC High-income countries

HIV Human immunodeficiency virus

HUU HIV unexposed uninfected

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LMIC Low- and middle- income countries

MAS Molteno Adapted Scale

MIC Middle income countries

MIHS Mother and Infant Health Study

NVP Nevirapine

PLWH People living with HIV

PMTCT Prevention of mother to child Transmission

SDQ Strengths and difficulties questionnaire

TDS Total difficulties score

UMIC Upper middle income country

UN United Nations

US United States of America

VTP Vertical transmission prevention

WHO World Health Organisation

ZDV Zidovudine