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Neurodevelopmental Intervention in Early-Treated HIV-Infected Children

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DECLARATION

I, Renate Strehlau, hereby declare that this Thesis is my own, unaided work. It is being submitted for the Degree of Doctor of Philosophy of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University. I confirm that I conducted the study in my personal capacity and met the qualifying criteria as the lead author for all publications arising from this study.

Renate Strehlau

19 January 2021, in Johannesburg

DEDICATION

This work is dedicated to my Mother, with my immense gratitude for her unfailing support, quiet strength and earnest prayers.

Soli Deo gloria

PUBLICATIONS & CONFERENCE PRESENTATIONS ARISING FROM THIS STUDY

Publications

Strehlau R, Aswegen T, Potterton J. Neurodevelopmental assessment of HIV-exposed uninfected and early-treated HIV-infected children: study protocol. BMC Research Notes. 2018;11(1):235. https://doi.org/10.1016/S0140-6736(11)60555-2

Strehlau R, van Aswegen T, Potterton J. Interventions Addressing Neurodevelopmental Delay in Young Children Infected With and Exposed to HIV: A Scoping Review. Rehabilitation Oncology. 2019;37(1):7-16. https://doi.org/10.1097/01.REO.0000000000000150

Strehlau R, van Aswegen T, Burke M, Kuhn L, Potterton J. A description of early neurodevelopment in a cohort of HIV-exposed uninfected children. AIDS Care. 2020:1-8. https://doi.org/10.1080/09540121.2020.1736257

Strehlau R, Burke M, van Aswegen T, Kuhn L, Potterton J. Neurodevelopment in early treated HIV-infected infants participating in a developmental stimulation program compared with controls. Child: care, health and development. 2020; (in press)

Conference Presentations

Strehlau R, van Aswegen T, Burke M, Potterton J. A description of early neurodevelopment in a cohort of HIV-exposed uninfected children. Wits University School of Clinical Medicine Research Day. University of the Witwatersrand, Faculty of Health Sciences, Johannesburg. Oral presentation: 23 October 2019.

Strehlau R, van Aswegen T, Burke M, Kuhn L, Potterton J. Neurodevelopment at 12 months of age among very early treated infants in Johannesburg, South Africa. AIDS 2020: Virtual (23rd International AIDS Conference), 6-10 July 2020. Poster presentation. Abstract reference number: A-AIDS2020-06232.

Strehlau R, van Aswegen T, Burke M, Kuhn L, Potterton J. Neurodevelopment at 12 months of age among very early treated infants in Johannesburg, South Africa. Wits Faculty of Health Sciences Research Day and Postgraduate Expo, Oral presentation: 15 October 2020. Abstract reference number: CSTH-O-06

ABSTRACT

It has been estimated that more than 200 million children under the age of five years in low- and middle-income countries are at risk of not reaching their developmental potential, with the largest at-risk population residing in sub-Saharan Africa. A multitude of biopsychosocial risks have been implicated in poor short- and long-term developmental outcomes, most notably: poverty, stunting and infection with the Human Immunodeficiency Virus (HIV).

Infection of an infant with HIV can result in significant neurological damage. The use of paediatric antiretroviral therapy (ART) has reduced the frequency of HIV-related adverse neurological and neurodevelopmental sequelae. However, children living with HIV infection and those uninfected but exposed to HIV, face cumulative hurdles as in Africa HIV is often accompanied with economic and social disparity.

Evidence has demonstrated the importance of the early childhood period for the acquisition of cognitive, motor, language, perceptual, socio-emotional and self-regulation abilities which are foundational for future academic and economic competencies as well as human capital achievements over the life course. The proven benefits of early stimulatory interventions on developmental outcomes resulted in the inclusion of access to quality early childhood development programmes as a Sustainable Development Goal in an attempt to promote the development of underprivileged children.

As part of this study a scoping review investigating interventions which have been used to mitigate or prevent neurodevelopmental delays in children exposed to or infected with HIV, was conducted. The existing evidence mapped out by the review revealed a wide variation in the type, duration and intensity of interventions. Of the ten studies included in the review only one

investigated an intervention which focused specifically on stimulating child development in young children infected with HIV through a home-based stimulation programme.

This study was designed as a non-randomised controlled intervention study aimed to describe neurodevelopment at 12 months of age in three distinct groups, namely: an observational, an intervention and a control group, using a multi-dimensional diagnostic test – the Bayley Scales of Infant and Toddler Development III-edition (BSID-III), in an urban centre in Johannesburg, South Africa. The observational and intervention group (IG) consisted of children with perinatally acquired HIV infection who started ART within the first month of life, in addition children in the IG participated in a year-long developmental stimulation programme; HIV-exposed uninfected children made up the control group. Children in the observational group (OG) who were older than one year at the time of study start were assessed when 24 or 36 months old.

Compared with the test reference mean, the 12 month BSID-III assessment scores of children in all three groups were encouraging. Children with perinatal HIV infection in the IG displayed a trend towards higher BSID-III mean composite scores in the cognitive, language and motor sub-scales, compared with OG children: 105 (SD 128) vs. 103 (SD 9), p=0.5252; 105.2 (SD 11.1) vs. 100 (17), p=0.1904; 99.5 (SD 9.24) vs. 99 (SD 11), p=0.8705, respectively. BSID-III scores were lower in children assessed at 24 and 36 months of age.

Despite early diagnosis and treatment, children infected with HIV are still at risk of poor developmental outcomes – secondary to both HIV infection and underlying social determinants of health. Strengthening health services to ensure mothers and children receive a comprehensive package including an early stimulation programme will help children infected with HIV to achieve their developmental potential.

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FORMAT OF THIS THESIS

This thesis is presented in the integrated format as described in the University of the Witwatersrand's Faculty of Health Sciences guide for PhD thesis formats.

The thesis begins with a synopsis of the research that was performed, outlining the study objectives and briefly describing the study setting and methodology employed. This has been included to allow the reader to appreciate the ensuing sections within the context of the study. Following the background synopsis is the introductory chapter which comprises a review of current and sentinel literature beginning with a description of the early childhood developmental period, highlighting the importance of these early childhood years and the long-lasting, far-reaching consequences if developmental needs are not met. Modifiable factors impacting childhood developmental outcomes, including infection with and exposure to HIV, within the South African context are then reviewed. After the identification of the problem and the importance thereof has been established, early developmental stimulatory programmes and strategies aimed at improving developmental outcomes, specifically within the complexities of children affected by and infected with HIV in the African setting, are discussed. The use of developmental assessment tools and ascertaining outcomes are then considered. Where applicable, each section contains an integrative narrative which weaves the themes discussed together with activities employed during the study.

Chapters 3 through 6 are comprised of publications arising from this study. Each chapter begins with details of the publication, including: title of the published article; list of authors; journal name; journal ISSN; year of publication; journal volume and page numbers; and the Digital Object Identifier (DOI). The publication details are followed by a short summary of the main points of the published manuscript and a description of the journal in which the article has been published. The specific contributions made by co-authors to individual manuscripts are specified in a tabulated format. Lastly, journal copyright and permission statements detailing

authorisations which have been granted by specific publishers in terms of manuscript reproduction as a part of the print and electronic version of this thesis are detailed. A brief note is included in which the main findings of the manuscript are highlighted.

The concluding chapter synthesises key findings arising from this study and relates them to the original research question. Practical application for implementation within the clinical setting is proposed within the bounds of the limitations encountered. Recommendations for future research conclude this section. Chapter-specific reference lists can be found at the end of each chapter.

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ABBREVIATIONS AND ACRONYMS

AB	Adaptive Behaviour
ADHD	Attention Deficit Hyperactivity Disorder
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
BFHI	Baby-Friendly Hospital Initiative
CD2015	Countdown to 2015
CD2030	Countdown to 2030
CHBH	Chris Hani Baragwanath Hospital
CHIDO	Child Health Intervention for Development Outcomes
CLHIV	Children Living with HIV
ECD	Early Childhood Development
EID	Early Infant Diagnosis
FAS	Foetal Alcohol Syndrome
FASD	Foetal Alcohol Spectrum Disorder
GMDS	Griffiths Mental Development Scales
HEU	HIV-Exposed Uninfected
HIV	Human Immunodeficiency Virus
HUU	HIV-Unexposed Uninfected

IG	Intervention Group
IMCI	Integrated Management of Childhood Illnesses
IQ	Intelligence Quotient
IUGR	Intra Uterine Growth Restriction
LBW	Low Birth Weight
LMIC	Low-and Middle-Income Country
LTFU	Lost to Follow-up
MDG	Millennium Development Goal
MISC	Mediational Intervention For Sensitising Caregivers
MRI	Magnetic Resonance Imaging
MTCT	Mother-to-Child-Transmission
MUAC	Mid-Upper Arm Circumference
NDoH	National Department of Health
NDP	National Development Plan
OG	Observation Group
PLHIV	People Living with HIV
PMTCT	Prevention of Mother-to-Child Transmission
POC	Point-of-Care
PSI-SF	Parenting Stress Index – Short Form
RCT	Randomised Control Trial
RMMCH	Rahima Moosa Mother and Child Hospital
RtHB	Road-to-Health Booklet

SDG	Sustainable Development Goals
SE	Social-Emotional
SGA	Small for Gestational Age
SSRI	Selective Serotonin Reuptake Inhibitors
TH	Thyroid Hormone
U5MR	Under-Five Mortality Rate
UN	United Nations
UNICEF	United Nations Children's Fund
WHO	World Health Organization

CHAPTER ONE

BACKGROUND AND STUDY SYNOPSIS

1.1. Overview

The period of early child development, from conception through until eight years of age, has been identified as a stage in the life course budding with potential. During these years, complex neural circuitry is established through the interplay of the environment, experiences and genetics[1]. Constructive early life experiences give rise to the promising possibility of impacting the remainder of the child's years into adolescence and throughout adulthood, impacting long-term health and even leading to intergenerational influences [2, 3].

However, it is estimated that 40-50% of children under the age of five years residing in low- and middle-income countries (LMIC) will never attain their full developmental potential as they are faced with a myriad of intense life stressors and pervasive difficulties, one of which being human immunodeficiency virus (HIV) infection [4-6].

Globally, great strides have been made towards the elimination of new paediatric HIV infections however, children in the African region still face the distinct risk of perinatal HIV acquisition as well as limited access to appropriate treatment for those infected with the virus [7, 8]. Although the destructive effects of paediatric HIV infection on the developing nervous system have been moderated through the use of antiretroviral (ARV) medication, neurodevelopmental delays are still evident and impact negatively on future developmental achievements of children infected with HIV [9]. The numbers of HIV-exposed uninfected (HEU) children are ever increasing, and concerns have been raised regarding evidence indicating that these children may also display lower mental and motor scores [10].

Early childhood development (ECD) programmes are defined by the World Health Organization (WHO) as interventions aimed at enhancing the physical, socioemotional, cognitive and motor development of children between birth and eight years of age [11]. ECD interventions have shown substantial and sustainable benefits on long-term neurodevelopmental outcomes[12] [13], but effective and feasible national programmes are needed as the burden of poor development is greater than previously estimated [14].

In summary, the developmental potential of millions of children is threatened. In particular children diagnosed with HIV infection as well as those uninfected with, but exposed to the virus. Effective interventions stimulating ECD have proven long-lasting effects on maximising human potential. The benefits of starting paediatric antiretroviral therapy (ART) at a very early age may be further expanded by including an ECD programme as part of the long-term holistic management of children infected with HIV.

1.2. Research Aim and Objectives

This study set out to describe the neurodevelopment, in terms of scores achieved on a multidimensional childhood assessment tool – the Bayley Scales of Infant and Toddler Development, III-edition (BISD-III) – in a cohort of young children infected with HIV and started on ART within the first month of life. BSID-III scores were compared with scores from a control group of children exposed to, but uninfected with HIV. Additionally, in view of the beneficial reports of early childhood stimulatory programmes on developmental outcomes, a sub-group of infants infected with HIV was enrolled in a year-long, home-based program aimed at stimulating the developing brain and potentially improving developmental outcomes. Assessment scores from the children participating in the stimulation programme were compared with scores obtained by the control group and the children infected with HIV receiving only the standard of care.

1.2.1. To describe the neurodevelopment of a cohort of early-treated children with perinatally-acquired HIV infection.

1.2.2. To describe the neurodevelopment of a cohort of children exposed to but uninfected with HIV.

1.2.3. To compare neurodevelopment of a cohort of early-treated children with perinatally-acquired HIV infection participating in an developmental stimulation programme with a cohort of early-treated children with perinatally-acquired HIV infection receiving only the standard of care.

1.2.4. To investigate associations between neurodevelopment, demographics and HIV-related characteristics.

1.3. Overview of Methodology

A brief overview of the study location and methodology of the study is included here in order to describe the context in which the study was conducted and to help contextualise the integrative narrative which is included throughout the literature review. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M170653), registered with the Pan African Clinical Trial Registry (PACTR201801002967587).

1.3.1. Study Location

This study was conducted at a single site, the Empilweni Services and Research Unit (ESRU), in Johannesburg, South Africa. Johannesburg, falling within Gauteng province, is the largest city in South Africa and although it is classified as Africa's wealthiest city [15] the province's 15.2 million [16] citizens are spread across diverse socioeconomic bands from the extremely affluent to those living in abject poverty. ESRU is comprised of a clinical services and a research unit and is located within the premises of the Rahima Moosa Mother and Child Hospital (RMMCH) which is approximately 10 km west of the Johannesburg city centre.

1.3.2. Study Participants

The children included in this study were selected from the Latency and Early Neonatal Provision of Antiretroviral Drugs (LEOPARD) trial. Participants in the LEOPARD trial were enrolled from two similar protocols (LEOPARD-observational (O) cohort and the LEOPAD-clinical trial (CT) cohort). The protocols enrolled children depending on the timing of their HIV diagnosis and initiation of ART after birth – the LEOPARD-CT cohort underwent birth point-of-care (POC) HIV testing within 48 hours of birth and started ART within 14 days of birth, while for the LEOPARD-O cohort there was no upper limit of age in terms of when the HIV diagnosis was made nor when ART was started. LEOPARD trial enrolment began September 1, 2013 until August 31, 2018. In addition to the cohort of children infected with HIV, between July 2016 and January 2018 a group of HEU neonates were enrolled as a control group in the LEOPARD trial.

As from September 1, 2017 we offered parents of children enrolled into the LEOPARD trial co-enrolment into the intervention group (IG) of the neurodevelopmental assessment study. Children enrolled in the LEOPARD study prior to the start of the neurodevelopmental assessment study made up the observational group (OG). In order to increase the number of children enrolled in the IG, children meeting inclusion criteria for the neurodevelopmental trial were also recruited from the Empilweni paediatric HIV clinic at RMMCH after LEOPARD trial enrolment had ended (September 2018 – January 2019).

The principal investigator on the neurodevelopmental assessment study, on which this thesis is based, is the Deputy Director at ESRU and was working as the site principal investigator on the LEOPARD trial. The investigator was one of the primary research physicians conducting the LEOPARD trial and caring for children in the cohort. The investigator thus had an existing relationship with parents and children in the OG, and worked closely with newly diagnosed children and their parents in the IG. The investigator was also involved in collecting data required for the LEOPARD trial.

1.3.3. Study Procedures

1.3.3.1. LEOPARD Trial-specific

Study procedures done as part of the LEOPARD trial for the cohort with HIV and for the uninfected controls are detailed in publications included as part of this thesis and can be found in Chapter 3 as well as in LEOPARD-specific publications [17, 18]. The clinical and pharmacological management of the children in the LEOPARD trial and laboratory testing procedures employed were not done as part of the neurodevelopmental assessment study and will not be detailed further in this section.

Follow-up after enrolment into the LEOPARD trial was weekly until 4 weeks and then monthly until six months of age. Children enrolled into the LEOPARD-CT study were seen two monthly, and children in the LEOPARD-O trial three monthly, until two years of age. Thereafter visits were scheduled for every three months. HEU children were seen at birth, 4, 8, 12, 24, 36 and 48 weeks of life.

1.3.3.2. Neurodevelopmental Study-specific

1.3.3.2.1. Enrolment and Follow-up

All mothers of neonates newly diagnosed with HIV infection were invited to enroll into the IG of the neurodevelopmental study. Caregivers unable to comply with follow-up; mothers with uncontrolled psychiatric illness; and those unable to provide informed consent were excluded from the trial, as were neonates with serious birth defects. Written informed consent was obtained from the child's mother according to Good Clinical Practice standards. Informed consent was obtained from the child's mother prior to conducting the BSID-III for all children in the OG already enrolled in the LEOPARD trial.

Specific neurodevelopmental study visits with the mother-infant dyad participating in the IG occurred every three months through the first year of life. Appointments were scheduled at a mutually convenient time for the clinic and the mother. Mothers were called the day prior to the clinic visit to remind them of their appointment. Mothers who missed follow-up appointments were contacted telephonically and if this was unsuccessful a home visit was attempted.

1.3.3.2.2. Intervention Group Programme

Within the first month of birth, infants enrolled in the IG began receiving stimulatory toys and books every three months according to a set schedule. The set of toys to be provided was developed after discussion with senior colleagues working in the field of development paediatrics – both doctors and physiotherapists. The toys were aimed at stimulating different developmental skills – cognition, speech and language, fine and gross motor skills, and socio-emotional development. For example, reading books and telling stories to stimulate language development. The rattle provided at birth would have been for the caregiver to use initially to encourage the baby to turn his/her eyes and head towards the sound produced when shaking the rattle. Use of the rattle was encouraged when the child learned to grasp objects at a later stage and shaking the rattle would stimulate the development of connecting activities with outcomes (cause-and-effect). Caregivers were encouraged to play peek-a-boo using the blanket provided and any of the other toys to stimulate the development of object permanence.

Table 1. 1 List of toys provided to each child participating in the stimulation programme

Child's age	Items provided
Birth	baby blanket, washcloth, rattle, booties and hat
3 months	handheld mirror, small ball (5cm), book, squeaky squeeze toy
6 months	ring stacker, large ball (15cm)
9 months	wooden blocks, plastic colourful stacking cups, book
12 months	wooden form board, toy car, plastic doll, picture book, crayons and paper

The toys were all new and safe use of the toys was demonstrated to the infant's mother. Use of the toys was explained to the mother who was encouraged to play with her child a couple of times each day when the baby was awake and calm. Feedback on the use of the toys was obtained verbally from the mother during follow-up visits. No formal written play diary was required to be completed by the mother.

Every three months, in addition to the toys, the mothers were provided with information cards detailing a home-based, parentally-driven developmental stimulation programme. The activity programme – used with permission – was developed as part of a South African study investigating developmental outcomes of children with congenital heart disease [19]. The selected information cards (0-18 months) have been included in Appendix A. Each set of information cards contained age-specific information under the following headings: a) What babies should do at this age – physical development; learning, thinking and solving problems; language and communication; and social and emotional skills, b) Warning signs of developmental delay (You should be worried if your baby does not…), c) Things you can do to help your baby's development, and d) Toys and items you can use at home. The information on the cards was in English and was accompanied by colourful drawings depicting toys and children engaged in various play activities. It was confirmed by all mothers that they were able to read and understand English. Each item on the information card was explained to the mother and she was shown how to stimulate the baby using the toys provided. The mother was encouraged to work through at least one of the suggested activities every day in addition to reading to her child daily. The cards were laminated so that they were more durable than paper or cardboard, and they were cut into the same size as the Road-to-Health Booklet (RtHB) for ease of storage during travel.

1.3.3.2.3. BSID-III Assessment Procedures

BSID-III developmental assessment was performed for children in both the pre-intervention OG and the IG. The assessment was done at 12 months of age for the IG and at the soonest birthday (12, 24, or 36 months) after September 2017 for the OG. A window period of 4 weeks was allowed for on either side of the ideal assessment time point.

The study principal investigator and physiotherapist underwent BSID-III-specific training prior to conducting any assessments. The training was conducted by a Professor from the Department of Physiotherapy from the University of the Witwatersrand who has extensive experience with the use of the BSID-III assessment tool in the South African context and is an expert in the field of paediatric neurodevelopment. The first ten BSID-III assessments were conducted with both assessors working together to ensure consistency of the implementation of assessment items. Inter-rater consistency was established but a formal reliability percentage was not calculated between the two assessors.

Assessments were conducted during the morning of the scheduled visit only if the mother and child were feeling well. Assessments were carried out prior to any required phlebotomy procedures. Prior to beginning the assessment the procedure was explained to the mother and it was ensured that the child was comfortable and not hungry or sleepy. Assessments were conducted in an uncluttered room in a quiet setting in the research clinic and assessments took between 60-90 minutes. The caregiver stayed with the infant throughout the assessment so that the infant felt comfortable and relaxed. The BSID-III was conducted in English. The test item was asked of the child in English in a uniform manner. Older children were encouraged to indicate to the tester, or to their mothers, if they did not understand the instruction. If the child did not understand the English instruction, the instruction was repeated to the mother and it was requested that she translate the test item into the child's preferred language. In the same way, if the child provided an answer in a language not understood by the tester, it was requested that the mother translate the child's answer into English for the examiner to understand. Although the two assessors were not fluent in all of the languages spoken by the children they had a basic grasp of the language, enough to know whether the mothers were interpreting the instructions correctly. Study visits were scheduled according to chronological age in weeks for term and pre-term infants. Children were assessed at 12 months chronological age and BSID-III scores calculated using corrected age. Assessors were not blinded to the infant's HIV diagnosis.

1.4. Conclusion

This introductory chapter has provided a brief overview of the critical nature of the early developmental period, the immediate and long-term importance of this period and the millions of children globally who are at risk of not reaching their full developmental potential in particular children infected with and affected by HIV. The aims of this study have been presented and the context in which the study was carried out has been described. The following chapter contains an in-depth discussion of the early developmental period, the risk factors which threaten a child's developmental outcome as well as protective influences enhancing development. The emphasis is on children diagnosed with HIV infection and those exposed to but uninfected with HIV and an integrative narrative is included throughout the chapter.

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CHAPTER TWO

INTRODUCTION AND LITERATURE REVIEW

2.1. Childhood Development

Childhood development describes the complex period of transition from conception, through infancy, toddlerhood, early and later school years, and adolescence until the child becomes an adult. The child undergoes significant biological and psychological maturational changes during this developmental time-period, acquiring and refining cognitive, language, motor, perceptual, socio-emotional, and self-regulation skills [1]. Adverse childhood experiences can have long-term physiological, genetic and epigenetic effects which can influence early learning systems, and subsequent health and development over the life course [2, 3].

The early years of life are characterised by rapid brain development and represent a critical period of risk during which negative influences can exert a lifelong impact. However, the first 1000 days i.e. from conception through to the end of the second year of life, have also been described as a window of opportunity during which the cornerstones of development can be established thereby underpinning future success [4].

This chapter introduces the concepts of the early developmental period of childhood and discusses consequences – during infancy, early childhood, the early school years, adolescence, adulthood and even inter-generational – arising from deprivation within spheres of the biopsychosocial framework during this period. Information included in this chapter was collated through database searches which included the NCBI PubMed, PsycINFO, Google Scholar, and the Cochrane Library. Although the search was not limited by publication type or date, only full-text English language articles were reviewed. Grey literature, including conference abstracts, was also searched.

2.1.1. The Period of Early Childhood Development

Human development is a lifelong process which can be defined as a systematic series of changes that occur in an individual throughout their lifetime, with certain periods – such as childhood – marked by the most rapid change. This systematic maturation takes place in all children and follows a relatively predictable progression of changes in the physical, cognitive, perceptual, motor, language, socio-emotional and self-regulation abilities [1, 5]. The rate of skill acquisition will vary between individuals, and future learning throughout childhood and into adulthood builds on these early foundational abilities [3].

Anatomically, during the first 24 months of life, the volume of the human brain increases at a rate not seen again during the lifespan [6]. The course of brain maturation through the processes of neuronal pruning and myelination is extremely vulnerable to environmental influences [7, 8].

The timespan of *early* development has been defined as the period from conception through birth until eight years of age [9]. Certain risks pose greater dangers at specific time periods e.g. the first 1000 days after conception is a period which is particularly sensitive to the effects of nutrition on growth and cognition [10] and although poverty has a far-reaching impact over the first five years of life, the child is most at risk during the first year of life [11].

Shonkoff and Phillips define a number of core concepts of human development in their book: From Neurons to Neighborhoods: The Science of Early Childhood Development. The authors state that human development is shaped by a "dynamic and continuous interaction between biology and experience" and that the development of children unfolds along individual pathways which are shaped by the interaction between sources of vulnerability and sources of resilience [12]. Childhood development is influenced by an untold number of elements and exposure to a variety of risks factors resulting in a cumulative impact on the child's developmental potential [13].

2.1.2. The Enduring Importance of the Early Developmental Period

The maturational and developmental changes that occur in the immature brains of infants and young children have been shown to be vulnerable to influences from both the child's external and internal environment. Long-term follow-up of children who suffered neglect during their early years has shown how experience plays an essential role in the architecture of the developing brain and children raised in institutions have shown serious socio-emotional and psychiatric disturbances [14], changes in brain grey and white matter volume [15], and on a molecular level – reduced chromosomal telomere length [16].

The process of neuroplasticity is responsible for experience-dependent structural and functional changes to the central nervous system. Neuroplasticity refers to the inherent capability of the CNS to undergo maturation and adapt structurally and functionally in response to both positive and negative experiences [17]. This relative malleability of the brain's synaptic connections and neural circuitry is heightened during pre- and post-natal time-sensitive periods and continues to a lesser degree through adolescence and adulthood [17].

The science of epigenetics has been described as "the study of stable alterations in gene expression by non-genomic mechanisms, resulting in stable alterations in phenotypes" [2]. It is the process whereby life experiences alter gene expression which in turn impact future developmental experiences, health, behaviour, and learning. Hertzman described this as "biological embedding" during which early experiences influence key biological systems and lead to different bio-developmental states [18]. Adult health events such as heart disease, diabetes, obesity, depression, accelerated aging and memory loss have been attributed to adverse early life experiences with resultant epigenetic changes [19]. Destructive behavioural choices such as smoking, illicit drug use, alcoholism, teen pregnancy, risky sexual behaviours have been linked with psychosocial adversity in childhood which in turn resulted in altered gene expression [20]. In this way, negative early life experiences resulting in epigenetic changes with subsequent altered gene expression can continue to impact an individual's life course as well as that of their

offspring and future generations. Considering the far-reaching and long-lasting impact of limiting childhood adversity and maximising early childhood stimulation, the importance of optimising a child's potential during the early-developmental period cannot be overstated.

2.2. The Global State of Early Childhood Development

The importance of ECD and the vast number of children in the world not having their basic early developmental needs met was highlighted in the initial 2007 Lancet Series on Child Development in Developing Countries [21-23]. The report estimated that in 2004, 219 million children (43% of children) under the age of five years living in LMICs were at risk of failing to achieve their cognitive developmental potential [21]. However, with the use of improved source data and revised definitions of extreme poverty and stunting – as proxy markers for estimating children at risk – the 2004 estimates were revised to 279.1 million children (51% of children under five years of age in LMICs), in 2016 [24]. Still using exposure to extreme poverty and stunting as markers of at risk for developmental delay, 2010 data showed that there has been a reduction in the number of at risk children under five years old in LMICs to 249.4 million (43% of children) [24]. The region with the greatest number of children at risk is sub-Saharan Africa with 66% of children under the age of five years potentially not reaching their maximal developmental abilities [24].

The term *developmental potential* is often used in association with ECD texts. A child reaches their developmental potential when they have acquired academic, behavioural, socio-emotional, and economic competencies, enabling accomplishments in these spheres [3].

Countdown to 2030 (CD2030) *for Maternal, Newborn and Child Survival* (www.countdown2030.org) is an innovative initiative launched in 2016 and follows *Countdown to 2015* (CD2015) which began in 2003. *Countdown* aims to establish a multi-disciplinary, multi-institutional collaboration which uses data to foster accountability in an attempt to bring about drastic changes required to achieve the targets of the Sustainable Developmental Goals

(SDGs) for ending preventable maternal, newborn and child deaths [25]. Data on country-specific health system and finance policies, as well as interventions aimed at improving women's and children's lives, is gathered and analysed to determine a country's progress in achieving improvements to women's, children's and adolescent's health.

The United Nations Children's Fund (UNICEF), in collaboration with the Nurturing Care for Early Childhood Development Metrics Joint Technical Working Group of *CD2030*, published data in 2019 from 138 profiled countries summarising 13 Key Facts on how young children are faring today (**Figure 2. 1**) [26]. The data paints a bleak picture in terms of children attaining their developmental goals, receiving early stimulation in the home and instruction in ECD, supervision in the home and exposure to violent discipline, stunting, exposure to untreated maternal HIV infection, and the under-five mortality rate (U5MR).

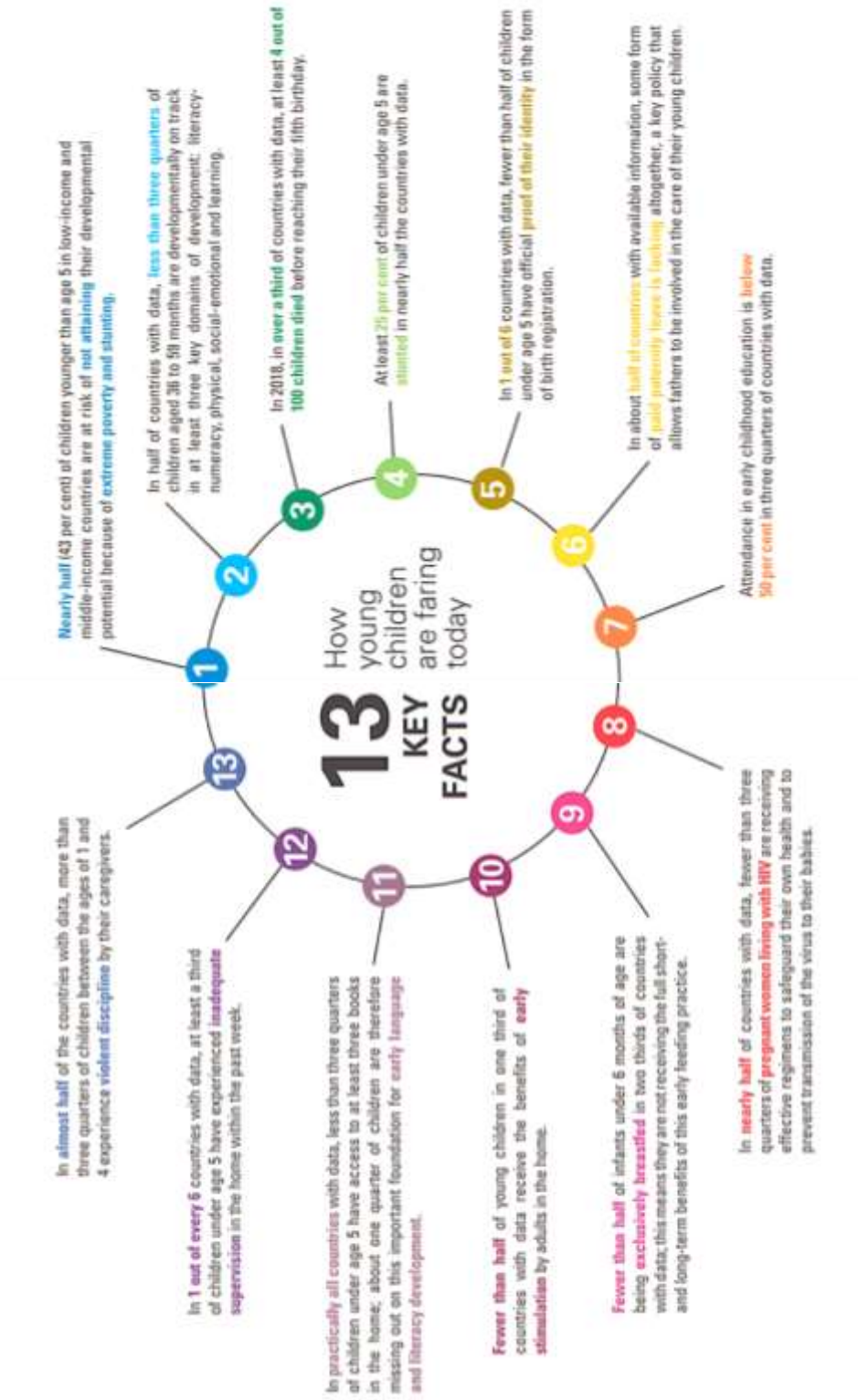

Figure 2. 1 Key Facts on how Young Children are Faring Today[26]

2.3. The Global State of Paediatric HIV

Although the paediatric HIV epidemic has been marked by the tragedy of many lost lives over the past 40 years, fast-moving scientific discoveries, prompt policy changes and advances in the clinical management of paediatric HIV infection have allowed the light at the end of the tunnel to shine a little brighter for the children infected with and affected by HIV infection.

The paediatric HIV epidemic reportedly started in San Francisco in the United States of America in 1982 – a 20-month-old infant contracted HIV after receiving a blood donation during the first month of life from blood products donated by an individual who was subsequently reported as being HIV infected [27, 28]. A week later the first cases of mother-to-child transmission (MTCT) were reported in four children all of whom were less than two years old, and although the exact details as we know them today were not fully understood at the time, the CDC attributed the illnesses to an infectious agent [29].

Subsequently, great strides in scientific discovery led to the understanding of the aetiology, epidemiology, clinical manifestations, treatment and prevention of HIV disease, but over the ensuing four decades we also mourned the loss of approximately 6.5 million (4.1-10.2 million) children under the age of 15 years who fell victim to this disease [30]. New infant HIV infections acquired through MTCT have been reduced to an estimated 160 000 (110 000-260 000) in 2018, a decrease of 41% from 280 000 (190 000-430 000) in 2010 [31], and an estimated 1.8 million (1.3-2.2 million) children aged between 0-14 years globally were living with HIV in 2019, of which only 53% (36-64%) had access to ART [30]. In South Africa, an estimated 62.7% (45.3-81.5%) of children living with HIV (CLHIV) aged 0-14 were receiving ART in 2018 [32].

Childhood HIV evolved into a chronic illness with clinicians reaching the unexpected milestone of transitioning adolescents with perinatally-acquired HIV infection from paediatric to adult HIV services [33, 34]. This shift to long term survival has seen a change in the management of paediatric HIV infection from acute care and the treatment of opportunistic infections, to the management

of long-term health complications and requirements. Health concerns in older children and adolescents with perinatally-acquired HIV infection include, among others: adherence to ART and management of ARV drug resistance [35]; mental health concerns [36]; neurocognitive impairments [37]; effects on the cardiovascular system of both ART and HIV infection itself [38]; chronic lung disease [39]; metabolic toxicities such as dyslipidaemia, insulin resistance and obesity [40]; deficits in bone architecture and strength [41].

Reduction in perinatal and postnatal HIV transmission rates has resulted in an increasing population of children exposed-to, but uninfected with HIV. The global number of HEU children can only be estimated by models incorporating country-specific use of ART and perinatal transmission rates. UNAIDS 2018 global estimates of the number of HEU children aged 0-14 years was 14.8 million (11.1-18.3 million) [42]. An estimated 1.4 million HIV-infected women give birth worldwide annually, and the success of maternal ART in preventing the transmission of HIV during these pregnancies results in approximately 1.25 million infants remaining HIV-uninfected [43]. However, despite not have contracted HIV infection these children seem to do less well than HIV-unexposed uninfected (HUU) children in comparable settings with evidence showing HEU children to be at higher risk of increased mortality and morbidity [44, 45].

2.4. Modifiable Risks Affecting Childhood Development

Various biopsychosocial factors have been investigated in term of their long- and short-term effects on childhood development. In a 2007 report for the WHO's Commission on Social Determinants of Health [46], Irwin, Siddiqi, and Hertzman describe various interdependent and interacting spheres of influence which play a role in impacting childhood development (**Figure 2. 2**) [47].

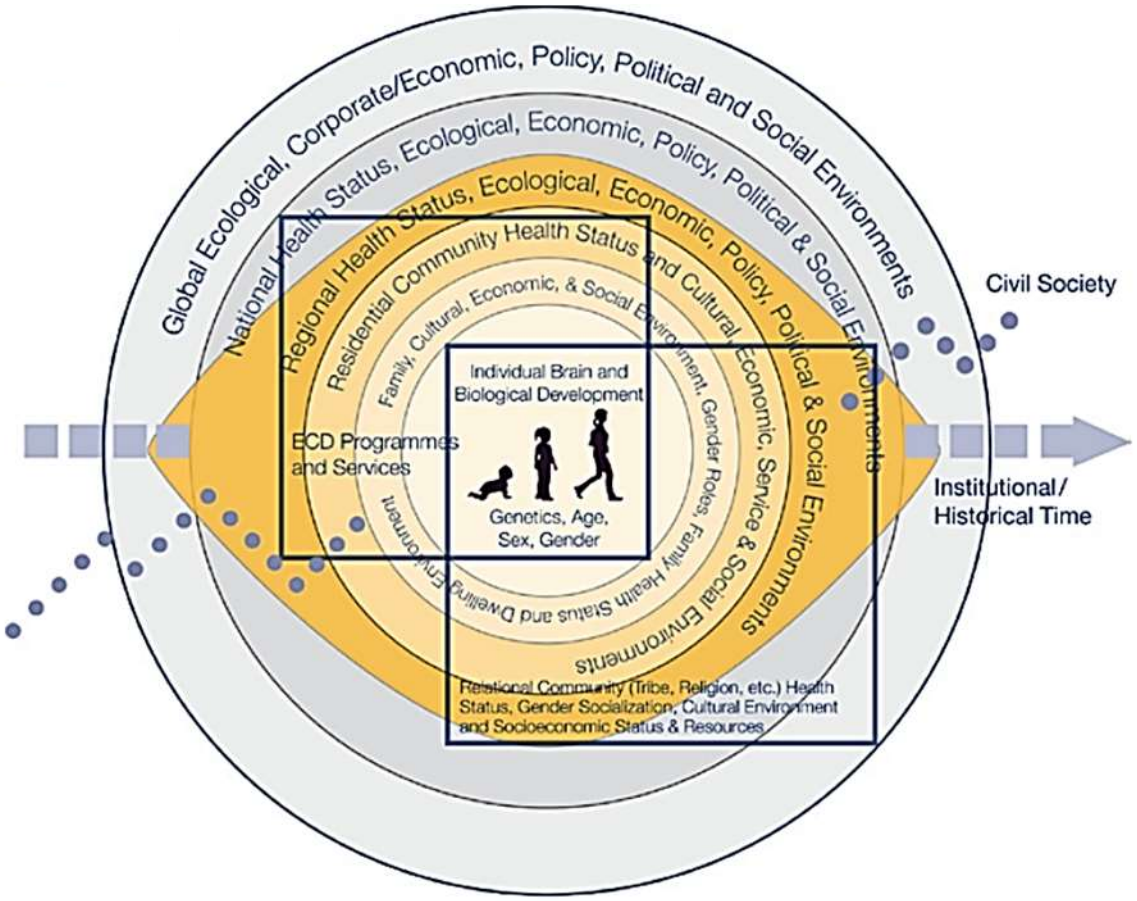

Figure 2. 2 Interdependent Spheres of Influence Impacting Childhood Development – The Total Environment Assessment Model of Early Child Development[47]

There exists a spider's web of interconnecting factors exerting their influence from the pre-conception period through the early developmental years, moulding and impacting every facet of the developing child. The following section discusses influences critical to the development of the child born in a LMIC under the subheadings of Nutrition; Infectious Diseases; and Psychosocial and Environmental risk factors.

2.4.1. Nutrition

2.4.1.1. Intra Uterine Growth Restriction

Poor maternal nutrition as a component of antenatal health can result in intrauterine growth restriction and babies that are born small for gestational age (SGA). SGA is defined as a neonate whose birth weight is less than the 10th percentile for that specific gestational age or two standard deviations below the population norms on the growth chart, while low birth weight (LBW) is defined as a birth weight of less than 2500 g [48, 49]. Neonates assessed as being born with clinical features of malnutrition and *in utero* growth restriction are labelled as having intra uterine growth restriction (IUGR) irrespective of their birth weight percentile [50]. IUGR commonly results from interplay between maternal, placental, foetal, or genetic factors and occurs when the brain is developmentally sensitive. Insufficient maternal nutrition during pregnancy can result in IUGR, specifically: maternal pre-pregnancy body mass index < 20 or weight < 45 kg; severe maternal starvation; and poor maternal weight gain during pregnancy [48].

The epidemiology of IUGR is closely linked to socioeconomic aspects of specific regions. Reports indicate foetal growth restriction being twice as common in resource-limited countries compared with developed counties. Data from the Child Health Epidemiology Reference Group indicated that growth restriction was evident in 19.3% of live births in LMIC [51].

Maternal HIV infection has been shown to adversely affect maternal and infant pregnancy outcomes. A systematic review published in 1998 – before the widespread availability of ART for pregnant women – incorporating data from 31 studies published between 1983 and 1996, reported the odds ratio of IUGR as 1.7 (95% CI 1.43-2.02) and LBW as 2.09 (95% CI 1.86-2.35) in infants born to women infected with HIV [52]. A more recently published systematic review and meta-analysis reporting perinatal outcomes associated with maternal HIV infection included 35 studies published from January 1980 through December 2014 which included data from 53 623 women. Analysis of the prospective cohort studies (n=20) showed maternal HIV infection to be

associated with an increased risk of LBW (relative risk 1.62, 95% CI 1.41-1.86) and SGA (relative risk 1.31, 95% CI 1.14-1.51). Retrospective cohort studies also suggest an increased risk of term LBW (odds ratio 2.62, 95% CI 1.15-5.93) with the strongest evidence for these associations being identified in sub-Saharan Africa [53].

Cognitive and neurodevelopmental abnormalities are among a variety of short- and long-term health and social consequences which have been shown to develop secondary to IUGR. Abnormalities occur from birth throughout the lifespan and include lower cognitive testing scores; language and motor delays; school difficulties; behavioural problems including attention deficit hyperactivity disorder (ADHD); cerebral palsy; perceptual performance difficulties; and low social competence [48, 54, 55].

Pregnant women with HIV infection from underprivileged socioeconomic settings in South Africa therefore face cumulative risks of giving birth to a baby with poor birth growth parameters, which in turn puts the child at risk of poor developmental outcomes. Interventions aimed at improving maternal nutrition, prior to and during pregnancy, with dietary supplementation balanced in protein and energy [56] and the inclusion of multiple micronutrients including iron and folic acid [57] have been shown to reduce the incidence of IUGR.

2.4.1.2. Childhood Undernutrition

Although growth is affected by multiple influences, linear growth retardation or stunting has gained precedence as the key indicator of chronic undernutrition in children [4]. Linear growth is the best measure with which to gauge the overall wellbeing of a child. Stunting is defined as a height-for-age below minus two standard deviations from the median height-for-age of the WHO Child Growth Standards [58]. UNICEF published statistics in 2016 reporting 36% of children aged 0-59 months living in sub-Saharan Africa to be moderately to severely stunted, exceeded only by South Asia (37%) with the world average reported to be 24%. The sub-Saharan urban (26%) rural (41%) disparity ratio was 1.5 [4].

The aetiology of stunting is multifactorial and results from a complex interplay between household, environmental, socioeconomic and cultural influences described in the WHO Conceptual Framework on Childhood Stunting [59, 60], depicted graphically in **Figure 2. 3**.

Figure 2. 3 World Health Organization Conceptual Framework on Childhood Stunting: Context, Causes and Consequences[61]

Retarded linear growth in CLHIV has been well documented throughout the HIV epidemic both in industrialised and developing countries; both prior to the availability of effective ART as well as into the paediatric ART era. CLHIV show improvements in their growth parameters (weight-for-age and height-for-age) after starting ART, but longitudinal cohort studies have shown HIV-positive children to remain shorter than uninfected children from comparable socioeconomic backgrounds [62, 63]. CLHIV are burdened with the long-term consequence of a chronic illness as well as reduced adult stature.

Undernutrition, especially in the first 1000 days from conception, which may result in stunting, has short- and long-term health and functional consequences. Stunting negatively affects a child's cognitive development leading to learning difficulties and poor educational performance [64, 65]. Children with ill health are denied the opportunity to play and learn and they therefore miss out on educational experiences which restricts their capacity to function as productive adults. Longitudinal studies have reported stunted children to experience poorer health in adolescence and adulthood [4]. Associations between shorter adult stature, lower wage earning potential and lost productivity have been shown [66, 67]. The 2007 Lancet review on child development in developing countries estimated that stunted children earn 20% less as adults compared with non-stunted individuals [21].

The reduction of the number of stunted children has been identified as a Global Nutrition Target for improved child health by the WHO. The goal is to reduce the number of stunted children in 2025 by 40% relative to the total number of children stunted in 2012, a reduction from 165 million to 100 million [68]. Although the global prevalence of stunting has decreased from 29.5% in 2005 to 22.9% in 2016, at the current rate of reduction the 2025 target will not be met [69].

Interventions with evidence demonstrating an improvement in maternal and child nutrition, and a subsequent reduction in the level of stunting, were summarised in a 2008 Lancet Series on Maternal and Child Undernutrition. Interventions which have been shown to be effective in reducing maternal and child undernutrition included: the promotion of breastfeeding and

complementary feeding, with or without provision of food supplements; maternal and child micronutrient interventions; general supportive strategies to improve family and community nutrition; and reduction of disease burden through promotion of handwashing and strategies to reduce the burden of malaria in pregnancy [70]. An update on the implementation and evidence for effectiveness of nutrition-based interventions aimed at reducing the global total of 165 million stunted children and 3.1 million deaths due to undernutrition was published in 2013 [71]. The authors suggest that nearly 1 million lives can be saved (15% of deaths of children younger than 5 years) with the scale-up of the core evidence-based nutrition interventions [71].

2.4.1.3. Micronutrient Deficiency

Micronutrients include vitamins and minerals which are derived from the diet and are essential for healthy development. Two micronutrients – iodine and iron – and their interplay with childhood growth and development will be discussed.

2.4.1.3.1. Iodine Deficiency

Iodine is utilised by the thyroid gland in the production of thyroid hormones (TH). TH is essential to normal physiological functioning. Severe iodine deficiency can lead to maternal and neonatal hypothyroidism [72]. In the developing foetal nervous system TH is essential for normal neuronal migration, myelination and synaptic transmission.[73]. During this developmentally critical period, insufficient TH results in irreversible damage to the developing brain with mental retardation and neurologic abnormalities, which can be prevented with the use of maternal iodine supplementation during the first and second trimesters of pregnancy [74, 75]. A 2005 meta-analysis which included 12 291 children younger than 16 years showed that the Intelligence Quotient's (IQ) of children growing up in iodine sufficient areas averaged 12.5 points higher than those in iodine deficient areas [76].

WHO data on iodine status collected from 192 WHO Member States between 1993 and 2003 are available from 126 countries. Overall, urinary iodine data covers 92.1% of the world's 6-12 year

old population. The report estimates that the iodine intake of 36.5% (285 million) of school-age children worldwide is insufficient [77]. It was reported in 2007 that progress has been made since 2003 and the percentage of school-age children at risk of iodine deficiency has decreased by 5% [78]. In Africa, an estimated 42.3% (49.5 million) of children have insufficient iodine intake [77], and in Southern Africa 31.6% (2.5 million) school-aged children (6-12 years old) were estimated as having insufficient iodine intake [77].

HIV infection per se has not been reported to directly result in iodine deficiency however; children with HIV infection who are living in poverty may potentially not achieve the recommended daily intake of iodine. Diarrhoeal disease and malabsorption secondary to untreated HIV infection may also result in iodine deficiency.

2.4.1.3.2. Iron Deficiency

Anaemia, or low haemoglobin concentration, can present as a manifestation of iron deficiency. The global prevalence of anaemia in children younger than five years of age in developing countries is estimated at 47% [79]. Iron deficiency anaemia, has been reported to impact the cognitive and behavioural development during childhood [22]. A 2001 review of studies on the effect of iron deficiency on cognitive development reported that children with iron deficiency anaemia in infancy continued to have poorer cognition, school achievement and behavioural problems into their middle school years, [80] although studies have failed to conclusively link the effects of childhood iron deficiency with poor cognitive outcomes due to the compounding effects of social disadvantage commonly present in children from iron deficient populations [79].

HIV-positive children have been reported as having a high prevalence of anaemia/iron deficiency [81]. A cohort study of CLHIV conducted in India (n=240), 43.3% on ART, reported iron deficiency to be present in 65.5% of the children (mean age 7.7 years) [82]. Data from six African countries analysed in a systematic review, reported that for each unit (g/dL) increase in haemoglobin, the risk of child death decreased by 24% in children aged 28 days-12 years [83].

Similarly, in HIV-positive children initiating ART, the presence of anemia is a strong predictor of mortality. A prospective Tanzanian trial of 3 144 children < 15 years of age, reported children with severe anemia (hemoglobin < 8.5g/dL) to have an 87% increased risk of overall death compared to children who were not severely anaemic [84].

Anaemia prevention strategies through improved dietary intake; fortification of commonly consumed foods e.g. flour, breakfast cereals, infant formula; provision of dietary iron supplementation; disease control e.g. prevention and treatment of malaria and deworming in helminth-endemic areas; and improving knowledge and education about the importance or iron and other micronutrients [79]. Programmes to mitigate iron deficiency in children in developing countries have shown evidence of improved motor and social-emotional (SE) outcomes [22]. The 2003 South African "R 504 Regulations relating to the fortification of certain foodstuffs" made the fortification of certain types of maize meal and flour – with vitamin A, thiamine, riboflavin, niacin, pyridoxine, folic acid, iron and zinc – mandatory [85].

2.4.1.4. Breastfeeding

The 2016 Lancet Series on breastfeeding presents conclusive evidence that the benefits of breastfeeding for children include fewer infections, increased intelligence, and probable protection against overweight and diabetes [86]. Breastfeeding has been shown to improve cognition and scores on IQ testing. A long-term randomised trial of 13 889 Belarussian children (assessed at a mean age of 6.5 years) reported the breastfeeding group as having higher means on all of the Wechsler Abbreviated Scales of Intelligence measures. The authors concluded that improvements in children's cognitive development resulted from prolonged and exclusive breastfeeding [87]. A systematic review and meta-analysis of evidence of the association between breastfeeding and performance in intelligence testing included 17 studies and reported that breastfed children achieved a higher IQ (mean difference: 3.44 points) [88].

Globally breastfeeding rates vary widely. More infants are breastfed in low-income countries than in high-income countries, and the duration of breastfeeding in high-income countries is

shorter [86]. The WHO recommends that infants are breastfed exclusively for up to six months of age, however, even in LMIC, only 37% of infants younger than six months are exclusively breastfed [86].

South African data, updated in 2010, from the WHO Global Data Bank on Infant and Young Child Feeding, reports the national total of ever having breastfed as 81.5% [89]. More recent data collected in 2016 as part of a UNICEF country analysis on infant and young child feeding, reports 82.6% (range: 80.0-94.9) of infants born in the preceding 24 months to have ever initiated breastfeeding, however, data from the same period shows that only 31.6% (range: 25.6-38.3) exclusively breastfed for six months [90]. The HIV epidemic has significantly impacted policy and programmatic recommendations as well as community and family attitudes towards breastfeeding [86]. The 2019 South African Department of Health prevention of mother-to-child transmission (PMTCT) guidelines recommend that mothers on ART breastfeed exclusively for six months where after breastfeeding can continue for 24 months or longer to compliment the infant or toddler diet [91].

RMMCH has adapted its policies and works in a manner which employs the strategies of a 'Baby-friendly Hospital'. Launched in 1991 by the WHO and UNICEF, the Baby-friendly Hospital Initiative (BFHI) aims to support practices that promote breastfeeding and maintain exclusive breastfeeding for the first six months of life [92]. All mothers delivering their babies at RMMCH are encouraged to exclusively breastfeed for six months. Additional counselling and PMTCT is provided for HIV-positive mothers.

2.4.2. Infectious Diseases

2.4.2.1. Human Immunodeficiency Virus Infection

The HI virus has an affinity for the human nervous system. This neurotropic virus enters the central nervous system (CNS) through a complex cascade of events involving alteration of the blood-brain-barrier and molecules including HIV envelope and regulatory proteins; products of activated monocytes; and activated brain endothelial cells [93]. It has been postulated that certain strains of HIV-1 may demonstrate greater neuro-virulence i.e. have an increased propensity to invade and damage the nervous system [94]. HIV-1 seeds itself throughout the nervous system during the stage of primary viraemia and is able to persist, in a replication-competent form, in certain cell types and anatomical sites (viral reservoirs) even in patients who have achieved viral suppression on ART [94]. From early on in the HIV epidemic neurodevelopmental consequences have been documented with a reported prevalence of 30-50% in antiretroviral treatment-naïve children [95, 96].

Viral invasion of the infant brain during vulnerable stages of development can have devastating consequences with greatest risk in those with early foetal or neonatal infection [97]. In HIV-infected adults structural brain changes have been demonstrated on magnetic resonance imaging (MRI) scans within one year of infection [98]. The severity and clinical manifestations of HIV-related neurodevelopmental consequences cover a wide-ranging spectrum of disorders. Affected infants and children may present with static or progressive encephalopathy, CNS compromise or no apparent CNS effects [99]. Children with a static or non-progressive encephalopathy continue to acquire new skills in the developmental domains, but function consistently below the mean on standardised assessments [100], while those with progressive encephalopathy show a continued decline in their level of functioning due to the loss of acquired skills [101]. Motor, cognitive, and language delays have been reported at various ages and stages of development [102-104], and affected children may present with a wide variety of neurologic and developmental impairments that do not easily fit into simplified classification systems [105]. The degree of neurological deficit is often proportional to the degree of immunosuppression, timing of infection[106] and stage of

HIV disease [107]. The risk of a child developing HIV-related encephalopathy has been reported to be higher in children born to mothers with more severe HIV disease – lower CD4 counts and higher HIV viral load (VL) – and in children with high plasma and cerebrospinal fluid VLs [108, 109].

The natural history of these adverse developmental and neurological consequences has been altered by the introduction of successful paediatric ART. Initiating ART early will delay, or hopefully prevent the onset of progressive encephalopathy and improve outcomes in children already presenting with CNS dysfunction [110, 111]. It has been postulated that *in utero* exposure of the infant to maternal ART results in 'treatment' of the infected baby. As a result the infant birth VL is lower and the negative consequences of widespread viraemia may be reduced. Data on infant birth VL values in relation to maternal ART and maternal VL has been collected from a longitudinal cohort study conducted at RMMCH and is being prepared for publication.

However, even when on suppressive ART, children may continue to be at risk of neurocognitive impairment [37]. Various mechanisms have been suggested as contributors to the continued neurocognitive deficits, the aetiology of which is likely multifactorial and include factors such as irreversible neuronal injury occurring prior to ART initiation [112-114]; ARV toxicity [114]; continued viral replication in the CNS despite suppressive ART [115, 116]; exposure to inflammatory responses within the CNS [117, 118]; combined with socioeconomic influences of the child's environment

Concern for the large numbers of HEU children has been raised with data indicating that these children, as with their HIV-infected counterparts, may also have lower mental and motor scores [119]. McHenry et al. reported meta-analysis data from 11 studies which show children with HIV and HEU children as having lower cognitive and motor scores on developmental testing compared with their HUU peers [119]. A higher incidence of autism spectrum disorder has been reported in HEU children as compared with HUU children – with higher rates of mitochondrial dysfunction secondary to HIV exposure proposed as a contributing factor [120]. Summarising

findings from recent large studies, Wedderburn et al. propose a conceptual framework explaining how HEU children are affected directly through HIV and ART-specific pathways, and indirectly through the amplification of the risks for poor growth and development in families affected by HIV [121]. A large South African study, reported by the same authors, investigated BSID-III scores of HEU and HUU children at 6 months and 24 months of age. The results indicate HEU children exposed to maternal HIV and ART as having increased odds of receptive and expressive language delays at 24 months of age [122].

2.4.3. Psychosocial and Environmental Risk Factors

2.4.3.1. Cognitive Stimulation

Emerson, Savage and Llewellyn published a 2018 report in which they estimated the prevalence of significant cognitive delay in LMIC [123]. They report that just less than 55 million children under five years of age have significant cognitive delay, and that this number could be reduced by 60% if three separate SDG were met – one being an acceptable amount of home stimulation for every child, and the other two – every mother achieving a secondary-level education and every household having access to improved water and sanitation [123].

Many diverse interventions have been employed in an attempt to improve childhood developmental outcomes. Interventions differ in many aspects e.g. their approach; components and duration of the intervention; age of child targeted; community, home or clinic based; and the assessment and reporting of outcomes. The heterogeneity of interventions and outcome measures makes it difficult to draw firm conclusions regarding the impact on developmental outcomes.

In a 2007 Lancet review series, Walker et al. summarise 16 experimental or interventional studies aiming to assess the effect of cognitive stimulation on young children from developing countries [22]. All studies but one reported significantly higher cognitive functioning in children

who were provided additional cognitive stimulation when compared to non-stimulated controls, with effect sizes ranging from 0.5-1.0 SD [22]. A 2017 systematic review included 48 studies and 24 interventions delivered in primary care settings to children aged 0-3 years old and reported an overall positive impact on child developmental outcomes [124].

Remarkably, interventions implemented during early childhood, especially in children younger than three years old, have been shown in longitudinal follow-up studies to positively influence a variety of adult outcomes, even if the children are also exposed to poverty and other adverse conditions [3]. Among other outcomes, childhood interventions have been shown to have beneficial effects on adult wage earning capacity [125], improved educational attainment [126, 127] and reductions in violence [127].

Research conducted at the Hariet Shezi Children's Clinic based at Chris Hani Baragwanath Hospital (CHBH) in Soweto, South Africa, investigated the outcomes of a home-based developmental stimulation programme after 12 months of follow-up. The clinic at CHBH provides care and treatment for HIV-infected children and although it services a different geographical area, is similar in function to the children's HIV clinic – the Empilweni Services and Research Unit (ESRU) – at RMMCH. Outcomes of the trial showed that despite the children exhibiting severe cognitive and motor delay, the children receiving the stimulation programme showed significant improvements in cognitive and motor development [128].

At the time during which this study was conducted children receiving care through the Empilweni Clinic at RMMCH were not routinely screened for appropriate cognitive, language or motor development. Children were only referred for screening and assessment if the clinician detected problematic development or behaviour, or if the mother raised any concerns. The child was then referred to the hospital's Occupational Therapy and/or Physiotherapy Departments. Early developmental screening questionnaires, behavioural and mental health screening questionnaires have since been included in the questionnaires completed at certain clinic visits.

2.4.3.2. In-utero Exposure to Drugs of Abuse and Prescription Drugs

One of the most common substances of use and abuse to which a developing infant is exposed is alcohol. Foetal exposure to ethanol in the prenatal period results in the development of Foetal Alcohol Syndrome (FAS) and Foetal Alcohol Spectrum Disorder (FASD) in which structural abnormalities of the developing brain result in specific phenotypic and neuro-behavioural consequences. The effects of prenatal alcohol exposure cannot be simply defined in terms of cognitive and behavioural abnormalities, as the features lie on a continuum on deficits. Structural changes to the shape and volume of the brain secondary to prenatal alcohol exposure have been definitively demonstrated as have functional brain activation abnormalities [129]. Although no population-based South African studies reporting on FASD have been done, in research specific to a school-going first grade cohort in the Western Cape Province of South Africa, May et al. reported the rate of FAS and FASD to be the highest of any reported community at 68.0-89.2 per 1000 [130].

The negative impact of maternal cigarette use on child development has been long established. Data published nearly 50 years ago reported longitudinal follow-up evidence of children exposed to maternal cigarette smoking during pregnancy which showed cigarette-exposed children to have a reduced physical height as well as delayed reading, writing and general ability, as compared to their non-exposed counterparts [131]. More recent research on a biological level has demonstrated that maternal cigarette use during pregnancy causes epigenetic changes resulting in dysregulated gene expression secondary to altered DNA methylation. These epigenetic changes may later affect future growth, behaviour and development [132].

Data published by the Human Sciences Research Council reported 17.6% of adult South Africans smoke tobacco products [133]. The prevalence in females was 7.3% and in males it was four times higher – 29.2%. The negative consequences of prenatal cigarette exposure was borne out in findings from the Birth to Ten Study in Johannesburg and Soweto, South Africa, which showed cigarette-exposed infants having significantly lower birthweights than infants not exposed to nicotine during pregnancy [134].

A thorough antenatal history should always be taken to establish to which prescription medications the new-born infant has been exposed. The long-term effects of *in utero* drug exposure may only become evident as the child matures. As an example, the commonly used anti-depressant medications – selective serotonin reuptake inhibitors (SSRIs) – fluoxetine and fluvoxamine given to neonatal mice resulted in a change in the morphology of excitatory neurons. As adults, the SSRI-exposed mice demonstrated impaired locomotor activity [135].

As per the South African Department of Health HIV treatment guidelines, antiretroviral medications should be initiated in all pregnant HIV-infected women who are not yet on treatment [136]. Concerns regarding the effect on the developing infant of ARVs taken during pregnancy have not been borne out in clinical trials. In utero and post-natal exposure to various ARVs has not been shown to have deleterious effects on neurodevelopmental outcomes in HEU children [137-140]. Health authorities recently issued a warning on the use of the integrase inhibitor dolutegravir in pregnancy and the possible risk of infant neural tube defects [141], however, further analysis of longitudinal data found no significant differences between dolutegravir and efavirenz-based treatments on any adverse birth outcomes although the follow-up period has been relatively short and further monitoring is recommended [142]. A birth registry documenting maternal ARV use and birth outcomes is in the process of being developed at RMMCH. This data will be used to scrutinise whether significant correlations exist between the use of various ART regimens during pregnancy and adverse birth outcomes.

2.4.3.3. Maternal Health and Depression

Depression is one of the most common psychiatric disorders. A WHO report estimated the global proportion of adults with depression in 2015 to have been 4.4% which represents 322 million people, of which 9% (29.19 million people) were from the African region [143]. Depression is more common among females (5.1%) than males (3.6%). The 2015 South African estimate for the number of people living with depression was 2.4 million (4.6% of the population) [143].

Accurate data on the prevalence of postpartum depression in LMICs is lacking. A systematic review published in 2012 found evidence for only 17/112 (15%) LMICs [144]. In this review the pooled prevalence of postpartum depression and anxiety was reported as 19.8% (95% CI: 19.2–20.6) which was higher than in high-income countries who have an estimated prevalence of 13% [144, 145].

Furthermore, HIV infection is associated with the development of depression. A recent 2019 meta-analysis of depression in patients with HIV infection reported the prevalence rate of depression as 31% (95% CI 28-34%) [146]. This may be due to the infection itself, side effects of ARV medication and the stigma and psychological aspects associated with HIV infection.

Taking all of these factors into account – depression being more common in females, having a higher prevalence in the post-partum period in LMICs and being associated with HIV infection – mothers with HIV infection in LMICs are at a significantly increased risk of developing depression. However, *routine* screening for maternal depression is not part of the ante- and postpartum care at RMMCH.

Maternal depression can have profound short- and long-term effects on various domains of childhood development. In the milieu of maternal depression the maternal-infant relationship is strained and the infant is brought up in a setting of constant negative affect. There is a distortion of communication of emotions which affects the infant's social and emotional development [147]. Early maternal bonding processes and mother-infant interactions are dysregulated [147, 148]. Communication, gross motor skills, personal-social and motor development in the child have been shown to be negatively impacted by maternal depression [149-151].

2.4.3.4. Environmental Influences

Brain maturation is shaped by the environment in which a child is raised. Greenough and Black describe two aspects of environmentally dependent brain maturation – experience-expectant and experience-dependent maturation [152]. In experience-expectant maturation, development is reliant on specific environmental influences and brain maturation will not occur unless the child is exposed to these experiences. Maturational processes occur in an orderly, predictable pattern [7, 152]. Experience-dependent maturation occurs when environmental exposures result in the generation of new synaptic pathways. In experience-dependent maturation synapses are not anticipating predetermined experiences at a given stage and experience-driven neural pathways differ between individuals depending on environmental exposure [7, 152]. Experience-expectant development is negatively influenced and suffers long-term effects when an infant receives inadequate levels of stimulation secondary to, for example, neglect, poor child rearing practices, maternal physical and mental ill health, malnutrition and poverty. Experience-dependent maturation is negatively affected by traumatic early-year life experiences such as abusive parenting, parental substance abuse and communities affected by violence and war.

Neurotropins are important chemical elements responsible for the health, survival and differentiation of neurons in the brain. The release of these chemical agents is regulated by neuronal activity which is stimulated by environmental input [7, 153]. In the absence of appropriate and sufficient environmental and caregiver input there is a reduction in neural stimulation which results in fewer neurotropins being produced which directly affects the health and survival of critical neurons [7, 153, 154]. These early insults during the critical period of brain development result in lifelong structural and functional changes. Insufficient stimulation can be secondary to environmental factors such as poverty, single-parent family structure, absence of childcare facilities, as well as maternal factors such as depression, illness, and low educational grade which commonly impact households affected by HIV [46, 155]

2.5. Essential Components of Nurturing Care

Five essential components for achieving optimal development were identified in the pivotal 2017 series published in The Lancet and the term *Nurturing Care* was coined, which refers to "health, nutrition, security and safety, responsive caregiving, and early learning – to be provided by the parents, extended family, community and environment [3]. This subsequently gave rise to the *Nurturing Care Framework* presented at the 71st World Health Assembly in 2018 which aims to provide clear focused goals and a way forward for improving childhood developmental outcomes from conception through the third year of life [156].

The components of the *Nurturing Care Framework*, as depicted visually in **Figure 2. 4**, good health, adequate nutrition, responsive caregiving, safety and security, and opportunities for early learning, are interlinked, of equal importance and are all necessary for the best possible developmental outcomes [156].

Each of these five components will be discussed as they pertain to a child growing up in South Africa with additional information when CLHIV and HEU children face increased risk or added challenges.

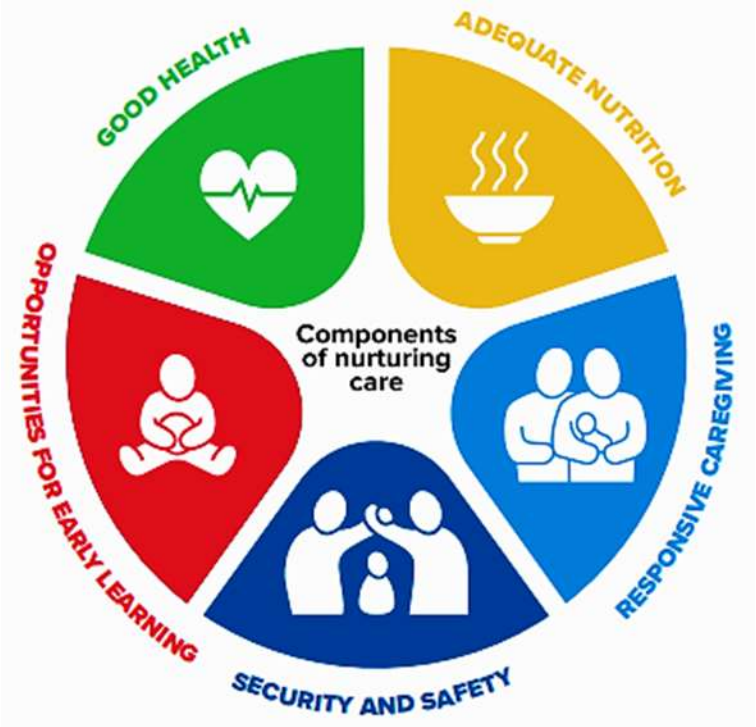

Figure 2. 4 The Five Components of the Nurturing Care Framework[157]

The five components of nurturing care are addressed in the current South African RtHB. This patient-held record has been assembled by the South African National Department of Health (SA NDoH) and is provided to every new parent upon discharge from a State-run hospital. The booklet comprises five themes/pillars, namely: Nutrition; Love; Protection; Health care; and Extra care which mimic the components of nurturing care outlined above. The themes of the RtHB relating to each of the five components of nurturing care will be discussed under the subheadings below.

2.5.1. Good Health

Health, as defined in the preamble of the mission of the WHO – and has not changed since 1948, is defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [158]. Through time and with the evolving complexities of the

modern age, this definition has been scrutinised and questioned. For example, an infant with perinatally acquired HIV infection attending the HIV management clinic at RMMCH will likely never achieve the 'absence of disease' and thus, according to the WHO definition, will never truly attain a state of complete health.

The health of a nation – it's social, economic and environmental conditions – can be extrapolated from the country-specific U5MR [159]. The U5MR is defined as the probability of a child, born in a specified year, dying before reaching the age of five, when subject to the current age-specific mortality rates of that period. It is expressed as the number of deaths per 1 000 live births [160]. Improved child survival is an objective of both the Millennium Development Goals (MDG) [161] as well as the SDG [162]. The MDG number 4A set out to reduce the U5MR by two-thirds, between 1990 and 2015. Indeed, significant progress was made towards achieving this goal with a reduction of more than half of the global U5MR between 1990 and 2015, which equates to a decrease from 90 deaths per 1 000 live births to 43 – or 6 million children in 2015 [163]. One of the greatest contributors to this success is the widespread vaccination of children against measles infection [163]. Sub-Saharan Africa continues to have the world's highest U5MR, and the current South African U5MR estimated by UNICEF's Data and Analytics team is 33.8 per 1 000 live births, compared, for example, with that of Sweden at 3 per 1 000 live births or at the other end of the spectrum Somalia with 121.5 deaths per 1 000 live births [164]. The main causes of death in children under five years of age are preventable: pneumonia, diarrhea, and malaria [163].

Another MDG which was an important focus area for South Africa was MDG number 6A: to have halted and begun reverse the spread of HIV/ Acquired Immunodeficiency Syndrome (AIDS) by 2015 [163]. The control of the paediatric HIV epidemic in South African has been a particular success story. The provision of maternal ART in order to eliminate MTCT was included in the 2015 South African Guideline for the Prevention of Mother-to-Child Transmission of HIV and Management of HIV in Children, Adolescents and Adults [165]. Provision of life-long ART for all HIV-infected pregnant women has dual purpose – management of maternal HIV infection, and reduction of the risk of infant HIV acquisition by

controlling maternal viral load and thus infectivity. The WHO South African Country Report estimates 87% of pregnant women living with HIV to have received ART for PMTCT in 2018 [166].

Early infant diagnosis (EID), routinely testing HIV-exposed infants, was implemented in 2004 with an HIV PCR test performed at six weeks of age [167]. Testing at an earlier time-point began at our institution in 2013 with the testing of high-risk infants *at birth*, which was subsequently changed in June 2014 to include *all* HIV-exposed infants. In addition, POC HIV testing technology was utilised in order to ensure fast result return to the mother of the newborn infant prior to discharge post-delivery [168]. Guideline changes to EID policy in 2015 recommended HIV PCR testing at birth for all HIV-exposed newborn infants [165].

The incidence of perinatal MTCT of HIV in South Africa has decreased steadily over the years. The first population-based survey conducted in 2010 to assess the impact of the PMTCT programme on MTCT reported a transmission rate of 3.5% [169]. Since that time remarkable progress has been made, a 2018 publication reported the national *in utero* MTCT rate as 0.9% with provincial rates ranging from 0.6-1.3% equating to 168-325 cases per 100 000 [170]. At RMMCH, during the period September 2013 through June 2016, 5 449 HIV-exposed infants were tested and 88 were confirmed as HIV-infected (1.61%) [168].

Ensuring a continuum of care after diagnosing HIV infection is crucial for the long-term health of the infant, through childhood and into adolescence. Initiation of effective ART and the uninterrupted provision of medication resulting in a suppressed viral load are essential. The three 90-90-90 targets towards achieving the 2020 goal to help end the AIDS epidemic are: knowledge of ones HIV status; access to ART; and achieving and maintaining viral suppression once on ART [171]. It was estimated that South Africa had achieved the first target, as in 2018 90% of people living with HIV (PLHIV) knew their status. South Africa falls short of achieving the second and third targets as only 62% of South African's requiring ART were receiving it (63% in children 0-14 years), and even more concerning was that only 54% of PLHIV on ART had

achieved virological suppression in 2018 [171]. Young CLHIV receiving ART are fully dependent on the actions of the adult caregiver. Hence there are many factors which may result in treatment interruption. The International Epidemiology Databases to Evaluate AIDS (IeDEA) Global Cohort Consortium reported 68% of CLHIV to have been initiated on ART by 24 months of age, but that there was a substantial risk of lost-to-follow-up (LTFU) prior to ART being started [172].

In line with the promotion of good health, the RtHB includes easy to understand information on the danger signs of childhood illnesses; the Expanded Programme of Immunisation Schedule; Vitamin A and deworming schedule; oral and dental hygiene; oral rehydration solution recipe to prevent dehydration in children with diarrhoea; and the documentation of HIV exposure, HIV testing and PMTCT medication given. Parents of the children enrolled for follow-up in this current trial were requested to bring the child's RtHB along to each study follow-up visit. The RtHB was reviewed by the study physician and the research nurse to ensure completeness. Results of HIV tests done as part of the research trial were recorded in the RtHB to ensure a continuum of care between the local clinic and the research site. Completion of the vaccination, vitamin A and deworming schedules were also checked and children were provided with any outstanding treatment. A copy of the RtHB was routinely made which proved to be extremely useful in the case of the lost RtHB.

2.5.2. Adequate Nutrition

Receiving a nutritionally replete diet is vital for optimal growth and development of every child, even more so for the child living with a chronic health condition. HIV disproportionately affects the poorer strata of the South African population which are also those more affected by poverty and food insecurity. There is however a fine balance between being nutritionally replete and of the correct weight and nutritionally deplete and overweight. The numbers of overweight children in South Africa have increased, yet this does not necessarily indicate the availability of excess food but rather points to the overconsumption of foods with a high caloric value but a low nutritional content [173].

Meeting the nutritional requirements of persons living with HIV is an integral component of comprehensive HIV care. The WHO has published comprehensive reports on the subject of nutrition in the face of HIV infection, including: the nutrient requirements for PLHIV; guidelines for the nutritional care of HIV-infected children, and nutritional interventions for improving the care of adults and children living with HIV. The following information has been taken from the WHO report summarising the evidence and recommendations for managing the nutritional requirements of CLHIV:

- Energy: in asymptomatic CLHIV the energy requirements are likely to increase by 10% in order to maintain body weight, and sustain physical activity and growth, as compared to HIV-uninfected children. Children with growth faltering should receive an additional 50-100% of the daily energy requirements in order to promote catch-up growth and prevent further deterioration,
- Protein and fat: there is no evidence of increased protein or fat requirements specifically related to HIV infection,
- Micronutrients: supplementation with vitamin A, iron (as treatment for iron deficiency anaemia), and zinc (included in the management of diarrhoeal illnesses) have been recommended. Micronutrients in doses exceeding the daily recommendation are not recommended. If the diet is of poor quality and unlikely to meet micronutrient requirements, a daily oral micronutrient supplement is recommended [174].

The information in **Table 2. 1** appears in the WHO's guidelines for the nutritional care of HIV-infected children and clearly shows the increased energy requirements for asymptomatic and symptomatic CLHIV as compared to HIV uninfected children [175].

Table 2. 1 Total Energy Needs of HIV-infected children (kcal/day)[176]

	Daily energy needs of HIV uninfected children*	HIV infected and asymptomatic 10% additional energy	HIV infected and poor weight gain or other symptoms 20% additional energy	Severely malnourished and HIV infected (post-stabilisation) 50-100% additional energy**
6-11 mo	690	760	830	150-220 kcal/kg/day
12-23 mo	900	990	1080	150-220 kcal/kg/day
2-5 yrs	1260	1390	1510	150-220 kcal/kg/day
6-9 yrs	1650	1815	1980	75-100 kcal/kg/day
10-14 yrs	2020	2220	2420	60-90 kcal/kg/day

**Based on average of total energy requirements for light and moderate habitual physical activity levels for girls and boys by age group. Joint FAO/WHO/UNU Expert Consultation, October 2001. ftp://ftp.fao.org/docrep/fao/007/y5686e/y5686e00.pdf*
***Management of Severe Malnutrition: a manual for physicians and other senior health workers. WHO, 1999*

Results from a large longitudinal cohort study conducted at RMMCH which monitored growth and body composition of CLHIV (n=553) in whom ART had been started when less than two years of age, showed the CLHIV to be shorter than their HIV-uninfected counterparts (n=300) despite being well controlled on ART. The CLHIV also displayed unfavorable lipids profiles including higher total cholesterol, triglyceride and low density lipoprotein values, independent of ARV regimen. Interestingly, there was a high prevalence of overweight (BMI-for-age z-score >1) in both the CLHIV and the uninfected children (14.4% vs. 21.7%, p=0.04) [177]. Further analysis conducted on this cohort of children, included a cross-sectional analysis of the dietary intake of CLHIV (n=220) compared with HIV-uninfected children (n=220) aged 5-9 years. Results showed that in both groups a large proportion (>80%) did not obtain the recommended daily energy intake, and that both groups were deficient in their intake of folate, vitamin A, vitamin D, calcium, iodine, and selenium [178].

Child undernutrition – including stunting, wasting, and vitamin and mineral deficiencies – coupled with child overweight or obesity is of growing concern in LMIC [179]. The "double burden

of malnutrition" in which a child is both stunted and overweight has been described in South Africa based on data from the National Food Consumption Survey (1999) which is the only national study conducted on food consumption and dietary patterns in children [180, 181]. A 2015 review of dietary surveys from the South African adult population brought attention to the lack of national adult food consumption data but reported that micronutrient deficiencies were highly prevalent, fruit and vegetables were the most commonly deficient food group, energy intakes were very low in informal settlements and very high in urban area, and that access to healthy food remained problematic [182]. According to the 2018 Global Nutrition Report, South Africa is on track to meet global targets to reduce the prevalence of under-five overweight, but off course to meet the under-five stunting target. The under-five overweight prevalence has decreased from 17.2% in 2012 to 13.3% in 2016. However, the 2016 national prevalence of under-five stunting was 27.4% which exceeds the developing country average of 25% [183]. The prevalence of the "double burden of malnutrition" is reported as 4.0% - the number of children both overweight and stunted [183].

Breastfeeding, infant and child feeding, and growth monitoring are given extensive coverage in the RtHB. Weight-for-age, height-for-age and weight-for-height growth charts for boys and girls and tables for recording mid-upper arm circumference (MUAC) are all included in the booklet. If growth faltering is noted – weight loss, inadequate increase in height/length, no increase/decrease in the MUAC, it is recommended that the primary health provider conduct a nutritional assessment or refer the child for further comprehensive management before the situation worsens.

Anthropometrical measurements, namely weight (kg), height (m), head circumference (cm), and MUAC (cm), were routinely taken from all children enrolled in this study at each follow-up visit. Trained nursing sisters utilised standardised techniques to ensure uniformity of measurements. Measurements were plotted onto the WHO weight-for-age, height-for-age and head circumference-for-age charts by the study physician. Growth faltering was addressed with the caregiver and nutritional advice on correct child feeding was provided. Social problems relating to poverty and food insecurity were commonly encountered and although referred to the social

services department, families did not often receive the assistance they required. Referrals to the hospital dietetics department were made for term infants and premature infants who displayed poor growth. Food supplements e.g. peanut butter, and food parcels were not provided to the family unless a donation had recently been received by the clinic. All children were prescribed a daily multivitamin solution which was started when the infant was six weeks old.

2.5.3. Responsive Caregiving

Parenting practices are intertwined with developmental outcomes of the child. Maternal responsiveness – defined as the reaction that the mother displays to the young child in everyday interactions and behaviours such as infant facial affect, vocalisation and exploration – has been described as especially significant to child development [184]. Responsiveness is reflected in everyday exchanges, between a parent and a child, which are recurring and meaningful [185], it is this child action and parent reaction that has been named as one of the principal precursors for the development of secure attachment in children [186]. Developing a warm and caring relationship with an adult caregiver is one of the pillars of nurturing care as it is as important as food and access to health services [12]. Parental responsiveness, investment of time, attachment, and devotion are considered to be good things which will help to positively shape the various facets of a child through the early developmental years. The link between maternal responsiveness and improved short- and long-term child health and development has been extensively researched and reported since the initial reports [186].

A review article on responsive parenting published in the Bulletin of the WHO examined interventions in developing and developed countries aimed at enhancing parental responsiveness and the effect thereof. The authors conclude that the benefits to the child of responsive parenting are wide-ranging and include psychosocial development, and improved health and physical growth [187]. Programmes employed to improve maternal responsiveness have been modestly effective in doing so which has led to better child health and development, especially for at-risk children [187]. A randomized control trial conducted in a peri-urban settlement in South Africa

(Khayelitsha) which delivered an intervention from late pregnancy and for the first six months post-partum by previously untrained local lay women, reported a significant positive impact on the mother-infant relationship with more sensitive and less intrusive maternal behavior [188]. Infant attachment was also impacted with higher rates of infant attachment seen at 18 months of age [188].

There can be many stressors for a new mother in a LMIC which may place the child at risk for poor and inconsistent parenting, these include: social risks – maternal depression, exposure to domestic violence, maternal stress arising from poverty, lack of support, and negative life experiences; and environmental risks – exposure to environmental toxins and infectious diseases [23]. Data on maternal education and household wealth collected from 853 households of children attending follow-up at ESRU and at the Perinatal Research Unit at CHBH, reported 7.4% of the mothers to have attended primary school only, 46% any grade of high school between grades 8-11, and 45.7% to have completed grade 12 [189]. The wealth index of the households was calculated from nine variables (number of rooms, the presence of inside faucet, toilet, electricity, television, radio, refrigerator, computer, and car) which were reduced to a single continuous variable. Of the households represented, similar numbers were classified as falling into the lower and middle wealth index (40.1% and 39.5% respectively) while 20.4% fell into the highest wealth index [189]. The cohort of children in this previous analysis closely represents the younger cohort currently in follow up at ESRU and included in this current study.

Although published many years ago, the manual from the WHO for 'Improving mother/child interaction to promote better psychosocial development in children' [190] is a valuable resource containing useful information for improving interactions between mothers and their infants. The essence of the sensitisation programme is to assist caregivers to recognise the needs of the child and to be aware of their own ability to provide loving care. The programme is encapsulated in the following information taken directly from the WHO document: "Eight Guidelines for Good Interaction: 1) Show your child you love him; 2) Talk to the child. Get a conversation going by means of emotional expressions, gestures and sounds; 3) Follow your child's lead; 4) Praise and appreciate what your child manages to do; 5) Help your child to focus his attention and share his

experiences; 6) Help your child make sense of his world; 7) Help your child widen his experience; 8) Help your child learn rules, limits and values" [190].

"Young children need a safe environment and loving caregivers who can help them explore the world around them. Ordinary loving things that you do such as holding, talking, playing and reading to your child are what helps them grow and develop" – this is the introduction from the second section of the RtHB entitled: "Love, play and talk for healthy development". The concept of responsive caregiving is encapsulated in this section with ideas for the caregiver detailing healthy infant and child interactions.

The intervention used in this study had a strong focus on responsive parenting. For each age group the developmental activity programme which was provided to the caregiver included a page containing a list of ideas and activities for the caregiver to engage in together with the child. Responsive parenting was emphasised, for example, the activity guideline for infants aged 0-3 months encouraged the caregiver to: 'Act excited and smile when your baby makes sounds. Copy your baby's sounds sometimes, but also talk normally to them using clear understandable language'. The details of the developmental activity programme have been included in Chapter One.

2.5.4. Opportunities for Early Learning

"Education is the great engine of personal development. It is through education that the daughter of a peasant can become a doctor, that the son of a mine worker can become the head of the mine, that a child of farm workers can become the president of a great nation. It is what we make out of what we have, not what we are given, that separates one person from another." [191]

– Nelson Mandela

Learning begins at birth. From the moment at which the umbilical cord is tied and severed a new-born infant begins to learn – how to breathe, how to cry, how to feed. These early and subsequent learning experiences will shape neural pathways, influence gene methylation and expression, and continue to exert influence over the individual's life course and even into future generations [192].

As the importance of ECD has been recognised, so too have the shortcomings of ECD programmes been made evident. In response to this the WHO has released a 2020 guideline providing global, evidence-informed recommendations on improving ECD [9]. The guideline includes four focus areas: responsive caregiving, early learning and development, caregiving to support healthy socioemotional and behavioural development, and combined caregiving and nutritional interventions. Data from 22 randomised controlled trials (RCT) were analysed to determine the impact of ECD programmes on various developmental domains. Caregiving interventions were found to have a positive impact on cognitive, motor, socioemotional development, and attachment outcomes, but no benefit was reported for language development, behavioural problems or height-for-age nor weight-for-age z-score improvement [9].

In line with the prioritisation of ECD in the South African National Development Plan (NDP) 2030, a comprehensive National Integrated ECD Policy (2015) was developed with the aim of transforming ECD service delivery in South Africa [193]. In South Africa, the responsibility for the provision of ECD services for children aged 0-2 years has been assigned to the NDoH. Ideas for learning through play and communication have been created and collated into user-friendly resources for parents and healthcare workers and are widely available from international organisations such as UNICEF and the WHO. Country-specific programmes are also available and although child development follows a similar trajectory for most children, country-specific ECD programmes may be nuanced with cultural and population-specific elements. Recently published ECD materials (April 2020) created by the South African Department of Social Development and Department of Basic Education in conjunction with UNICEF, to assist parents and caregivers with early learning ideas, are freely available online

(https://www.unicef.org/southafrica/reports/tshwaragano-ka-bana-lets-play-learn-and-grow-together-1-10) through the "Tshwaragano ka Bana - Let's play, learn and grow together" initiative [194].

The RtHB does not provide much information on early learning. Only a few activities for parents on how to stimulate early learning – talking, singing, exploring everyday objects, telling stories and reading to children, are mentioned. The focus of the intervention provided to the caregiver in our study was the stimulation of early learning. For each age group expected developmental milestones were listed on the information card. Ideas for play were suggested and toys and items in the home that could be used to stimulate early learning were proposed.

2.5.5. Safety and Security

Environmental dangers pose a threat to all members of a community with children being particularly vulnerable. Dangers include road traffic and pedestrian vehicle accidents, drownings, burns, falls, poisonings and exposure to violence [195].

Sadly, South Africa is known as having a pervasive culture of violence which taints the lives of most of its citizens including children. Longitudinal follow-up data from children in the Soweto-Johannesburg area in the Birth to Twenty Plus study found that over the past two decades 99% of the sample had been exposed to or experienced violence, either in the home, school or community [196] and of those with intense personal experience of violence, nearly 50% were exposed to the violence in their own homes [196]. As with exposure to other negative influences, exposure to violence during the formative years of childhood can have long-lasting effects by impacting developing neural networks resulting in the impairment of multiple brain structures and neuroendocrine systems [197, 198]. This disruption in turn gives rise to a variety of behavioural, health and social problems which become the determinants of future adult health [197].

Globally, the top three causes of child injury resulting in death are: road traffic injuries (22.3%), drowning (16.8%), and fire-related burns (9.1%) (**Figure 2. 5**) [195]. In South Africa, death due to non-natural causes or unintentional injuries accounted for an estimated 7.9% of deaths in children under-five years of age in 2015, with a higher percentage (9.0%) estimated by UNICEF taking into account underreporting and misclassification of cause of death [199]. Once a child passes the age of five, unintentional injury becomes the greatest threat to survival.

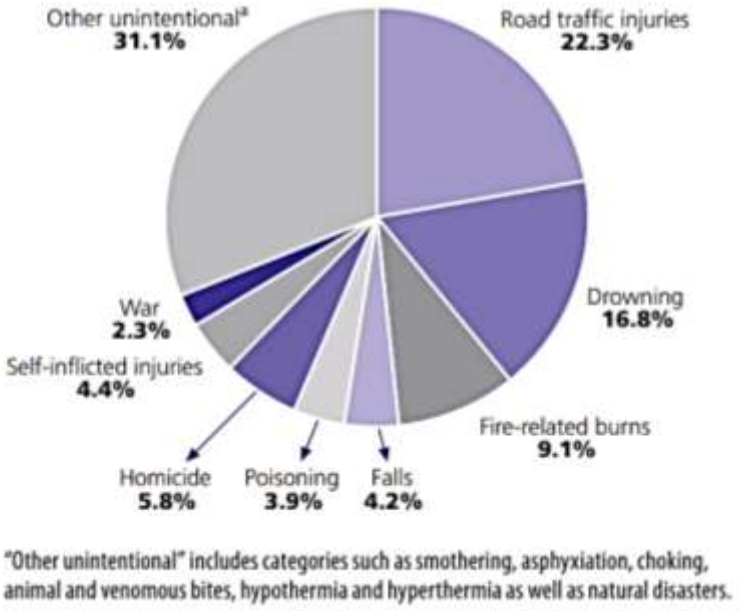

Figure 2. 5 Distribution of Global Child Injury Deaths by Cause, 0-17 years, 2004[200]

The risk of sustaining a non-intentional injury has been closely linked to socioeconomic factors, such as: family income, maternal education, single-parent families, number of children in the household, maternal age, and type of housing [195, 201]. For example, children from poor communities may be subject to ineffective parental care and supervision, and be exposed to hazardous environments without access to safe areas for play, poorly ventilated, overcrowded homes with unprotected open-fire cooking and heating, and potential toxins such a high lead-content paint.

Tackling the mammoth task of addressing violence, maltreatment and non-intentional childhood injuries as well as the underlying social determinants of these societal ills, begins with educating caregivers, families and communities with the aim of preventing them becoming unwitting perpetrators.

2.6. South African Strategies for the Improvement of Children's Health

South Africa has adopted a number of global initiatives with the aim of improving child health and reducing infant and U5MR. The Integrated Management of Childhood Illnesses (IMCI) is an evidence-based strategy launched by the WHO in 1994 aimed at reducing child morbidity and mortality and promoting growth and development in children under five years of age [202]. As a WHO Member State, South Africa adopted the IMCI in 1998 as part of the primary healthcare strategy delivering health care to children under five years old [203]. The focus of IMCI is on the physical wellbeing of the child, it does not include information on nurturing care nor on ECD.

In 2015 at the United Nations (UN) Sustainable Development Summit in New York, the UN – of which South Africa is a member – adopted the 2030 Agenda for Sustainable Development incorporating the 17 SDGs [204].

Figure 2. 6 Sustainable Development Goals Icons[205]

The SDGs build on the MDGs (which included the goal of universal access to primary education) [163] with the fourth goal comprehensively discussing education throughout the life course. SDG number 4 states: "Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all", and with particular reference to ECD: "by 2030, ensure that all girls and boys have access to quality early childhood development, care and pre-primary education so that they are ready for primary education" [204].

The goals of the South African NDP 2030 are closely aligned with the SDGs. Chapter 9 of the NDP lays out the objectives regarding education and training. The first two objectives relate directly to ECD (emphasis own):

- "Make early childhood development a top priority among the measures to improve the quality of education and long-term prospects of future generations. Dedicated resources should be channelled towards ensuring that all children are well cared for from an early age and receive appropriate *emotional, cognitive and physical development stimulation*.
- All children should have at least 2 years of pre-school education" [206].

The executive summary of the NDP lists four actions in line with the two objectives on education and training. They include: implementing a nutrition programme for pregnant women and young children; designing and implementing a childhood care and development programme for all children under the age of three years; state funding is to be increased to ensure access to two years of ECD prior to grade one; and coordination between departments with similar agendas to ensure the common goal is achieved [206]. ECD has been identified in the NDP as an essential provision for children trapped in inter-generational cycles of poverty and inequality [207].

The National Integrated Early Childhood Development Policy was adopted by the South African Cabinet in 2015. The aim of this policy is to promote the health, nutrition, development and well-being of young children using a multi-sectoral approach [207]. The Integrated ECD policy recognises the responsibility of government for the provision of a comprehensive and quality ECD programme for *all* young children and their caregivers especially through the first 1 000 days [208]. The policy is inclusive of the components of nurturing care including food and nutritional support, parenting support, and early care and learning in particular for young children living in poverty and those with disabilities. In line with the Integrated ECD policy and the need to re-structure child-health services in South Africa, are two tools – the redesigned RtHB and the Side-by-Side Initiative. The Side-by-Side campaign aims to ensure that the health messages in the RtHB reach the caregivers of young children and equip them with information to provide nurturing care [207]. The campaign describes the supportive relationship between the caregiver and child and also the caregiver and the healthcare provider, with the central message: "You are central to your child's nurturing, care and protection – and their lifelong health outcomes. Your healthcare worker is there to support you" [207, 209]. The public health approach of the Side-by-Side campaign incorporates large scale interventions aimed at the community – radio broadcasts, Facebook page and Side-by-Side website (www.sidebyside.co.za), outlines the role of the primary healthcare clinic in providing ECD services and establishing referral networks, and aligns the responsibility of the community health worker with the five pillars of the RtHB [209].

2.7. Components of Effective ECD Programmes

The preceding sections highlight that successful ECD programmes need to be integrated into the health, education, social and economic sectors of a country. The five components of nurturing care and child care and development programmes have been described. This section summarises evidence detailing the key elements of successful early stimulation, learning and education programmes. Each sub-heading identifies a key component for the effectiveness of early learning interventions as outlined in a report published by the World Bank Group [210]. This section deals with intervention programmes in general and not those with a specific focus on children affected with HIV. Although features of ECD programmes may be carried over and used in programmes aimed at CLHIV and HEU children, Sherr et al. – in a 2014 systematic review – reported that although effective interventions were available for children affected by HIV there exists a need for evidence-based interventions to be built and scaled up specifically for this vulnerable group of children [211].

2.7.1. Engage Both Parents and Other Caregivers

Stimulating and teaching a child should not be an activity restricted to early learning centers or school environments, but should be initiated and continued by a child's parents and caregivers throughout the day and during everyday activities. Children are often raised in dynamic families which change in structure and may not resemble the classic nuclear family. All caregivers – extended family, grandparents, and even neighbours – should somehow be engaged with the child stimulation programme. A 2016 UNICEF document outlining standards for ECD parenting programmes in LMIC, recommends parenting programmes identify and include all caregivers independently of age, gender and family relation with the child [212]. Parenting programmes encouraging parental involvement and teaching better-quality parenting behaviour have been shown to result in young children achieving higher developmental assessment scores [213]. Similarly, in elementary school children, those with highly involved parents had enhanced social functioning and fewer behavioural problems [214]. The role of responsive parenting and child stimulation is not one restricted only to the mother or female caregiver; much published data

exists highlighting the important role which fathers play in the child's future educational attainment and social behavior [215-217].

2.7.2. Timing and Duration

Although there is limited data in the literature on the ideal time for an ECD intervention to begin for a child or the family, there seems to be a consensus that the younger the age when developmental stimulation programmes are started, the greater the effect [218-220]. As has been discussed, the first 1 000 days post-conception are a developmentally critical period for the foetus and infant. During this period the brain responds readily to input across the developmental domains. A summary of early evidence concluded that programmes which begin at an early age and continue the longest show the greatest benefits [221]. In their discussion paper, Baker-Henningham and Lopez Boo discuss outcomes of a family-based early intervention programme in St Lucia, The Caribbean which showed improved cognitive development in children who began participating between 6-18 months as compared with children who began at 18-30 months who experienced no gains [222]. If we take reading and language development as an example, high-intensity storybook reading started by parents during the first year of the infant's life showed increased performance for language skills and higher broader social communication scores [223].

ECD programmes need to be of sufficient duration to show beneficial outcomes. The greatest benefits have been reported from interventions which are started early in life and continue for an extended period [222, 224].

2.7.3. Participatory, Interactive Activities

Participatory activities for early developmental stimulation can involve activities involving the caregiver, child-focused activities, or a combination of the two.

Parent-focused interventions providing support and education to mothers, fathers and/or caregivers have been piloted and implemented with positive results. One such example is the Better Parenting Programme which has been rolled-out in Jordan to 200 centers nationwide. The programme targeted fathers in particular, but also included mothers. Results from the group participating in the programme showed an improvement in parents reading books and playing with their children. There was also an improvement in parenting knowledge and the use of explanations during discipline [225]. Extensive research has been conducted in Uganda by Boivin et al. into the effects of a caregiver training programme on child development. A year-long mediational intervention for sensitising caregivers (MISC) programme incorporating a biweekly training intervention for caregivers was provided to sixty Ugandan pre-school child/caregiver dyads. The children of the caregivers randomised to the MISC group showed greater gains on visual-spatial memory testing and learning compared with controls. While the adults participating in the MISC group improved significantly on a caregiving quality score and were also less depressed [226].

As the caregiver/child dyad is an intertwined unit it can be reasoned that interventions engaging both parts of the dyad would result in the greatest impact. A large study with components engaging both the caregiver and the HEU and HIV-infected infant aged 0-24 months has been trialed in Zimbabwe [227]. The Child Health Intervention for Development Outcomes (CHIDO) programme is a multicomponent intervention incorporating many of the elements of the Nurturing Care Framework; an internal savings and lending scheme to increase household income; and active support and home visits by community care workers [228]. Although the intervention resulted in reduced parental distress it did not have an impact on overall child development. The study raises important issues about the complexity of "parenting in poverty" and despite a comprehensive, well-developed intervention, levels of food insecurity and caregiver anxiety and depression derailed possible developmental benefits [227].

2.7.4. Emphasise Play and Language

"Work consists of whatever a body is obliged to do. Play consists of whatever a body is not obliged to do." – Mark Twain (1835-1910) in *The Adventures of Tom Sawyer*.

There have been many definitions of play suggested through the years. How play is viewed has been coloured by religious and social influences of the time, and although much has been written about the subject, no consensus definition for play has been achieved. What is not disputed however is the importance of play for healthy physical, social, emotional, psychological, communicative, cognitive and cultural growth and development [229, 230]. The play capacity and ability of a child is influenced by the overall health of the child as well as their maturational level. Play in children with chronic diseases, may be impeded by difficulties, such as recurrent hospitalisations, which can delay developmental milestone achievement [229]. Developmental stimulation programmes may need to be modified for children living with chronic diseases and activities adjusted when considering physical limitations such as pain and fatigue.

Play consists broadly of two components – interpersonal play and object play, and both need to be incorporated in ECD activities. Interpersonal play involves direct, face-to-face, dynamic social interactions with the goal of having fun [230]. The stimulation programme used in the research presented in this thesis included interpersonal play activities: "Talk, read, sing and play with your baby during feeding, dressing and bathing"; "Act excited and smile when your baby makes sounds. Copy your baby's sounds sometimes, but also talk normally to them using clear understandable language". Object play develops when an infant begins to take note of the surrounding environment and interacts with objects within that environment [230]. Children being raised in settings of poverty and limited resources may not be able to enjoy shop-bought children's toys; however everyday objects within the home environment can be repurposed and fashioned into a toy for a child. Each of the age-specific information sheets provided to the caregivers participating in the stimulation programme used in the study reported in this thesis

contained a section detailing ideas of objects in the home that can be used in play activities. For example, making a rattle using an empty pill container filled with rice grains or maize pips.

Play and language development are intricately related. Vocalisations and language are observed when children of all ages are engaged in play activities. Hearing-children rarely play quietly. A review of published literature from some years ago (1984) concluded that language is used to facilitate play and that play stimulates innovation in language and motivates language use and practice [231]. A more recent review (2006) of the interplay between language and play drew similar conclusions, reporting that play provided a supportive context for language learning and was highly beneficial to the development of children's language skills [232].

A historically interesting aside relating to language and play was discovered in Johann Heinrich Pestalozzi's (born January 12, 1746) "How Gertrude Teaches her Children: An attempt to help mothers teach their own children" [233]. Chapter 7 of this historically fascinating text discusses the teaching of sounds, words and language to the child, and an excerpt from the text is included below (**Figure 2. 7**) [233]. This text from a bygone age echoes ideas from current research on the importance of early stimulation of childhood language development.

VII

The first elementary means of instruction is, then,

SOUND.

This leads to the following special means of instruction:

I. *Sound teaching,*[1] or training the organs of speech.

II. *Word teaching,* or teaching about single objects.

III. *Language teaching,* or the means whereby we are led to express ourselves accurately about well known objects, and about all we know of them.

I. SOUND TEACHING

Is divided into teaching sounds spoken, and sounds sung.

OF SOUNDS SPOKEN.

In regard to these, we cannot leave it to chance whether they be brought to the child's ear sooner or later, combined or separately. It is important that they reach his consciousness in their whole compass as early as possible.

This consciousness should be perfect in him before his power of speech is formed; and the power of repeating them easily should be complete before the forms of letters are put before his eyes, or the first reading lessons begun.

The Spelling Book[2] must therefore contain all the sounds of which speech consists, and these should, in every family, be brought to the ear of the child in the cradle, be deeply impressed and made unforgettable by constant repetition, [8] even before he is able to utter a single one.

How Gertrude Teaches Her Children.

No one can imagine, for it is not seen, how the utterance of these simple sounds, ba ba ba, da da da, ma ma ma, la la la, etc., may rouse the observation of infants and please them; nor what can be gained for the general power of learning, by the early knowledge of these sounds

Figure 2. 7 Excerpt from "How Gertrude Teaches her Children to Play: An attempt to help mothers teach their own children", 1894 [233]

Children with language impairments will have completed less years of education, and achieved lower outcomes in the cognitive, academic and language domains when compared with language-unaffected peers [234]. A pre-school child's verbal ability has been shown to be positively related to their level of social competence [235]. Although the reading of books and telling of stories are vitally important in language development, adult-child conversations are strongly associated with healthy language development and caregivers should be encouraged to engage with children in two-sided conversations [236].

If the successful development of speech, language and communication are considered cornerstones for productive functioning during later childhood, adolescence and adulthood, ECD programmes should ideally place great emphasis on this facet of development. The activity programme (Appendix A) utilised in the study presented in this thesis included the expected age-appropriate language development milestone for each age group as well as the provision of ideas for caregivers to stimulate language development.

2.7.5. Utilise Local Knowledge, Materials and Existing Delivery Systems

ECD and parenting programmes should be adapted to culturally-specific, existing, positive child rearing practices within a community [237]. Certain aspects of an ECD programme need to be flexible in order to integrate into community practices while still maintaining standards and approved programme content. Introducing new ideas into a community can be a sensitive issue and parents tend to be more receptive when they are able to participate in the process of learning and sharing knowledge [212]. ECD facilitators should have an awareness of local cultural and linguistic practices as this will help towards parental acceptance and implementation of the programme [23]. Ideally, evidence-based ECD practices should be merged with cultural practices and traditional beliefs.

Children's toys and games can be constructed using readily-available, low-cost materials commonly found in the home. The activity programme used as part of this study provided caregivers with information and ideas about how to safely make toys from everyday household

objects (Appendix A). For example, mothers were told how to use their empty, clean ARV containers as stacking blocks. The ARV containers could also be filled with sand to use as a shaker when singing to the child.

Integration into existing service delivery platforms is an effective way of implementing wide-scale roll-out of new programmes. Making use of the strengths of existing delivery platforms could be beneficial in terms of saving time and money, reduced training needs for facilitators already familiar with certain features of existing interventions, and accessing existing materials which can be used as building blocks for knowledge expansion [212]. In South Africa, the Philani Maternal, Child Health and Nutrition Trust was established in 1979, offering a clinic- and home-based health and nutrition programme to a population of approximately one million people living in the informal settlements outside Cape Town [238]. As the project expanded, the need for child learning centers was realised, and the existing Philani programme was used as a platform and expanded to include an ECD programme [238].

2.7.6. Programme Intensity and Frequency of Contact between Providers and Participants

The intensity of an intervention refers to how often the parent-child dyad is exposed to the intervention. For home-based parent-executed interventions the caregiver is encouraged to engage with the intervention on a daily basis, perhaps even a number of times each day. Interventions which involve health worker home visits or clinic-based interventions are less intense as practically the intervention cannot be provided daily. Positive correlations between intervention intensity and outcomes have been reported – the greater the intensity of the intervention the greater the benefits to both the mother and the child [222]. Caregivers of infants and young children benefit from frequent interactions with healthcare or community workers for support, encouragement, evaluation of ECD activities being implemented in the home and education and training on ECD activities as the child grows. Children aged 6-30 months from a deprived urban population in Jamaica, for whom home visits were conducted every two weeks

showed better developmental assessment scores compared with those receiving monthly or no visits (control group) [239]. A 2008 review of parental involvement in services and activities offered through early childhood home intervention programmes reported that it was both logically and empirically evident that outcomes were stronger when participants were more involved [240], however caregiver participation is a complex subject and caution needs to be exercised when applying this conclusion broadly to all programmes.

Whilst the optimum intensity remains mostly undefined it stands to reason that if interventions of greater intensity result in greater benefit, children may receive greatest benefit from interventions which are incorporated into daily child rearing practices.

2.7.7. Quality and Continuous Monitoring and Evaluation

ECD programmes need to be of a sufficiently high quality in order to provide the expected outcomes. Low quality programmes are unlikely to result in the intended child and family outcomes. Maintaining quality – in terms of adherence to implementation standards – across varying settings and systems can be challenging. Small-scale interventions and pilot projects perform well when evaluated for quality, but when programs go to scale it can be challenging to maintain the uniformity of the intervention [222].

Britto, Yoshikawa and Boller, in their article published by the Society for Research in Child Development, grouped the themes defining of the quality of ECD programmes according to world regions. Dimensions of quality of programmes in high-income countries included safety and adequacy of physical environments; the nature of the interactions between the teacher/caregiver and the child; staff knowledge, education and training; and the comprehensiveness of the programme, while in LMIC quality indicators included attention to cultural feeding and caregiving practices; provider training; and the inclusion of physical growth monitoring and psychosocial interventions [241].

The quality of interventions has largely been measured through achievements on childhood developmental assessments, as well as general health parameters such as childhood mortality rates and growth indicators, however these indicators no not provide information about the actual quality of the services provided [241]. The quality of programmes needs to be continuously assessed through monitoring and evaluation, and improvements made as required to ensure programme relevance and maximum results yield [212]. Staff involved in providing ECD services require support, supervision and systematic in-service training to ensure that the quality of the intervention is maintained.

2.8. Assessment of Neurodevelopment

Assessing developmental progress and achievements in young children requires assessment tools which are valid, reliable and feasible for use in varying settings. One needs to be judicious in the choice of a screening or assessment tool when selecting from the plethora of available tools. A Toolkit for measuring ECD in LMIC has been produced by the World Bank and aims to assist providers in selecting, adapting, implementing and analysing data obtained from the various child developmental measurements [242]. The World Bank Toolkit includes 147 assessment tools – 41 from the 2009 version and an additional 106 for children aged 0-8 years in the 2017 edition – of which 44 percent originated from LMIC or were developed simultaneously for multiple countries [242].

2.8.1. Assessment of Neurodevelopmental Streams and Domains

The assessment of a child's developmental competencies is achieved by combining information provided by a detailed parental history – including a developmental history, the use of developmental screening and assessment tools, and a thorough physical examination [243]. The longitudinal surveillance of development is a process which takes into account underlying risk and protective factors, parental concerns, and observances of the child's developmental abilities in pre-determined developmental domains along the continuum of age [243].

Obtaining a parental history of developmental milestone achievement is a key starting point. The healthcare worker should reference a comprehensive paediatric milestone chart which incorporates the three primary streams of neurodevelopment – neurocognitive, neuro-motor and neuro-behavioural – when eliciting a developmental history [244].

As development occurs along a continuum, the pattern of developmental milestone acquisition should be charted when obtaining a history of milestone achievement, or over serial follow-up visits. Delay in development, defined as a significant lag in developmental milestone acquisition, can be classified according to three patterns – a static, progressive or acute pattern [243] (described previously in section 4.2.1. specifically in relation to HIV infection). Charting a developmental history and obtaining age-specific information for milestone acquisition is an important rate of developmental milestone acquisition across time.

The pattern of development in term of which developmental domains are affected may become more evident as developmental milestones are charted. Dissociative delay – difference in rates of acquisition across the developmental domains [243] – has been described in CLHIV with different developmental domains affected to varying degrees by numerous immunological, opportunistic infectious comorbidities and treatment factors.

For the purposes of assessment and analysis, development as a whole has been divided into specific developmental domains. Although neatly compartmentalised for definition purposes, developmental domains do overlap with one another and skill sets for one domain are also required for another. The descriptions of the various developmental domains are not always consistently defined across sources. A useful table of developmental domain descriptions from World Bank Toolkit has been included here – **Table 2. 2** [242].

Developmental assessments tools do not all measure each of the developmental domains. Of the 100 tools identified by Boggs et al. for ECD outcome measurement, only 27 covered at least three developmental domains, and the majority did not assess hearing and vision [245].

Table 2. 2 World Bank Toolkit description of early childhood developmental domains[246]

Domain	Description
Cognitive Skills	The processes or faculties by which knowledge is acquired and manipulated, including abilities such as memory, problem solving, and analytical skills
Language Skills	The ability to understand and express verbal communication
Motor Skills	The ability to control and coordinate gross movements of the legs and arms (e.g., jumping, throwing) and fine movements of the fingers
Executive Function/Self-Regulation/ Effortful Control	Intentional control over behavior and cognition. Executive function includes abilities such as inhibitory control, cognitive flexibility, attention, and working memory
Temperament	Biological influences on the experience and expression of emotion, including extraversion/surgency (positive affect, activity level, impulsivity, risk-taking), negative affectivity (fear, anger, sadness, discomfort), and effortful control (attention shifting and focusing, perceptual sensitivity, inhibitory and activational control)
Social-Emotional Skills	The regulation of emotional responses and social interactions, which is a function of both temperament and self-regulation, including behavior problems, social competency, and emotional competency
Personal-Social/Adaptive Skills	The ability to perform daily-life skills, such as self-feeding, dressing, toilet training, interacting with others, and adjusting to new situations
Pre- and Early-Academic Skills	Skills needed to learn reading and math, such as counting and letters
Approaches to Learning	Behaviors related to how children become engaged in learning experiences, such as the ability to stay focused, interested, and engaged in activities

2.8.2. Types of Developmental Measurements

Developmental assessment measures can be classified as screening vs. ability tests. Screening has been defined as *"the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment"* [247].

Wilson and Jungner (1968) described several fundamental principles which should be considered prior to the implementation of a screening programme: the condition is an important health problem with a high prevalence in the community being screened; accepted treatment for the condition needs to be available; facilities for further investigation, diagnosis and treatment need to be available; there needs to be a recognised latent or early symptomatic stage of the condition which is being screened for thus providing an opportunity for intervention; there needs to exist a suitable screening test which is quick to perform and has an acceptable margin of error; the screening test needs to be acceptable to the population being screened; the natural history of the condition is fully understood; and the cost-effectiveness of case-finding should be balanced in relation to expenditure [248]. Developmental screening – with the use of standardised questionnaires – is designed to identify those who require further developmental evaluation [243]. An example of a developmental screening tool developed in the South African context is the infant gross motor screening test, which was developed by Hilburn *et al* for use specifically in CLHIV living in developing countries [249]. Another screening tool developed to detect moderate to severe global developmental delay in young CLHIV was developed by the Division of Developmental Paediatrics at the Red Cross War Memorial Children's Hospital in the Western Cape, South Africa. A preliminary validation study reported this low-cost, rapid screening tool to have a sensitivity of 78.6% [250].

In contrast to screening tests, evaluation of developmental ability is a more complex process which is aimed at making developmental diagnoses [243]. Ability tests assess the maximal skill level within developmental domains and provide a summary across domains for a child at a given age. Scores from ability assessments are frequently standardised and produce a normal distribution of assessment results in a typically developing population [242]. Although ability tests can provide comprehensive information on developmental capability, the use of ability tests is constrained by a number of factors. The BSID-III ability test for example is time consuming; requires trained professionals working in controlled environments; makes use of expensive test kits; and test adaptation to local languages and cultural contexts calls for substantial technical skills and financial resources – factors which make the test unfeasible for use at scale [251]. The use of ability tests in under-resourced countries can be constrained by limited financial means for the purchase of and training in specific tools; copyright considerations; limited training opportunities; literacy of assessors, and language and cultural differences [252].

The Toolkit for measuring ECD prepared by The World Bank Group includes an informative summary table of the ideal characteristics of ability assessments, and has been included here (**Table 2. 3**) [242].

Table 2. 3 Ideal Characteristics of a Child Developmental Assessment Tool vs. Reality[246]

Ideal	Reality
The test score represents the child's true ability in a certain domain.	Every assessment method introduces measurement error. A test that has high reliability and validity minimizes such error
The test is appropriate, interpretable, and has high reliability and validity in all contexts and cultures, including groups with different ethnic and socio-economic backgrounds within the same country.	Test items and procedures that are appropriate, reliable, and valid in one context or group may not be so in another.
The test shows variance in scores at all ages and ability levels.	Many tests are appropriate only for a limited age range, while children outside that age range score at floor (minimum score) or ceiling (maximum score). Screening tests are not designed to show variance in typically developing children, who normally score at ceiling.
The test is relatively easy to administer	Many tests require high levels of training and expertise to administer.
The test can be administered quickly and at low cost.	Many tests are time-consuming and expensive to administer.
The test provides information on all developmental domains.	Assessing additional domains adds to the time and resources required for training and administration.
The test score is relevant to a child's practical function in daily life, and therefore relevant to inform policies and programs.	The practical relevance of many tests of low-level cognitive abilities and neural measures has not yet been quantified.
The test is a good indicator of future success.	Child development continues to be malleable throughout childhood, reducing the predictive validity of early assessments. The predictive validity of many tests is not known, especially in low- and middle-income countries.
The specific brain systems and neural mechanisms underlying test performance are well-understood	For many tests, especially those measuring global cognitive function, the underlying neural systems and mechanisms are not well-understood.
The impact of health, nutrition, and environmental factors on the test score is well-understood.	Due to small numbers of studies and heterogeneity in measurement tools across studies, it is generally not known which specific tests are particularly sensitive to specific exposures common in low- and middle-income countries.

An extremely useful and comprehensive summary rating article published by Boggs et al. in 2019 identified ECD measurement tools used in one or more LMIC, available for use in children less than two years old and assessing three or more developmental domains [245]. Sixty-one tools met inclusion criteria – 22 individual-level screening tools, 33 individual-level ability tools, and five population-level tools (one tool met criteria as both a screening and an assessment tool and was included in both categories) [245]. Twenty-seven tools met inclusion for rating for accuracy and feasibility using an existing ratings approach. Of the individual-level screening tools rated, the Guide for Monitoring Child Development rated the strongest, followed by the Parents' Evaluation of Developmental Status, and lastly the Ages and Stages Questionnaire [253-255]. The Intergrowth 21st Neurodevelopment Assessment rated highest as an individual-level ability tool [256] and on a population-level, the Caregiver-Reported Early Child Development Instruments rated strongest in validity and reliability [257].

In the study presented in this thesis we made use of the individual-level ability tool the BSID-III, to assess neurodevelopment. From the rating publication referred to in the above paragraph, the BSID-III rated second to the Intergrowth 21st Neurodevelopment Assessment and was on par with the Griffiths Mental Development Scales (GMDS) [245]. The BSID-III is a tool developed in North America and caution needs to be exercised when using assessment tools in populations other than those for which they were developed – cross-cultural bias will be discussed further in the following section. Data has been published regarding the use of the BSID-III in African children. BSID-III scores obtained from repeated assessments carried out in a cohort of Malawian children from ten weeks to 30 months of age, showed the test scores not to be equivalent to the US-based norms and the researchers suggested continued use of the tool with the creation of new population-specific test norms [258]. The BSID have been normed for used in the South Africa population [259] and can be used with a moderate degree of diagnostic accuracy to identify young children in need of intervention to prevent late school entry [260]. A South African study conducted on healthy children with no neonatal risk factors showed BSID-III scores to fall below the 50th centile but within the test-defined normal range for cognitive, language and motor function, when assessed before and after the first year of life [261]. Although, contrasting South African data evaluating BSID-III test scores in children aged between 2-13 months reported

cognitive, language and motor scores to be significantly higher than the reference population means [262]. The use of control groups when using the BSID-III as an ability test in children with specific comorbidities is important for accurate data interpretation.

The BSID-III has also been used to assess development of CLHIV, using HEU children as a control group. Whitehead et al. compared BSID-III scores pre-ART and six months post-ART initiation in a cohort of South African CLHIV less than 12 months of age, to an age-matched HEU control group [263]. BSID-III scores for the CLHIV were lower than scores from the HEU control group, and although improvement in test scores was seen post-ART start, motor and language development remained significantly delayed in the CLHIV at six months of follow-up[263]. Similar results have been reported from a Zimbabwean study – comparing BSID-III scores in CLHIV to an HEU control group within the first year of life – in which CLHIV achieving significantly lower scores in all three test domains [264].

2.8.3. Important Characteristics of Developmental Assessments

2.8.3.1. Predictive Validity

The view of childhood development on the continuum over the life course leads to parents and developmental healthcare workers looking to the future and attempting to predict the long-term potential and future outcomes for a child. The predictive validity of a test refers to the association of test scores obtained at a single early time-point with future test scores and achievements of the child [242]. A strong association between early test scores and later achievements prove the test as being a meaningful indicator of the child's future ability. A general consensus exists in the literature of the limited predictive validity of assessment results in children aged less than two years old, with a stronger predictive validity for future academic performance for assessments conducted from the age of three years and upwards [265, 266]. The BSID-III has been reported to have strong predictive validity for cognitive ability in four year old pre-school children [267] and scores at year one of age have also been shown to be predictive of late school entry [260].

2.8.3.2. Reliability and Validity

Test *reliability* refers to "how consistently a measure produces similar results for a child or group of children with repeated measurements over a short period of time" [242]. Reliability can be increased by ensuring that tests are administered under uniform conditions. *Inter-rater reliability* is achieved through training in test administration with the goal of reducing measurement error and eliminating assessor bias [242]. The *validity* of a test or a test item refers to "the degree to which a measure accurately assesses behaviours or abilities that reflects the underlying concept being tested" [245].

Reliability data for the BSID-III has been evaluated through studies examining internal consistency, inter-rater agreement and test-retest stability. Results indicate the test to be reliable and the scales to maintain an acceptable degree of precision [268]. According to the rating scale used by Boggs et al. the BSID-III scored well – achieving the highest rating on the validity scale (validity ideally against educational outcomes up to age five with a standardised test), and second highest rating on the reliability scale (somewhat below widely accepted threshold, rigorous methods of testing but in one continent only) [245].

The BSID-III normative data were collected from a population of children in North America, which was stratified on variables such as age, sex and parental education. Approximately 10 percent of the normative population displayed specific clinical diagnoses such as, Down syndrome, premature birth and SGA [268] The test should ideally exhibit good reliability and validity in populations other than those in which they were developed. Studies conducted in countries outside of the United States have shown scores from the BSID-III to overestimate or underestimate performance of certain groups of children at risk of developmental disorders, such as premature infants and infants with congenital cardiac disorders [269-271].

2.8.3.3. Cultural Bias

It cannot be assumed that developmental assessment tools developed in North America and Europe are applicable for use in Africa. Even within the African continent, there exists a wide array of populations and cultures across which assessment tools may not be relevant.

Three approaches have been undertaken when attempting to address cross-cultural bias: develop an entirely new assessment tool specific for a specific population; adaptation of an existing tool; or employing the use of a control group of healthy children to whom the children affected by the condition being investigated can be compared [258]. An example of the creation of a new culturally-appropriate, locally-applicable screening tool is the Malawi Developmental Assessment Tool, and an ability tool – the Kilifi Developmental Inventory [272, 273].

Maintaining the psychometric properties of a developmental tool when adapting it for use in an African context can be complex as adaptation will impact assessment findings and generalisability [252]. Adaptation methods include: language translation; replacing test items; modifying materials, procedures and even assessment domains [252]. The most commonly adapted comprehensive developmental ability tools for young children in Africa are the GMDS, the BSID (BSID-I 1969, BSID-II 1993, BSID-III 2006) and an adaptation of the Mullen Scales of Early Development [252]. Analysis results from translated and culturally and linguistically adapted Mullen Scales of Early Learning across four South African languages showed that test adaptation did not advantage or disadvantage children based on their home language [274].

Specifically within the context of HIV infection in sub-Saharan Africa, the Kaufman Assessment Battery for Children (I and II) has been shown to be used successfully in different African countries and across various cultural contexts as a tool to identify cognitive impairment in children and adolescents [275]. A large study including children from South Africa, Malawi, Uganda and Zimbabwe reported the Kaufman Assessment Battery for Children, 2nd edition, Test of Variables of Attention, Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition and

Behavior Rating Inventory for Executive Function to be valid and reliable tools for evaluating the neuropsychological impact of HIV in African children aged between 6.6-8 years of age [276].

2.8.3.4. Assessment of All Developmental Domains

No one ECD assessment tool is able to assess all of the developmental domains as well as meet all of the criteria defining a good test instrument. Cognitive, language and motor domains are reported as those most commonly assessed in individual-level ability tests, while tools in this category most commonly omitted testing attention/executive function, disability, vision and hearing domains [245]. The BSID-III assesses the following domains: cognition, language (receptive and expressive communication), motor (fine and gross motor), social emotional (SE) and adaptive behaviour (AB) [268].

We chose to conduct three of the five BSID-III subscales; namely, cognitive, language and motor subscales, to meet our aim of describing neurodevelopment in our study cohort. The AB and SE subscales are the two subscales of the BSID-III which consist of parent/caregiver-completed questionnaires. Logistically, completing all five BSID-III subscales in addition to the other study-related procedures which needed to be carried out would have required the parents/caregivers to spend a longer time in the clinic. We found this to be problematic for caregivers who needed to attend still attend their place of employ on the day of the study follow-up visit. Out of past experience we observed that oftentimes a non-primary caregiver, such as a grandmother or other family member, attended the follow-up visit with the child. Alternate caregivers are unable to accurately complete required parent-completed questionnaires.

Few studies in the published literature include the AB and SE subscales of the BSID-III and a knowledge gap exists in the use of these subscales to predict outcomes in CLHIV. Recent studies on the use of the BA and SE subscales in premature, HIV-unexposed infants have reported these subscales to be important in providing a comprehensive description of functioning in extremely premature infants born at < 28 weeks gestational age [277]. These scales have also been described

to successfully predict associations with cognitive and behavioural outcomes in school-aged children when conducted on premature infants between 18-24 months of age [278].

2.9. Key Indicators for Monitoring the Impact of Early Childhood Development Initiatives

Indicators of child development provide countries with the ability to set targets, distribute resources, and monitor programme progress and effectiveness, however, no one such globally accepted indicator exists [23]. Providing information on the threats to ECD and a country's progress towards reducing or eliminating these threats, as well as the level of support and services available in the five component areas of the Nurturing Care Framework, provides an indirect measure of ECD [279]. Although additional indicators would be helpful, the data indicators chosen are largely available for most countries and country-specific progress can be tracked and compared with other countries [279]. **Figure 2. 8** shows the current South African profile of indicators interconnected with ECD, published by the CD2030 collaboration [279].

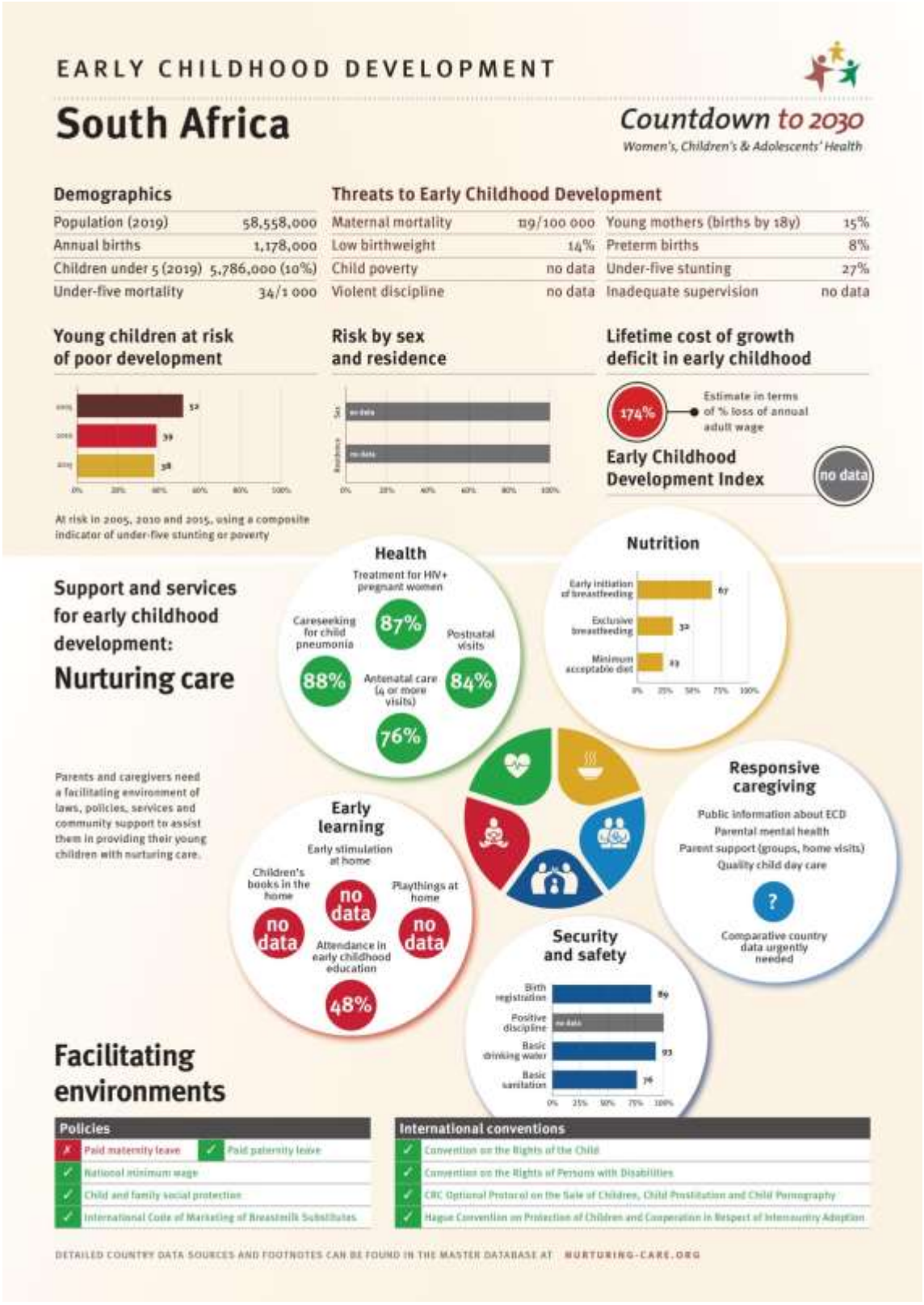

Figure 2. 8 Country Profile for South Africa: Indicators Interconnected with Early Childhood Development[279]

2.10. Conclusion

Millions of children globally are at risk of not reaching their full developmental potential, yet the risks they face are largely modifiable. Chapter Two describes the importance of the early childhood period on the developmental potential and future health and wellbeing over the life course. The biggest threats to childhood development are discussed and contextualised specifically to CLHIV and HEU children within the South African population. Interventions aimed at preventing the loss of this human potential are discussed within the context of the five components of the Nurturing Care Framework with a focus on early childhood developmental stimulation programmes.

Chapter Two provides the background against which this research investigating the neurodevelopmental outcomes of early-treated CLHIV and HEU children was conducted.

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CHAPTER THREE

SCOPING REVIEW

3.1. Publication Details

This chapter is presented as a published article. A scoping review was conducted to map evidence describing interventions which have been employed to mitigate or prevent neurodevelopmental delays in children exposed to or infected with HIV. In conducting the review we aimed to gain a better understanding of ECD interventions which have been employed successfully and thereby learn from the successes of these interventions, possibly implementing them in our project, as well as avoiding potential problems and pitfalls described by other researchers.

3.2. Journal Details

Table 3. 1 Publication Specifics

Title of publication	Interventions Addressing Neurodevelopmental Delay in Young Children Infected With and Exposed to HIV: A Scoping Review
Authors	Renate Strehlau, Tamryn van Aswegen and Joanne Potterton
Journal name	Rehabilitation Oncology
ISSN	2381-2427, 2168-3808
Year	2019
Volume	37 (January)
Pages	7-16
DOI number	DOI:10.1097/01.REO.0000000000000150

The scoping review was submitted to the journal of *Rehabilitation Oncology* in response to a call for manuscripts for a special issue highlighting the importance of the rehabilitation team in the context of HIV infection in both children and adults. The journal is the primary peer-reviewed resource for publishing articles relating the physical therapy and rehabilitation in oncologic medicine. Rehabilitation Oncology is indexed in Cumulative Index to Nursing Administration and Health Literature (CINAHL), EBSCO A-Z, Ex Libris, Journal Guide, ProQuest Summons, and Scopus. The journal is published by the American Physical Therapy Association.

3.3. Author Contributions

Author contributions are listed based on the CRediT (Contributor Roles Taxonomy) author statement which was developed to recognise individual author contributions [1]. Definitions of each term can be found in Appendix B. For ease of reference, the roles are listed as a table with individual author contributions shaded.

Table 3. 2 Details of Author Contributions

	Strehlau	van Aswegen	Potterton
Conceptualisation	■		■
Methodology	■		■
Validation	■	■	■
Formal analysis	■		
Investigation	■	■	
Data Curation	■		
Writing - Original Draft	■		
Writing - Review & Editing	■	■	■
Visualisation	■		
Supervision			■
Project administration	■		

3.4. Rights and Permissions

Lippincott – as an imprint of the publishing conglomerate Wolters Kluwer – allows the author to deposit a final peer-reviewed manuscript on his/her personal website, university's institutional repository or employer's intranet only after twelve months have passed from the article's publication date. Only the final peer-reviewed manuscript of the article may be used in a thesis. The final peer-reviewed manuscript *may not* be replaced with a proof of the final article. Included in this thesis is the non-final version of an article published in final form in Strehlau R, van Aswegen T, Potterton J. Interventions Addressing Neurodevelopmental Delay in Young Children Infected With and Exposed to HIV: A Scoping Review. Rehabilitation Oncology. 2019 Jan 1;37(1):7-16.

3.5. Summary of Findings

The scoping review conducted with reference to the question: "What interventions other than ART have been employed to mitigate, improve or prevent adverse neurodevelopmental outcomes in HEU and HIV-infected preschool children?" identified ten studies meeting the inclusion criteria, of which only one made use of a home-based stimulation programme aimed to improve developmental outcomes. Identified studies varied widely in the duration and intensity of the intervention. The review concluded that although it is known that there are many children at risk of poor developmental outcomes secondary to HIV infection, at the time that the review was conducted few studies had been done investigating interventions aimed at improving developmental outcomes for children affected by or infected with HIV.

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INTERVENTIONS ADDRESSING NEURODEVELOPMENTAL DELAY IN YOUNG CHILDREN EXPOSED TO AND INFECTED WITH HIV: A SCOPING REVIEW

Abstract

Background

Neurodevelopmental delays have been documented in children living with and affected by the Human Immunodeficiency Virus (HIV). Early childhood stimulation programmes can positively impact neurodevelopmental outcomes and have a far-reaching impact beyond childhood.

Objective

To conduct a scoping review mapping evidence describing interventions aimed at mitigating or preventing neurodevelopmental delays resulting from exposure to or infection with HIV in preschool children.

Methods

Electronic databases of PubMed, PsycINFO, CINAHL Plus, Google Scholar and the Cochrane Library, reference lists of identified articles and grey literature were searched. Title and abstract and full text reviews were conducted independently by two reviewers. Study location, design, sample size, age of cohort, child's HIV serostatus, antiretroviral treatment availability for children or caregivers, neurodevelopmental assessment tool used and details of the intervention and comparison groups was documented.

Results

Ten studies meeting predetermined inclusion and exclusion criteria were identified. Six studies focused on training provided to the child's caregiver of which one offered an intervention focused specifically on stimulating child development through a home-based stimulation programme. Four studies provided a child-directed intervention. Interventions ranged in duration from ten days to 15 months. Intensity of the intervention varied from three times per day to

biweekly. Interventions were aimed at children in the neonatal period throughout the preschool years.

Conclusion

Many children are at risk of poor neurodevelopmental outcomes due to HIV. Few studies investigating interventions aimed at addressing this problem were identified. Further research into effective interventions aimed at improving childhood neurodevelopmental outcomes in the context of HIV, is required.

Introduction

The transformative *Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive* [1] has been instrumental in reducing mother-to-child transmission of the Human Immunodeficiency Virus (HIV). However, children continue to be infected with HIV. The 2017 report from the Joint United Nations Programme on HIV and AIDS (UNAIDS) states that globally 160 000 (100 000 – 220 000) children <15 years old were newly infected with HIV in 2016, and 2.1 million (1.7 million – 2.6 million) children <15 years old were estimated to be living with HIV in 2016.[2] These numbers indicate that health programmes managing children infected with HIV are still necessary and potentially valuable.

HIV is defined as a neurotropic virus which has the propensity to infect cells in the central nervous system.[3, 4] This may result in neurocognitive impairment in children infected with HIV.[5, 6] Neurological manifestations of the virus were described early on in the epidemic in both children and adults. [7-9]

Child neurodevelopment is influenced both positively and negatively by innumerable environmental, social, parental and individual factors.[10, 11] Childhood HIV infection can have a direct negative impact on neurocognitive development. A 2009 systematic review of 54 studies showed that 81% of the studies reviewed reported HIV infection as having a detrimental effect on neurodevelopment in affected children.[12] An updated 2014 systematic review by the same lead author concluded that children infected with HIV were still at risk of cognitive delays in some domains and may make up a group with special educational needs.[13] Developmental delays

have been described in cognitive development[14, 15], receptive and expressive language abilities [16], and in fine and gross motor skills. [17] Long-term behavioral and emotional difficulties [18] and psychiatric disorders[19] have been described in children and adolescents living with HIV.

Eastern and Southern Africa have the greatest number of children under the age of 15 years infected with HIV – estimated at one million (930 000 – 1.2 million).[2] This region is comprised of low-income and low-middle-income countries which have well documented barriers to basic education for children[20], and poorly developed organisations and programmes to deal with the increased developmental and educational needs of large numbers of children with developmental delay due to HIV. Inability to benefit from education and long term lower productivity are consequences of a poor start in life.[21]

It has been reported that *in utero* exposure to maternal HIV can have a detrimental outcome on the neurodevelopment of HIV-exposed uninfected (HEU) children.[22] Conflicting data exists concerning whether neurodevelopmental outcomes in HEU infants are adversely affected by exposure to maternal antiretrovirals (ARVs) – either through *in utero* exposure or by postnatal exposure through ingested breastmilk. However, two recently published large cohort studies have confirmed previously available evidence finding no early neurodevelopmental differences between HEU (both when exposed to maternal triple antiretroviral treatment (ART) and maternal monotherapy only) and HIV-unexposed uninfected (HUU) infants. [23, 24] This is reassuring considering the expanding population of HEU infants.

Paediatric ART has shown remarkable benefits in the prevention and reversal of the negative developmental consequences of HIV infection. Infants initiated on ART at an early age i.e. less than 3 months of age, performed as well as HIV-uninfected infants in all domains except locomotion, while infants who deferred ART initiation had lower scores on all domains tested.[25] HIV-related neurodevelopmental shortfalls have been shown to improve in children taking ART with a longer duration of ART resulting in decreased impairment.[26-28] Access to ART for children living in regions with the greatest HIV burden i.e. Eastern and Southern Africa, is however not universal and was reported to be 63% [56–71%] in 2015.[29]

However, not all negative neurodevelopmental consequences related to HIV infection can be ameliorated by ART. A 2014 systematic review by Sherr et al. reported on interventions aimed specifically at reducing cognitive delay in HIV-infected and HEU children.[30] Four published studies were included in the review and effective interventions included: a coping skills intervention, home-based stimulation programme, Computerised Cognitive Rehabilitation Therapy, and a Mediational Intervention for Sensitising Caregivers. The authors concluded that special educational interventions need to be incorporated into programmes and policy as a matter of urgency. The necessity for expanding existing maternal and child health services to include interventions aimed at improving neurodevelopmental outcomes is echoed in publications by UNICEF in collaboration with the South African Department of Health, as well as the World Health Organization (WHO).[31, 32]

We conducted a scoping review to map existing literature describing interventions which have been employed with the aim of mitigating, improving or preventing childhood neurodevelopmental delays resulting from exposure to and infection with HIV in young children.

Methods

In conducting this scoping review we followed the methodological framework set out by Arksey and O'Malley in their definitive 2005 publication.[33] Updated methodological guidance was obtained from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: extension for Scoping Reviews (PRISMA-ScR)[34] as well as from other methodological publications.[35-37] The framework described by Arksey – namely, identifying a research question, identifying relevant studies, study selection, charting the data and collating and reporting the results – is followed in this scoping review.

Identifying the research question

In keeping with the objective of a scoping review, to collate data from across a broad field of knowledge, the following Population-Intervention-Comparison-Outcome (PICO) question was formulated to guide our search, "What interventions other than ART have been employed to mitigate, improve or prevent adverse neurodevelopmental outcomes in HEU and HIV-infected preschool children?" Consistent with the PICO of this scoping review, we did not aim to

examine the outcomes of the interventions described in the various studies, as our intent was not to perform a systematic review nor a meta-analysis of effectiveness.[38]

Search terms were clearly defined during the initial stages of planning the scoping review in order to guide the search strategy of the two independent reviewers. The period of early childhood is defined by the Convention on the Rights of the Child as the period of survival, growth and development in children below eight years of age.[39] For the purpose of this scoping review we chose to limit the upper age of inclusion to six years of age so as to only include children who had not yet started formal schooling. The minimum age was any time during the antenatal period if the intervention had been provided to the mother during pregnancy. A child infected with HIV was defined as having a reactive direct (DNA and/or RNA polymerase chain reaction) or indirect (HIV antibody) test for HIV any time after birth. A child who was exposed to but uninfected with HIV was defined as having been exposed to maternal HIV infection while *in utero* and during the breastfeeding period but who tested HIV uninfected during postnatal follow-up.

The American Physical Therapy Association describes an intervention as a purposeful, skilled interaction of a physical therapist or other healthcare provider with the child to enable them to reach goals and outcomes that are consistent with their diagnosis and prognosis.[40] We searched for clinical trials which made use of interventions aimed at modifying developmental outcomes.

Studies which utilised recognised, standardised child assessment tools and reported outcomes related to neurodevelopmental functioning, namely cognition, receptive and expressive communication, fine and gross motor performance and behaviour, were included in this scoping review.

Identifying relevant studies

In May 2018, we searched the databases of NCBI PubMed, PsycINFO, CINAHL Plus, Google Scholar and the Cochrane Library database to identify relevant literature. Our search included existing systematic reviews and scoping reviews, reference lists of identified articles publications for which full text articles were available and grey literature. We excluded case reports of <10 subjects, unpublished theses and unpublished conference material. We limited our search to

English articles. In order to include as much evidence as possible we did not search a specific timespan; rather the timeframe searched was limited by the specific database.

Search terms included: HIV, HEU, child, preschooler, caregiver, intervention, stimulation, neurodevelopment, language-, cognitive- and motor-development. The search terms used are listed in Table 1. Terms were adapted for the different databases.

Table 1. Electronic Database Search Terms

Search term	Variation
HIV	Human immunodeficiency virus, acquired immunodeficiency, acquired immunodeficiency syndrome, human immunodeficiency virus infection, HIV-positive, HIV-infected, perinatally acquired HIV, HIV-exposed, HIV-exposed uninfected
Children	Infant, baby, newborn, neonate, toddler, child, children, pediatric, young, preschool/ler
Intervention	Stimulation, training, train, program, programme, rehabilitation, rehabilitate, education, educate, teach, teaching, caregiver
Neurodevelopment	Neurocognitive, neurocognition, development/al, neurodevelopment/al, psychomotor, language development, cognitive development, cognition, motor development, impairment

Study selection

The following inclusion criteria were applied during the search and selection process, studies were to: (1) include at least one of the defined study populations i.e. HIV-infected and/or HEU children, (2) only include children <6 years of age, (3) include studies in which a clearly described intervention was aimed at either the child and/or the caregiver with the aim of the intervention to improve the neurodevelopmental outcomes of the child, (4) standardised neurodevelopmental assessment tools were used to assess neurodevelopment and at least one neurodevelopmental domain – namely cognition, language or motor function – was reported on, (5) HIV-infected children were ART-naïve or had been started on ART. The authors held an initial meeting to define the inclusion and exclusion criteria. Two reviewers (RS and TvA)

independently reviewed abstracts and full text articles and if there was uncertainty about whether an article should be included a discussion was held with all authors (RS, TvA, and JP) and a final decision made. Regular discussions were held throughout the process to define and redefine search terms and strategies.

Searching the databases listed above identified 531 articles (Figure 1). The greatest number were retrieved from PubMed – 880 hits when the search terms were applied to the entire text, and 435 after the list was reviewed and collated with search terms applied only to title and abstract. In searching PsycINFO we retrieved 96 hits. And when duplicates were excluded no new titles were found in CINAHL Plus, Google Scholar and the Cochrane Library database. Articles were selected and added to a database and 35 duplicates removed. The titles and abstracts of the remaining 496 were reviewed independently by two reviewers (RS and TvA) from which 27 were identified for full-text review. From the reference lists of these 27 articles a further 10 titles were chosen for review. Applying the inclusion and exclusion criteria to 37 full text articles resulted in 27 being excluded – reasons for exclusion: study population older than six years, n=7, content not applicable to our search, n=15, and the study not having an intervention, n=5 (Figure1).

Grey literature sources included, CDC Stacks (https://stacks.cdc.gov/), Centre for Reviews and Dissemination (https://www.york.ac.uk/crd/), GreyLit (http://www.greylit.org/), National Information Center on Health Services Research and Health Care Technology (https://hsrr.nlm.nih.gov/), Open Grey (http://www.opengrey.eu/) and NICE Guidance, Public Health topics (https://www.nice.org.uk/search/). The grey literature search yielded no results for our defined PICO question and stipulated inclusion and exclusion criteria.

PsycINFO search

The PsycINFO database was searched through the EBSCOhost platform. An unqualified, global search was conducted which ran the search through the default fields according to the database algorithm ranking the fields in order of importance. The following search fields were included: text, title, author, subjects [exact], abstract, keywords and table of contents.

1. (Infant or baby or new-born or neonate or toddler or child or pediatric or young or pre-schooler) (140 502)
2. HIV/ (51 273)
3. (Human immunodeficiency virus or acquired immunodeficiency or acquired immunodeficiency syndrome or human immunodeficiency virus infection or HIV-positive or HIV-infected or perinatally acquired HIV or HIV-exposed or HIV-exposed uninfected) (709)
4. 2 or 3 (51 286)
5. Intervention/ (373 547)
6. (Stimulation or training or program or rehabilitation or education or teach or caregiver) (56 008)
7. 5 or 6 (416 310)
8. Neurocognitive/ (16 898)
9. (Neurocognition or development or neurodevelopment or psychomotor or language development or cognitive development or cognition or motor development or impairment) (52 772)
10. 8 or 9 (69 115)
11. 1 and 4 and 7 and 10 (96)

Figure 1. Search strategy flow chart

Charting the data

Data from the identified studies were extracted and entered directly into an electronic database created for this purpose. Variables collected included, author; year of publication; country in which study was conducted; study design; cohort size; number of caregivers, children with HIV and HEU children; age of child cohort; size of the intervention and control group and details of the comparison; numbers of caregivers and children with HIV taking ART; neurodevelopmental assessments utilised and details of the developmental domains the specific tests are assessing; specifics of the intervention; results; conclusions and study limitations.

Collating, summarising and reporting the results

We conducted a descriptive, numerical summary analysis using data from identified studies which examined the countries where the research was conducted, age of children in the cohorts, sample size and duration of the intervention.

A qualitative thematic analysis was completed describing the types of interventions used, whether the intervention was aimed at the caregiver or the child or both, whether the intervention was used in a cohort of HIV-infected or HEU children and whether maternal or child ART was used in conjunction with the intervention. Trends in the utilisation of various neurodevelopmental assessment instruments were also examined.

Results

Ten studies were identified describing interventions aimed at improving neurodevelopmental outcomes in HIV-infected and HEU preschool children (Table 2). All identified studies were conducted as randomised controlled trials. Eight of the studies took place in African countries, namely Uganda (4), South Africa (2) and Tanzania (2). One study was conducted in the Dominican Republic and one study did not report study location.

Our inclusion criteria were set to include studies in which the cohort was less than six years of age. Ages in the ten selected studies ranged from a gestational age between 12-27 weeks through to five years of age. We included one study by Hernandez-Reif et al. which included children up to eight years old as in this study the analysis grouped the cohort into children aged 1.5-5 years and 6-8 years of age due to the age limitation set by the developmental assessment scale used.

The study by Scafidi & Field had the smallest sample size (n=28) as well as the shortest duration of the intervention and follow-up (10 days), but the participants received the interventional massage therapy three times a day.[41] Study populations in the other trials ranged from 52-327 children and the duration of the intervention ranged from 12 weeks to 15 months. The longest follow-up period was 12 months after the final time point at which the intervention had been provided to the child. Interventions varied in intensity as to how often they were provided to the child or caregiver. Caregivers in the four Ugandan studies were seen biweekly for 12 months and were taught skills which were performed daily by the caregivers during everyday child-caregiver interactions in the home.[42-45] Similarly, in the study by Potterton et al. the caregivers were equipped with skills to improve daily play interactions with the children in the home environment.[46] The two studies utilising massage therapy differed in the intensity of the intervention – the children in the study by Hernandez-Reif et al. received biweekly massage therapy,[47] and in the study by Perez et al. the caregivers were equipped with the skills to conduct the massage in the home environment on a daily basis.[48]

Interventions were aimed at either the mother/primary caregiver or the child. One study included an intervention aimed solely at the mother, namely maternal antenatal and postnatal oral vitamin supplementation, although, the infants were also exposed to the multivitamins *in utero* and postnatally through breastfeeding. In all four Ugandan studies the intervention was aimed at the mother/primary caregiver, and children were impacted through caregiver training and development of parenting skills. Nutritional support packages were provided to the mother-child dyad in three studies in addition to the study specific intervention. The interventions in six studies focused on caregiver training and relied on the caregiver to continue to provide the intervention, as taught, in the home environment for the study duration. One study relied on the caregiver providing a daily multivitamin supplement to the child. In two studies the children received the intervention directly from the study team for the duration of the study.

We included studies with interventions aimed at both HIV-infected and HEU children. Interventions aimed at children who had been diagnosed with HIV were identified in four studies. In these study populations, not all the children were taking ART. The percentage of children in whom ART had been started ranged from 0-86%. ART initiation would have been influenced by availability and country-specific pediatric ART initiation guidelines in place at the

time the study was conducted. Four studies included HEU children, and one reported HIV seroconversion of a child during the follow-up period. Two studies included children exposed to maternal HIV infection but the child's HIV diagnosis was not specifically reported.

The use of maternal/caregiver ART was not widely reported, but this is important as caregiver wellbeing has been shown to impact the wellbeing of the child.[49] Seven studies did not report on the use of caregiver ART, one study specifically reported that antenatal maternal ART had been unavailable at the time the study was conducted. One study only reported on the maternal prevention of mother-to-child-transmission (PMTCT) regimen used, and another reported both the maternal PMTCT regimen as well as the use of antenatal ART.

A wide variety of child neurodevelopmental assessment instruments were used to asses development, with some studies using more than one tool. As per our inclusion criteria, studies were required to employ validated neurodevelopmental assessment tools measuring at least one of the following: cognitive ability, receptive and/or expressive language ability (communication) and fine and/or gross motor performance. The following assessment tools were utilised: Bayley Scales of Infant Development version II and version III (BSID-II/III), Behavior Rating Inventory of Executive Function-Preschool version (BRIEF), Brazelton Neonatal Behavior Assessment, Child Behavior Checklist (CBCL), Color Object Test (COAT), Developmental Profile-II (DP-II), Early Child Vigilance Test (ECVT), Griffiths Scales of Mental Development (GSMD) and the Mullen Scales of Early Learning (MSEL).

Interventions

Interventions identified in the studies have been grouped into three subgroups according to the recipient of the intervention/interventional training, i.e. (1) Interventions aimed at training the child's primary caregiver, (2) interventions provided directly to the child, (3) intervention provided directly to the child's mother.

1. *Interventions aimed at training the child's primary caregiver*

The four studies carried out in Uganda all utilised a similar intervention [42-45] whereby the caregivers randomised to the intervention group received training on the Mediational Intervention for Sensitising Caregivers (MISC) model. The MISC training programme provides strategies for caregivers to enhance day-to-day caregiver-child interactions and thereby aim to

advance the cognitive development of the child. MISC does not rely on toys, equipment or educational resources. The caregivers were trained during hour-long biweekly sessions alternating between the child's home and the research office. The training was conducted over a 12 month period. The caregivers in the comparison control groups of the four Ugandan studies received training on a nutrition and hygiene information program designed by the Uganda Community Based Association for Women and Child Welfare (UCOBAC). The UCOBAC program is reported to meet the minimum standard of care for Ugandan families affected by HIV. The UCOBAC training was provided to the caregivers in the control arms during hour-long biweekly sessions alternating between the child's home and the research office over a 12 month period. In two of the studies, one with HIV-infected and the other with HEU children, the caregivers in both the intervention and control groups were provided with biweekly nutritional support packages in addition to the caregiver training. [42, 45]

The South African study[46] provided the caregivers of young HIV-infected children with a developmental stimulation program structured around activities of daily living with developmentally appropriate play incorporated into activities such as bathing and feeding. Home programs were also individually structured according to the needs of each child as indicated by the child's performance on the BSID-II. Caregivers were provided with children's books and were encouraged to read and talk with their children in the home. The home program was updated every three months over the period of one year.

The second South African study in which the intervention was aimed at the child and taught to the caregiver was a study in which mothers were trained to massage their HEU infants for 15 minutes per day from study enrolment at six weeks of age through to when the child reached nine months of age.[48] Study participants were seen at two-weekly intervals at the study clinic and nutritional support packages were provided to mothers.

Although the Tanzanian study did not require parental training as such, the intervention was caregiver dependent as caregivers were requested to provide their HEU children with a daily multivitamin supplement starting during the second month of life.[50]

2. *Interventions provided directly to the child*

Two studies provided an intervention directed at the child without requiring caregiver training or involvement. Both of these interventions provided massage therapy to the children. In a very early study published in 1996 researchers massaged HIV-exposed neonates for three 15-minute periods during three consecutive hours daily for 10 days while the neonates were in the hospital ward after birth.[41] The second study enrolled older children infected with HIV onto a study lasting 12 weeks in which children were massaged for 20 minutes twice weekly by trained researchers.[47]

3. *Intervention provided directly to the child's mother*

One study reported child neurodevelopmental outcomes based on a maternal intervention in which mothers were provided with antenatal and postnatal vitamin supplements.[51] Infants were indirectly exposed to the vitamin supplement *in utero* and while breastfeeding and received no further intervention.

Caregiver, family, socioeconomic and child demographics were reported in all the studies. Maternal factors reported included age, anthropometrical measures, CD4 count, WHO HIV disease stage, level of education, marital status, relationship to the child (biological mother vs. caregiver), level of partner support, anxiety, depression, functional impairment, mental pain and parenting stress levels. The household socioeconomic position was documented by reporting household income, material possessions, number of adults and children living in the house, whether each child had their own bed, food security and variety, and amount of money spent. The population of children in each study was well described in terms of sex (in all but one study), gestational age, anthropometry and absence of serious neurological problems.

Discussion

Interventions used to enhance child development included caregiver training (4 studies), massage provided to the children (3 studies), and vitamin supplementation to mothers or children (2 studies), and a stimulation programme (1 study). An ideal intervention addressing early childhood stimulation should target the different aspects of child neurodevelopment. This is especially true in HIV-disease which has been shown to affect different developmental domains to varying degrees.[26, 52, 53] A literature review detailing existing early childhood stimulation

interventions in developing countries concluded that joint mother-child interventions consisting of hands-on, practical activities carried out by the mother on a daily basis in the home environment resulted in the most favourable neurodevelopmental outcomes.[54]

It has been reported that interventions with a greater frequency and intensity of interactions between the provider and the child, as well as those with a longer duration, showed better outcomes.[54] Programmes which equip caregivers with child rearing skills which can be used daily in the home would therefore have the most enduring outcomes and have the advantage of extending the benefits to other children in the home. In the studies which we identified, training the caregivers on the MISC programme, massage therapy skills and a home-based stimulation programme would have had more enduring effects than an intervention directed at the child only and provided by a trained provider for a limited period of time.

The timing of the studies we reviewed differed regarding the age of the child at which the intervention was started. Only one intervention – a massage programme – started shortly after birth and continued for a ten day period while the neonates were admitted in the ward. Half of the interventions were initiated after the first year of life. Optimal timing of an intervention depends on the type of intervention and its targeted outcome [55] as abilities have differing times at which they develop – the "sensitive period".[56] Earlier may not mean better with respect to all developmental domains.

Children uninfected with HIV, but who have been exposed to maternal HIV infection have been reported as having worse neurodevelopmental outcomes when compared to HUU children. A recent meta-analysis reviewing data on the neurodevelopmental performance of HIV infected, HEU and HUU children, reported both HIV infected and HEU children as having worse neurodevelopmental outcomes when compared to HUU children.[22] Environmental confounders and the complexity of HIV infection in the family need to be considered when comparing developmental outcomes of HEU and HUU children. Child rearing is impacted by maternal health and wellbeing, and HIV infection is often associated with poverty and adverse social circumstances[57] which can have a negative impact on early child development. Of the ten studies we identified, only four interventions were aimed at HIV infected children.

Implications for future research

Further research is required evaluating the content, duration, intensity and timing of developmental interventions to ensure maximum benefits in terms of improving childhood developmental outcomes. Small scale interventional studies should be tested for generalisability and usability with the aim to incorporate the interventions into paediatric HIV management programmes.[31] A systematic review of effectiveness is needed evaluating interventions aimed at reducing a broad array of neurodevelopmental delays. This would assist in decisions concerning comprehensive paediatric HIV management policy.

The 2012 WHO review on developmental difficulties in early childhood states that there have been few studies done to directly examine the effectiveness of interventions to prevent developmental difficulties in young children.[32] There is a need for future research investigating documented interventions and their outcomes.

Limitations

For the purpose of this scoping review we limited the age range of the participants included in the studies to less than six years old as we wanted to include only preschool children who had not yet benefitted from education received from attending formal schooling. The limited age range would have excluded studies in which the intervention was aimed at a wider age range of children. Our search would also have been limited by the availability of information as set by our review question and it is thus possible that information has been omitted. Our database search was concluded on 25 May 2018 and studies matching our inclusion and exclusion criteria published after this date would not have been included in our search. We did not conduct the optional final step involving key stakeholder and consumer consultation as described in scoping review methodology. [36] Further consultations may have added additional insights into developmental interventions.

Conclusion

Globally, many children continue to be affected by or infected with HIV. Despite effective ART, HIV-related neurodevelopmental delays are still evident. We searched for studies with interventions, other than ART, aimed at preventing or improving adverse neurodevelopmental outcomes in these children. Of the studies identified, only one provided a home-based programme specifically aimed at stimulating neurodevelopment. In view of the number of

children affected by the HIV pandemic and the paucity of data found addressing our research question, further research investigating interventions to improve neurodevelopmental outcomes is warranted.

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Table 2. Summary of Studies with Interventions Aimed at Improving Neurodevelopmental Outcomes

Authors and Country	Study Design	Sample Size (N)	NHIV	NHEU	Comparison group e.g. HIV+ vs HIV-	CART	MART	Formal measure of child development	Domain measured	Intervention
Bass et al. (2017) Uganda	RCT	118 women-child dyads, 2-5 yrs	118	_	HIV-infected children of caregivers receiving MISC (N=58) vs. HIV-infected children of caregivers receiving UCOBAC (N=60)	39 (67.24%) MISC group 35 (58.33%) UCOBAC group	Not reported	MSEL, COAT, ECVT, BRIEF	MSEL-Visual reception, gross motor skills, receptive and expressive language. COAT-memory. ECVT-sustained attention. BRIEF-executive function	Caregiver directed, 12 month duration, biweekly caregiver training: MISC vs. UCOBAC. Biweekly nutritional package to both groups (control group)

Authors and Country	Study Design	Sample Size (N)	NHIV	NHEU	Comparison group e.g. HIV+ vs HIV-	CART	MART	Formal measure of child development	Domain measured	Intervention
Boivin et al. (2013) Uganda	RCT	120 women-child dyads, 16 months-5 yrs	120	_	HIV-infected children of caregivers receiving MISC (N=60) vs. HIV-infected children of caregivers receiving UCOBAC (N=60)	30 (50%) MISC group 34 (56.7%) control group	Not reported	MELS, COAT, CBCL	MELS-motor, language, cognition. COAT-memory. CBCL-internalising and externalising symptoms	Caregiver directed, 12 month duration, biweekly MISC caregiver training program vs. UCOBAC (control group)
Authors and Country	Study Design	Sample Size (N)	NHIV	NHEU	Comparison group e.g. HIV+ vs HIV-	CART	MART	Formal measure of child development	Domain measured	Intervention
Boivin et al. (2013) Uganda	RCT	119 women-child dyads, 2-4 yrs	_	119	HEU children of caregivers receiving MISC (N=60) vs. HEU children of caregivers receiving UCOBAC (N=59)	_	Not reported	MELS, COAT, CBCL	MELS-motor, language, cognition. COAT-memory. CBCL-internalizing and externalizing symptoms	Caregiver directed, 12 month duration, biweekly MISC caregiver training program vs. UCOBAC (control group)

Authors and Country	Study Design	Sample Size (N)	NHIV	NHEU	Comparison group e.g. HIV+ vs HIV-	CART	MART	Formal measure of child development	Domain measured	Intervention
Boivin et al. (2017) Uganda	RCT	221 women-child dyads, 2-3 yrs	_	221	HEU children of caregivers receiving MISC (N=112) vs. HEU children of caregivers receiving UCOBAC (N=109)	_	Not reported	MSEL, COAT, ECVT, BRIEF	MSEL-Visual reception, gross motor skills, receptive and expressive language. COAT-memory. ECVT-sustained attention. BRIEF-executive function	Caregiver directed, 12 month duration, biweekly MISC caregiver training program vs. UCOBAC (control group). Biweekly nutritional support package to both groups
Hernandez-Reif et al. (2008) Dominican Republic	RCT	52, 2-8 yrs	48	_	HIV-infected children receiving massage therapy (N=26) vs. HIV-infected children receiving play therapy (N=26)	None	Not reported	CBCL, DP-II	CBCL-internalizing and externalizing symptoms. DP-II-physical age, self-help age, social age, academic age, communicative age.	Child directed, 12 week duration, biweekly 20 minute massage vs. biweekly 20 minute play session (control group)

Authors and Country	Study Design	Sample Size (N)	NHIV	NHEU	Comparison group e.g. HIV+ vs HIV-	CART	MART	Formal measure of child development	Domain measured	Intervention
McGrath et al. (2006) Tanzania	RCT	1078 pregnant women. 327 infants assessed, ages 6-18 months	Not reported	327	HEU children of mothers having received Vit A only (N=180), MVT with Vit A (N=169), MVT without Vit A (N=147), placebo (N=158)	Not reported	None	BSID-II	MDI-cognition, receptive and expressive language PDI-fine and gross motor	Maternal antenatal and postnatal supplement – Vit A only, MVT with Vit A, MVT without Vit A or placebo
Manji et al. (2014) Tanzania	RCT	2387 infants, Age 6 wks-24 months. 206 infants assessed at 14-17 months	14	192	HEU children: oral MVT (N=93) vs. placebo (N=99)	Single dose NVP within 72hrs of birth	Single dose NVP during labour. Antenatal ART: MVT group N=34 (36.6%), placebo group N=26 (26.3%)	BSID-III	MDI-cognition, receptive and expressive language PDI-fine and gross motor	Child directed: daily oral MVT supplement vs. placebo from 6 wks of age until assessed at 15 months

Authors and Country	Study Design	Sample Size (N)	NHIV	NHEU	Comparison group e.g. HIV+ vs HIV-	CART	MART	Formal measure of child development	Domain measured	Intervention
Perez et al. (2015) South Africa	RCT	161, 6 wks-9 months	_	161	HEU children receiving massage therapy (N=73) vs. HEU children receiving no massage (control group, N= 88)	Single dose NVP within 72hrs of birth	AZT during pregnancy and single dose NVP during labour	GSMD	GSMD-locomotor, social, hearing/speech, hand-eye coordination and performance scale	Child directed, 15min daily massage, from 6 wks until 9 months of age. Nutritional support packages were provided to both groups
Potterton et al. (2009) South Africa	RCT	122, 10 months-2 yr 6 months	122	_	HIV-infected children receiving home-based stimulation program (N=60) vs. HIV-infected children receiving no program (N=62)	37 (86%) intervention group and 42 (85.7%) control group at 12 month assessment	Not reported	BSID-II	MDI-cognition, receptive and expressive language PDI-fine and gross motor	Child directed, home stimulation program, updated 3 monthly for 12 months

Authors and Country	Study Design	Sample Size (N)	NHIV	NHEU	Comparison group e.g. HIV+ vs HIV-	CART	MART	Formal measure of child development	Domain measured	Intervention
Scafidi & Field (1996) Country not stated	RCT	28, Birth-through day 10 of study duration	Not specified	28	HEU children receiving massage therapy vs. HEU children receiving no massage (control group)	_	_	Brazelton Neonatal Behavior Assessment	Habituation, orientation, motor behavior, range of state, regulation of state, autonomic stability, abnormal reflexes	Child directed, massage therapy, 3 15-minute periods during 3 consecutive hours daily for 10 days

AZT – Zidovudine, BSID-II – Bayley Scales of Infant Development Version II, BRIEF – Behavior Rating Inventory of Executive Function-Preschool version, CART – Child on ART, CBCL – Child Behavior Checklist, COAT – Color Object Test, CS – Cross Sectional, DP-II – Developmental Profile-II, ECVT – Early Child Vigilance Test, GSMD – Griffiths Scales of Mental Development, MART – Mother on ART, MDI – Mental Development Index, MISC – Mediational Intervention for Sensitizing Caregivers, MSEL – Mullen Scales of Early Learning, MVT – multivitamin, NHIV – number HIV+ children, NHEU – number HEU children, NVP – Nevirapine, PDI – Psychomotor Development Index, RCT – Randomised Controlled Trial, UCOBAC – Uganda Community Based Association for Child Welfare Program, Vit A – vitamin A.

CHAPTER FOUR

STUDY PROTOCOL

4.1. Publication Details

Chapter Four is presented as a published article. The study protocol was adapted into manuscript format for publication in *BMC Research Notes*. The manuscript contains a short introduction describing the risk of children worldwide not achieving their full developmental potential and specifically children who are HIV-infected who are subjected to the additional risk of the virus negatively impacting brain development during the vulnerable period of early childhood. The potential protective benefits on developmental outcomes of an ECD programme used in conjunction with paediatric ART lead the reader into a description of the methodology employed in the study.

4.2. Journal Details

Table 4. 1 Publication Specifics

Title of publication	Neurodevelopmental assessment of HIV−exposed uninfected and early−treated HIV‑infected children: study protocol
Authors	Renate Strehlau, Tamryn van Aswegen and Joanne Potterton
Journal name	BMC Research Notes
ISSN	1756-0500
Publication Date	06 April 2018
Volume	11
Article number	235
DOI number	DOI:10.1186/s13104-018-3331-8.

BMC Research Notes is a journal based in the United Kingdom and published by BioMed Central. The journal includes articles related to biochemistry, genetics and molecular biology and the field of general medicine. The journal is committed to sharing research protocols, initial observations, scientific data sets, and observations.

4.3. Author Contributions

Author contributions are listed based on the CRediT author statement which was developed to recognise individual author contributions [1]. Definitions of each term can be found in Appendix B. For ease of reference the roles are listed as a table with individual author contributions shaded.

Table 4. 2 Details of Author Contributions

	Strehlau	van Aswegen	Potterton
Conceptualisation	■		■
Methodology	■		■
Resources	■		■
Writing - Original Draft	■		
Writing - Review & Editing	■	■	■
Visualisation	■		
Supervision			■

4.4 Rights and Permissions

References

1. Allen L, O'Connell A, Kiermer V. How can we ensure visibility and diversity in research contributions? How the Contributor Role Taxonomy (CRediT) is helping the shift from authorship to contributorship. *Learned Publishing*. Jan 2019;32(1):71-74. doi:org/10.1002/leap.1210

Strehlau et al. BMC Res Notes (2018) 11:235
https://doi.org/10.1186/s13104-018-3331-8

BMC Research Notes

RESEARCH NOTE

Open Access

NEURODEVELOPMENTAL ASSESSMENT OF HIV-EXPOSED UNINFECTED AND EARLY-TREATED HIV-INFECTED CHILDREN: STUDY PROTOCOL

Renate Strehlau[1*], Tamryn van Aswegen[1] and Joanne Potterton[1,2]

Abstract

Objective: Sub-Saharan Africa has the highest prevalence of children at risk of not achieving their developmental potential, attributable largely to the human immunodeficiency virus (HIV) pandemic coupled with negative environmental factors. Childhood developmental stimulation programmes can mitigate adverse outcomes.

Methods: Neonates testing HIV positive at birth will be initiated on antiretroviral treatment (ART) and receive an age-appropriate stimulation program, updated at 3 monthly intervals through the first year of life. Neurodevelopment at 12 months of age will be assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Outcomes will be compared with HIV-infected and HIV-exposed uninfected children (HEU) not having received the stimulatory intervention. Associations between neurodevelopmental outcomes, environmental factors, and parental stress will be investigated. The study will take place at a single site in Johannesburg, South Africa. This non-randomised controlled intervention study, with a single non-blinded comparative intervention group, aims to investigate whether an early childhood stimulation programme used in conjunction with ART initiated at birth can positively impact neurodevelopmental outcomes at 1 year of age in children infected with HIV.

Trial registration 15 January 2018, Pan African Clinical Trial Registry PACTR201801002967587

Keywords: Early childhood development, HIV, Early antiretroviral treatment

Introduction

Worldwide an extraordinary number of children are at risk of not developing their full potential. Using poverty and stunting as proxy markers for estimating children at risk of early childhood developmental (ECD) delays, a 2010 Lancet Global Health report estimated that 249.4 million children (43% of all children in 2010) under the age of 5 years living in low- and middle-income countries (LMIC) were at risk of not reaching their developmental potential [1]. Sub-Saharan Africa was reported as having the highest prevalence of children at risk—66% in 2010. The HIV pandemic in South Africa contributes to this statistic with 240,000 (210,000–260,000) children under 15 years of age infected with HIV [2].

The human immunodeficiency virus is neurotropic and invasion of the developing infant brain results in significant negative neurodevelopmental consequences [3]. Reported developmental shortfalls include delays in motor, cognitive, and language development [4]. Careful assessment of the child's developmental abilities is important as children may continue to acquire new skills, but function consistently below the age-related developmental norm on standardised assessments [5]. The severity of the neurological deficit is increased relative to the degree of immunosuppression, stage of HIV disease [6], and timing of ART initiation. ART started at a young age is associated with improved neurocognitive outcomes [7, 8]. However, despite suppressive ART, neurodevelopmental delays—which may at times be quite subtle—continue to persist into childhood [9] raising concern for the adolescent years [10].

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Data describing developmental trajectories of HEU children is conflicting with some studies reporting cognitive and motor deficits [11], but these may also be attributed to co-varying risks related to parental HIV infection such as poverty, disruption in schooling, and reduced wellbeing [12].

Effective interventions stimulating ECD can have far-reaching positive outcomes, but little is known about the long-term impact of an intervention started at birth in conjunction with early antiretroviral treatment (ART) initiation. The primary aim of this study is to assess neurodevelopmental outcomes of early-treated HIV-infected children receiving an age-appropriate stimulation program and compare them with HIV-infected and HEU children not having received the stimulatory intervention. In addition, associations between neurodevelopmental outcomes, environmental factors, and parental stress will be examined.

Main text

The study is designed as a non-randomised controlled intervention study.

Subject selection

Study participants will be recruited from an existing cohort of early-treated HIV-infected and HEU children enrolled onto a clinical trial investigating viral latency and early neonatal provision of anti-retroviral drugs (NCT02431975). Children enrolled and in follow-up in the existing cohort will be offered inclusion into this study, making up the assessment only group. New-born infants will be offered co-enrolment onto the existing study and will make up the group receiving the intervention as well as the assessment. Refusal to participate in one protocol will not jeopardise inclusion onto the other. The trial will be conducted at Rahima Moosa Mother and Child Hospital (RMMCH), Johannesburg, South Africa. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M170653) and registered with the Pan African Clinical Trial Registry (PACTR 201801002967587). Caregiver written informed consent will be obtained.

Sample size

All children in the existing cohort will be enrolled and assessed using the BSID-III at a single time-point i.e. either at 12, 24 or 36 months of age. 45 children will be enrolled into the intervention group. Hutchings and Potterton, investigating developmental outcomes of HIV-infected and HEU infants [13] reported average cognitive composite scores of 100.31 ± 12.75 for HEU and 75.89 ± 17.69 for HIV-infected infants. Groups of 45 will provide > 90% power to detect a mean cognitive composite score difference of 25 assuming a standard deviation of 17. Hutchings also reported a mean composite language score of 96.28 ± 10.13 and 77.18 ± 16.22 and mean composite motor score of 106.16 ± 10.20 and 79.71 ± 20.91 for HEU and HIV-infected groups respectively. Groups of 45 participants provide > 90% power to detect a difference of 25 in the mean language and motor scores assuming a standard deviation of 16 and 20, respectively. Feasible study enrolment period; number of births per month at RMMCH; and maternal and neonatal HIV prevalence were considered when planning the sample size.

Inclusion and exclusion criteria

Children less than 36 months enrolled onto the existing cohort trial are eligible for inclusion. Newborn HIV-infected infants initiated on ART whose caregiver provides informed consent will be included. Caregivers unable to comply with follow-up; serious birth defects; uncontrolled maternal psychiatric illness; and inability to provide informed consent will result in study exclusion.

Study procedures

Trained assessors will conduct the BSID-III on children enrolled from the existing cohort at a single time point. Inter-rater reliability of BSID-III administration will be established. Prematurity will be corrected until 24 months chronological age for a gestational age < 37 completed weeks.

The BSID is a direct assessment test using test kit objects to evoke a response. Five developmental domains are evaluated: cognitive, motor, language, social-emotional and adaptive behavior [14]. The BSID have been normed in South Africa [15].

The intervention group will receive a standardised set of developmentally stimulating toys. At three-monthly intervals, additional items will be provided (Table 1).

Caregiver information cards developed in South African as part of a developmental activity programme will be provided three-monthly [16]. The card explains what is expected of a child at certain ages in terms of physical,

Table 1 Items provided to the intervention group through the first year of life

Child's age	Items provided
Birth	Baby blanket, washcloth, booties and hat, rattle
3 months	Mirror, small ball, book, squeaky toy
6 months	Ring stacker, large ball
9 months	Wooden blocks, stacking cups, book
12 months	Wooden form board, toy car, plastic doll, picture book, crayons and paper

cognitive, language and socio-emotional development. Play ideas and indications of possible developmental delay are included.

BSID-III will be conducted on the intervention group at 12 months of age. The intervention includes visible components—educational toys and parental information cards—and clinic files of these children will be marked to ensure they receive the intervention. Consequently, neither study participants nor assessors are masked to the intervention assignment. Furthermore, by nature of the timing of the assessment conducted at the 12 month follow-up visit the assessor would be able to deduce that the child received the intervention. Assessors have been trained to complete the assessment regardless of exposure to developmental interventions. Baseline comparability in the HIV-infected infants will be established.

Study measures

Demographic and health-related variables will be collected from the patient's files for participants enrolled in the existing cohort. Infant data includes birth history; serial anthropometric data; morbidity data; ART history; concurrent medication; immunisations; feeding history; and laboratory data i.e. HIV viral load, HIV total nucleic acid test, CD4 count, and full blood count (FBC). Maternal data consists of: serial anthropometric measurements; ART history; and laboratory data i.e. HIV viral load, CD4 count, and FBC. Permission for data use has been granted by the database holder and site clinical staff are aware of the aims and logistics of the study.

Composite scores for the three developmental sub-scales of the BSID-III which are administered with direct child interaction—cognitive, motor, and language—will be recorded [14]. Raw scores are converted to scaled scores which are used to derive the composite score for each subscale.

The household survey and the Parenting Stress Index-Short Form (PSI-SF) will be completed with the child's caregiver. The household survey is a self-styled questionnaire gathering data about the household in which the child lives. Questions cover the following categories: family structure; number of household members diagnosed with HIV; parental nationality; employment; cigarette and alcohol use; water and sanitation measures; type of housing; exposure to sexual abuse and physical violence; childcare arrangements; and access to electricity and basic electronic household items. The household survey consists of a broad set of variables as ECD is influenced both negatively and positively by a myriad of factors [17–19]. The PSI-SF is the condensed version of a self-reported screening tool used to explore parental stress levels associated with parenting children aged 1 month–12 years [20]. Maternal HIV infection can impact parenting skills which in turn influences the child's wellbeing, ECD and childhood outcomes [21, 22].

Data analysis

De-identified data from paper case report forms will be entered into a secure database. Statistical calculations will be performed using SAS version 9.4 (Cary, North Carolina, USA). Anthropometric Z-scores will be calculated using WHO software [23]. P-values will be two- tailed and p-values < 0.05 will be considered statistically significant.

Descriptive statistics will describe the characteristics of the early-treated perinatally HIV-infected children enrolled in the existing cohort in terms of demographics, growth parameters, and HIV-related factors. Composite cognitive, language and motor scores will be described. Continuous variables with normal distribution will be described using means and standard deviation with a 95% confidence interval. Frequency tabulations and percentages will be used to describe categorical variables. "At risk" of developmental delay will be defined as any composite score less than 85, and "delayed" as a score less than 70 [24]. Number of children in these two categories will be explored and associations between patient and disease characteristics investigated using the Chi squared test at 5% level of significance. Mean composite scores will be compared between children assessed at 12, 24 or 36 months of age using ANOVA.

Mean composite scores and number of children "at risk" or "delayed" in each subscale will be compared between early-treated HIV-infected and HEU infants assessed at 12 months of age. T tests will compare demographic, clinical and anthropometrical data between groups. The analysis will be expanded to include the HIV-infected infants having received the ECD intervention. The Chi squared test and Kruskall-Wallis 1-way ANOVA will be used to measure variable difference between groups.

Univariate and multiple regression analyses will be performed to establish associations with poor outcomes on the three subscales i.e. composite scores less than 70 or 85. Variables used to establish associations with poor outcomes will include maternal antenatal and postnatal health-related factors, infant birth data, infant health and HIV-related variables, and data pertaining to socioeconomic status and parental stress. Logistic regression will be conducted on various risk factors for each subscale and a score of ≤ 85 will constitute a poor outcome.

Conclusion

HIV puts early neurodevelopment of HIV-infected and HEU children at risk [4, 11]. ECD interventions should form part of the management of HIV-infected and HEU children [25]. We will compare neurodevelopmental outcomes of early-treated HIV-infected children receiving an age-appropriate stimulation program with early-treated HIV-infected and HEU children not receiving an intervention.

Limitations

Although comprehensive, the household survey may not include all confounding variables as development is influenced by innumerable factors. Children in the HEU control group would be exposed to the same confounders as the HIV-infected infants. Use of toys and materials is caregiver dependent—children may not be given the intervention in the home environment. Use of the intervention depends on parental acceptance in accordance with cultural norms and child rearing practices. Use of the intervention will be carefully explained to the caregiver and the caregiver will be encouraged to initiate play and interact with her infant. Sufficient time will be allowed for answering questions and repeating explanations. Study attrition will reduce the planned cohort size. Caregivers returning at incorrect study time points will result in children missing the ideal BSID assessment age. The following measures will be undertaken to maintain the cohort in follow-up. Caregivers will be provided with appointment cards for follow-up visits, and study visits will be scheduled for a mutually convenient day. Caregivers will receive a telephone call to remind them of their study visit the day before the visit is due. Visits will be rescheduled if caregivers are unable to honour their appointments. Completion of the assessment depends on the availability of trained assessors. Two assessors have been trained to ensure an assessor is available when scheduling appointments. Assessment bias may occur as assessors have not been blinded to the intervention group; however, assessors have been trained to conduct the assessment in a standardised manner for all participants.

Abbreviations

ART: antiretroviral treatment; BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition; ECD: early childhood development; FBC: full blood count; HEU: HIV exposed uninfected; HIV: human immunodeficiency virus; LMIC: low- and middle-income countries; PSI-SF: Parenting Stress Index-Short Form; RMMCH: Rahima Moosa Mother and Child Hospital.

Authors' contributions

RS, JP contributed to the conception and design of the study. RS, TvA, JP have been involved in drafting the manuscript and editing for intellectual content. All authors read and approved the final manuscript.

Author details

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the ongoing nature of the study but are available from the corresponding author on reasonable request.

Consent for publication

Not Applicable.

Ethics approval and consent to participate

The study has been approved by the Human Research Ethics Committee of the University of the Witwatersrand (Clearance Certificate M170653). The trial has been registered with the Pan African Clinical Trial Registry (PACTR 201801002967587). Written informed consent is obtained from all study participants prior to inclusion in the study.

Funding

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Publisher's Note

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CHAPTER FIVE

NEURODEVELOPMENT IN HIV-EXPOSED UNINFECTED CHILDREN

5.1. Publication Details

Children exposed to maternal HIV infection *in utero* but who did not acquire the infection at birth were included in this study as a control group, and this group of children makes up an important population in its own right. Chapter Five is presented as a published article and addresses the objective of describing neurodevelopment in a group of HEU children at 12 months of age.

5.2. Journal Details

Table 5. 1 Publication Specifics

Title of publication	A description of early neurodevelopment in a cohort of HIV-exposed uninfected children
Authors	Renate Strehlau, Tamryn van Aswegen, Megan Burke, Louise Kuhn and Joanne Potterton
Journal name	AIDS Care, Psychological and Socio-medical Aspects of AIDS/HIV
ISSN	0954-0121 (Print) 1360-0451 (Online)
Publication Date	02 Mar 2020 (Online)
Page number	1-8
DOI number	DOI:10.1080/09540121.2020.1736257

AIDS Care is an international, multidisciplinary, peer-reviewed journal covering topics including public, environmental and occupational health as pertains to HIV/AIDS care and treatment. In

the same way in which HIV and AIDS infection affects many facets of lives from the individual through to the community, the journal aims to publish work from many different sectors and so address the global impact of HIV/AIDS.

5.3. Author Contributions

Author contributions are listed based on the CRediT author statement which was developed to recognise individual author contributions [1]. Definitions of each term can be found in Appendix B. For ease of reference the roles are listed as a table with individual author contributions shaded.

Table 5. 2 Details of Author Contributions

	Strehlau	van Aswegen	Burke	Kuhn	Potterton
Conceptualisation	■				■
Methodology	■				■
Validation	■				■
Formal analysis	■				
Investigation	■	■	■		
Resources	■				■
Data Curation	■	■			
Writing - Original Draft	■				
Writing - Review & Editing	■	■	■	■	■
Visualisation	■				
Supervision					■
Project administration	■				
Funding Acquisition	■				

5.4. Rights and Permissions

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5.5. Summary of Findings

The publication in *AIDS Care* describes the BSID-III assessment results achieved by the control group of infants who were exposed to maternal HIV infection but remained HIV-uninfected at 12 months of age. Successful PMTCT has resulted in fewer infants infected with HIV but a larger number of HEU infants and children. This group of children is of particular interest as the long-term effects of *in utero* exposure to maternal HIV and maternal ART are studied. HEU children are also born into families in which the caregiver may be experiencing poor health coupled with the many psychosocial aspects affecting the overall health of families affected by HIV. BSID-III scores – cognitive, language and motor domains – were compared with the BSID-III test reference means. The mean scores of the HEU children for all three domains assessed were just greater than the mean described for the norm-referenced population. Significant differences were found between boys and girls in the language subscale with girls achieving higher scores in the receptive language component. No associations were found between assessment scores and growth or exposure to maternal ART. The children remaining in follow-up may however have represented a biased sample as mothers with better health indicators were more likely remain in follow-up. As child developmental outcomes are closely related to maternal wellness results from the group assessed may have been influenced by retention bias.

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A description of early neurodevelopment in a cohort of HIV-exposed uninfected children

Renate Strehlau, Tamryn van Aswegen, Megan Burke, Louise Kuhn & Joanne Potterton

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A description of early neurodevelopment in a cohort of HIV-exposed uninfected children

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ABSTRACT

Introduction: Successful strategies preventing mother-to-child HIV transmission have resulted in increasing numbers of uninfected children exposed to maternal HIV and ART in-utero, and while breastfeeding. Some reports describe exposure as impacting neurodevelopment. *Methods*: This cross-sectional analysis included 49 of the 70 HIV-exposed uninfected (HEU) birth-enrolled children as the control arm of an observational cohort study of early treatment in HIV-infected infants in Johannesburg, South Africa. We used the Bayley Scales of Infant and Toddler Development-3rd Edition (BSID-III) to assess neurodevelopment at 12 months of age. Cognitive, language and motor subscale composite scores and performance categories were analysed. We evaluated associations between BSID-III performance categories and cohort variables. *Results*: Evaluating composite scores according to performance categories showed a higher percentage of scores in the average, high average and superior categories as compared to test reference norms. Maternal BMI $\geq$ 25 kg/m^2 and mid-upper arm circumference $\geq$ 32 cm were associated with higher than average infant language scores. Six children scored below average (<90) – three in the cogitive and three in the language subscale. *Conclusion*: No developmental delay was found in ART-exposed HEU children at 12 months of age. A small number of at-risk children suggest ongoing screening, referral and follow-up is needed.

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Introduction

Perinatal infection with the neurotropic human immunodeficiency virus (HIV) has been shown to impact negatively on the developing central nervous system (CNS) (Epstein et al., 1988). This, together with other factors, can affect the attainment of neurodevelopmental milestones in children infected with HIV. The following developmental domains have been shown to be affected to varying degrees in infected children – cognitive function, receptive and expressive language abilities, and fine and gross motor skills (Baillieu & Potterton, 2008; Foster et al., 2006).

Successful prevention of mother-to-child transmission (PMTCT) programmes have eliminated MTCT in several countries (UNAIDS, 2016), however, MTCT continues to be of concern in African countries. National South African data reported the MTCT rate as 0.9% (2016–2017) (Goga et al., 2018) and a recent South African publication reported the incidence of perinatal transmission as being 1.6% in birth-tested infants (Technau et al., 2018). Although concern for HIV-exposed infants has been expressed since the early years of the epidemic, the focus of paediatric HIV has now shifted to include the increasing number of HIV-exposed uninfected (HEU) children (Belman et al., 1996; Msellati et al., 1993; M. Nozyce et al., 1994).

It has been postulated that HEU children are also at risk of neurodevelopmental delays through various mechanisms, including; differences in microstructural integrity of brain white matter (Tran et al., 2016), and antenatal and postnatal exposure to maternal antiretroviral therapy (ART) (Williams et al., 2010). Published reports vary with some groups reporting delays in certain developmental domains (Kerr et al., 2014; Van Rie et al., 2008) while others have reported no differences in HEU children compared with HIV-uninfected unexposed (HUU) children (Chaudhury et al., 2017; Springer et al., 2012).

The aim of this study was to describe neurodevelopmental assessment results at 12 months of age from a single cohort of HEU children from similar socioeconomic backgrounds.

Methods

Study participants

A cohort of infants confirmed as HEU was enrolled at birth as the control group of an early antiretroviral treatment (ART) trial for perinatally-infected infants. Between July 2016 and January 2018 we enrolled 70 HEU neonates at Rahima Moosa Mother and Child Hospital (RMMCH), Johannesburg, South Africa. Only healthy neonates with no congenital abnormalities or history of significant birth trauma were enrolled.

Study procedures

As per the National Health Department Guidelines, HIV PCR testing was performed on all infants born to HIV-infected women or women whose HIV status at delivery was unknown (South African National Department of Health, 2015). A whole blood sample, obtained by venipuncture, underwent testing at the National Health Laboratory using the COBAS® TaqMan® HIV-1 Qualitative Test Version 2·0 (Roche Molecular Systems, Inc., Branchburg, NJ). A sample from the same blood draw was tested simultaneously using the point-of-care (POC) Cepheid Xpert® HIV-1 Qualitative assay (Cepheid, Sunnyvale, CA) thus allowing for the same-day return of HIV PCR results.

HIV-exposed neonates testing HIV PCR negative at birth were started on a PMTCT regimen according to the South African Department of Health Guidelines in place at the time (South African National Department of Health, 2015). Daily nevirapine (NVP) syrup with or without twice daily zidovudine (AZT) syrup – depending on maternal HIV viral load, timing of maternal ART initiation and feeding choice – was started. Repeat infant HIV PCR testing was performed four weeks after prophylaxis discontinuation. Mothers were counselled on infant feeding choices – either six months of exclusive breastfeeding or appropriate formula feeding, with the introduction of complementary foods at six months of age.

HEU infants were seen at the RMMCH research clinic at birth, 4, 8, 12, 24, 36 and 48 weeks of life. At each visit clinical data including infant and maternal anthropometry was collected. Blood for infant HIV PCR testing was taken at birth, 4, 8, 12 and 48 weeks of life and the viral load of breastfeeding mothers was monitored three monthly. Special care was taken in following-up infants displaying stigmata of possible HIV infection.

Infants in follow-up at week 48 were assessed using the BSID-III, within a window of four weeks. All assessments were carried out by two trained assessors – a study physician and a physiotherapist. Assessors were not blinded to the infant's HIV diagnosis. Assessments were conducted in an uncluttered room in a quiet setting, only if the infant was well, and were done prior to study-required phlebotomy procedures. The caregiver stayed with the infant throughout the assessment. Assessments were conducted in English with parental translation if the infant did not understand the English instruction. The BSID-III is a norm-referenced standardised assessment and scores from 12 month old black South African urban infants were found to be comparable to the scores of the infants in the United States (US) used to establish the BSID-III normative values (Rademeyer & Jacklin, 2013; Richter et al., 2016). BSID-III scores obtained in this study were compared to the US normative data.

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Johannesburg, South Africa) and the Institutional Review Board of Columbia University (New York, NY, U.S.A.). The children's legal guardians provided written informed consent prior to study-related procedures being carried out.

Statistical analysis

Raw scores obtained for each of the five subscales were converted into scaled scores. The mean of each scaled score for the reference population was 10 (range 1–19, SD 3). Scaled scores were then converted into composite scores, expressive and receptive language and fine and gross motor subscales were combined resulting in three composite scores – cognition, language and motor – having a reference norm of 100 (range 40-60, SD 15) (Bayley, 2006).

We interpreted composite scores in relation to the standard deviation units below the reference mean. A child was classified as having developmental delay when composite scores fell below the reference mean by 1.5 standard deviation units in two or more subscales, or when the score in one domain fell below the mean by two standard deviation units (Bayley, 2006).

Subscale composite scores can also be described in terms of a child's level of performance ranging from *extremely low* (69 and below) to *very superior* (130 and above) according to scores from the theoretical normal curve and US reference population (Bayley, 2006). We described the cohort's performance using this more qualitative interpretation, but due to the small sample size, when determining associations between variables and performance category outcomes we grouped the top three performance categories together and compared children scoring above average (110- ≥130) to those categorised as average and below (109- ≤69).

Weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), BMI-for-age (BAZ), mid-upper arm circumference (MUACZ) and head-circumference-for-age (HCAZ) z-scores were calculated using the World Health Organization (WHO) Anthro software (v 3.2.2). Underweight, stunting and wasting were defined as per WHO definitions (World Health Organization, 2010). Maternal mid-upper arm circumference ≥ 32.0 cm was classified as obese (Todorovic et al., 2003).

Continuous variables were normally distributed and described as means with a 95% CI. Chi-squared or Fisher's exact tests were used to compare categorical and event frequency data and t-tests to compare means. Analyses were conducted using Statistica software version 13.5.0.17 (TIBCO Software Inc).

Results

A total of 70 HEU newborn infants were enrolled for follow-up (mean age 0.77 days, SD 0.49). One infant died at 25 days and another was diagnosed as HIV infected at 290 days of age. Of the remaining 68 children, 11 were lost to follow-up, four parents requested transfer to another health care facility and four missed the scheduled assessment date. The remaining 49 (70%) children had a Bayley-III assessment (Figure 1).

All children except one were born by vaginal delivery, and 34 (48.6%) were male. The mean gestational age, by Ballard Score, was 39.8 weeks (range 36–42 weeks). Mean birth weight of the cohort was 2910 grams (SD 0.41) and 17 children were classified as low birth weight at < 2499 grams (range 2185–2485 grams). All infants were HIV-exposed and tested HIV uninfected on birth point of care and confirmatory laboratory HIV PCR testing. Breastfeeding was started in 49 (70%) infants. Table 1 details the cohort enrolment characteristics.

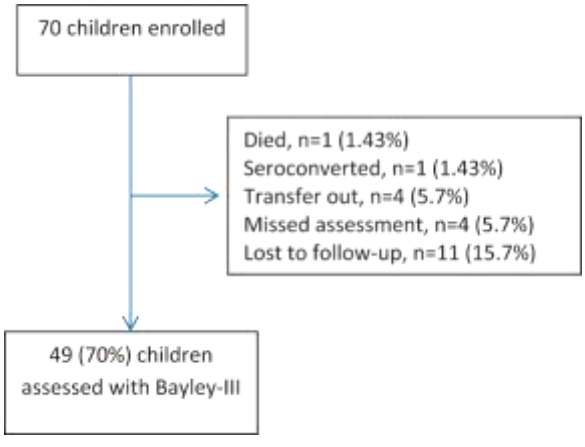

Figure 1. Follow-up of HIV-exposed uninfected children from enrolment through 48 weeks.

Table 1. HIV-exposed uninfected infant and maternal characteristics at study enrolment.

Infant characteristics at enrolment (*N* = 70)	Valid N	
Male, n (%)		34 (48.6%)
Age at enrolment (days), mean (SD)	70	0.77 (0.49)
Gestational age by Ballard Score (weeks), mean, (SD)	70	39.77 (1.28)
Vaginal Delivery, N (%)	70	69 (98.57)
Breastfeeding initiated at birth, N (%)	70	49 (70)
Birth Anthropometry	70	
Weight (kg), mean (SD)		2.91 (0.41)
Length (cm), mean (SD)		46.80 (2.24)
Head circumference (cm), mean (SD)		33.73 (1.26)
Birth weight < 2499 (g), N (range)	70	17 (2185-2485)
Birth Z-scores, mean (SD)		
Weight-for-age Z-score	70	−0.82 (0.93)
Length-for-age Z-score	70	−1.51 (1.19)
Weight-for-length Z-score	53	0.31 (1.04)
Head circumference-for-age Z-score	70	−0.41 (1.04)
Received ddNVP, n (%)		70 (100)
Duration ddNVP (days), mean (range)	67	47 (3–187)
Received additional AZT for PMTCT, n (%)		14 (20)
Age AZT PMTCT started (days), mean (range)	14	4 (0-9)
Duration AZT PMTCT (days), mean (range)	13	39 (3–92)
Maternal Characteristics at Enrolment (*N* = 70)		
Maternal age at enrol (years), mean (SD)	70	29.7 (5.33)
Parity, N (%)	70	
≤2		36 (51.43)
≥3		34 (48.57)
Experienced previous death of a child, N (%)	70	12 (17.12)
Started ART before this pregnancy, N (%)		25 (35.71)
ART started during this pregnancy, N (%)		44 (62.86)
ART started ≤ 12 weeks, N (%)		7 (15.91)
ART started > 12 weeks ≤ 24 weeks, N (%)		27 (61.36)
ART started > 24 weeks, N (%)		10 (22.73)
No ART, N (%)		1 (1.43)
ART regimen at delivery: EFV, TDF, FTC	69	69 (100)
HIV VL (copies/mL) closest to delivery, N (mean)	53	
50–1000		45 (134.6)
> 1000		8 (27 516.25)
unknown		17 (24.29)
CD4 cell count (cells/uL) closest to delivery, N (%)	60	
<200		9 (15)
Mean CD4 (range)		136.2 (61–198)
200–< 500		32 (45.71)
Mean CD4 (range)		342.63 (214–494)
500–1000		19 (31.67)
Mean CD4 (range)		681.84 (500–980)
unknown		10 (14.29)
Enrolment BMI, mean (SD)	69	26.9 (5.38)
Enrolment MUAC, mean (SD)	69	28.25 (3.74)

ddNVP-daily dose nevirapine, AZT-zidovudine, PMTCT-prevention of mother-to-child transmission, ART-antiretroviral treatment, EFV-efavirenz, TDF-tenofovir, FTC-emtricitabine, HIV-human immunodeficiency virus, VL-viral load.

Seven children were hospitalised during the first year of life; four within the neonatal period (mean age 18.75 days, SD 11.73).

Mean maternal age at delivery was 29.7 years (SD 5.31). This was the first child for 12 (17.1%) women and 14 (20%) reported having had a previous child death. ART was started during this pregnancy in 44 (62.9%) women, 25 (35.7%) started ART before this pregnancy, and one woman was not on any ART during

Table 2. Enrolment characteristics of children and mothers having completed the week 48 follow-up visit compared with those no longer in follow-up at week 48.

	Completed week 48 and had a BSID-III assessment (N = 49)	LTFU before week 48 and not having a BSID-III assessment (N = 21)	*p*
Infant enrolment characteristics			
Male, n (%)	24 (48.98)	10 (47.62)	0.9175
Birth Anthropometry			
Weight (kg), mean (SD)	2.92 (0.41)	2.89 (0.42)	0.7815
Length (cm), mean (SD)	46.48 (2.28)	47.09 (2.19)	0.3031
Head circumference (cm), mean (SD)	33.77 (1.24)	33.66 (1.34)	0.7409
Birthweight<2499(g),N(%)	11 (22.45)	6 (28.57)	0.5869
Birth Z-scores			
Weight-for-age Z-score, mean (SD)	−0.7974 (0.93)	−0.88 (0.96)	0.7449
Length-for-age Z-score, mean (SD)	−1.58 (1.20)	−1.34 (1.16)	0.4414
Weight-for-length Z-score, mean (SD)	*N* = 31		
0.35 (1.03)	*N* = 18		
0.23 (1.08)	0.6611		
Head circumference-for-age Z-score, mean (SD)	−0.39 (1.00)	−0.46 (1.14)	0.7977
Received additional AZT for PMTCT, N (%)	7 (14.29)	7 (33.33)	0.0700
Maternal enrolment characteristics			
Maternal age at enrol (years), mean (SD)	29.29 (5.39)	30.67 (5.10)	0.3222
Started ART before this pregnancy, N (%)	21 (42.86)	5 (23.81)	0.0133
ART started during this pregnancy, N (%)	27 (55.10)	16 (76.19)	0.0991
ART started ≤ 12 weeks, N (%)	4 (14.81)	3 (18.75)	0.7381
ART started > 12 weeks ≤24 weeks, N (%)	17 (62.96)	9 (53.25)	0.6673
ART started > 24 weeks, N (%)	6 (22.22)	4 (25)	0.8367
No ART, N (%)	1 (2.04)	0	0.5128
HIV VL (copies/mL) closest to delivery, N	40	13	
≤ 1000	34 (85.0)	11 (84.62)	0.9737
> 1000	6 (15)	2 (15.38)	0.9737
CD4 cell count (cells/uL) closest to delivery, N	44	1	
Mean (SD)	461 (218.34)	303.81 (172.60)	0.0047
<200	5 (11.36)	4 (25)	0.1944
Enrolment BMI, mean (SD)	27.67 (5.43)	*N* = 20 24.96 (4.70)	0.0552
Enrolment MUAC, mean (SD)	28.81 (3.77)	*N* = 2026.87 (3.37)	0.0499

BSID-III-Bayley Scales of Infant and Toddler Development, Third Edition; LTFU-lost to follow up; AZT-zidovudine; BMI-body mass index; MUAC-mid upper arm circumference.

the pregnancy. Of those starting ART during the pregnancy, 7/44 (15.9%) started at ≤ 12 weeks gestation (mean 7.86 weeks), 27/44 (61.4%) started between 12-≤24 weeks (mean 18.5 weeks) and 10/44 (22.7%) after 24 weeks (mean 29.6 weeks). The ARV regimen of all women on ART included efavirenz, tenofovir and emtricitabine. The HIV viral load closest to delivery for most women (45/53, 84.9%) was between 50–1000 copies/ml. Just under half (46.7%) had a CD4 cell count <350 cells/uL (range 61–344) closest to delivery (Table 1).

In the LTFU group a greater number of infants were assessed at being at high risk of HIV acquisition and a higher proportion of mothers were more likely to have started ART during the current pregnancy ($p = 0.0133$); to have a lower mean CD4 cell count closest to delivery ($p = 0.0047$); and have lower mean enrolment BMI ($p = 0.0552$) and MUAC ($p = 0.0499$) measurements (Table 2).

The Bayley-III assessment was conducted on 49 children, 49% male, at a mean age of 372.5 days (IQR 336-350). Mean composite scores for cognitive, language and motor subscales were 103.35 (SD 11.55), 105.92 (SD 12.28) and 103.31 (SD 7.34), respectively. No children were classified as having development delay in terms of having composite scores less than 1.5 SD below the mean in two domains or a composite score less than two SD below the mean in one domain. When composite scores were evaluated according to

Table 3. Percentage of 49 HIV-exposed uninfected children in each performance category according to BSID-III composite subscale scores compared to normative reference data[a].

	Cognitive subscale (%)		Language subscale (%)		Motor subscale (%)	
	Study population	Normative sample	Study population	Normative sample	Study population	Normative sample
Extremely Low (≤69)	0	2.2	0	2.5	0	2.5
Borderline (70–79)	0	6.7	4.08	7.6	0	6.1
Low Average (80–89)	6.12	16.4	2.04	14.4	2.04	14.1
Average (90–109)	65.31	50	51.02	51.4	69.39	49.3
High Average (110–119)	12.24	16.1	32.65	14.2	26.53	18.7
Superior (120–129)	16.33	6.7	10.2	7.9	2.04	7.1
Very superior (≥130)	0	2.2	0	2.2	0	2.2

BISD-III – Bayley Scales of Infant and Toddler Development, Third Edition.
[a]Bayley (2006, pp. 113–114).

performance categories, we found a higher percentage of scores in the average, high average and superior categories when compared to theoretical norms (cognitive subscale) and the reference population (language and motor subscales) (Table 3). In the cognitive subscale, children were 2.4 times more likely to be in the superior performance category, while in the language subscale they were 2.3 times more likely to be in the high average performance category, when compared to the normative data. No children were categorised as having extremely low or very superior performance.

Composite score comparison between males and females showed no significant differences apart from the language subscale (mean 102.29, SD 10.49 vs. mean 109.40, SD 13.09. $P = 0.041$) (Table 4). Comparing scaled scores for receptive communication, females had significantly higher scores than males (mean = 11.76, SD 2.99, and mean = 10.13, SD 2.49, $p = 0.043$, respectively). No sex difference was found in the expressive communication scaled score.

At the time of the Bayley-III assessment mean LAZ-score and HCAZ-score showed significant improvement from birth (−0.73, $p = 0.0002$ and 0.32, $p = 0.0003$, respectively). WLZ-score showed a non-significant decrease (−0.11, $p = 0.0964$). No significant association was found between children who were underweight, wasted or stunted and composite subscale scores.

We examined characteristics of the infants (exposure to breast milk, birth weight, having been admitted in the first year of life) and mothers (BMI, MUAC, time of ART initiation in relation to this pregnancy, and viral load result closest to delivery) and found two significant association with the Bayley's performance category achieved. Maternal BMI > 25 kg/m^2 and MUAC ≥ 32 cm one year post-delivery were associated with a significantly greater number of children achieving a composite score ≥ 110 (0.0096 and 0.0178 respectively).

Discussion

We describe the Bayley-III assessment scores of a cohort of young HEU children. At 12 months of age cognitive, language and motor composite scores were just greater than the mean described for the norm-referenced population (Bayley, 2006).

Developmental outcomes in HEU children have been described. Studies from South Africa – one using the BSID-III to assess and compare HEU vs. HIV-infected children on ART in the first year of life (Whitehead et al., 2014), and the other using the Griffiths Mental Development Scales comparing HEU and HUU children at 18 months of age (Springer et al., 2012) – reported no developmental delay in HEU infants although sample sizes were small. Similarly, results from sub-Saharan African (SSA) studies found HEU children ($n = 313$) in Botswana to

Table 4. BSID-III scaled and composite score results of the HIV-exposed uninfected children remaining in follow-up after 48 weeks and comparison of results between males and females.

Assessment results	All ($N = 49$)	Males ($N = 24$)	Females ($N = 25$)	p
Age at assessment (days), mean (IQR)	372.5 (336-350)	372.5 (337-349.3)	372.4 (336-360)	0.99
Cognitive subscale				
Scaled score, mean (SD)	10.67 (2.3)	10.33 (2.28)	11 (2.33)	0.32
Composite score, mean (SD)	103.35 (11.55)	101.67 (11.39)	104.96 (11.71)	0.32
Language Subscale				
Receptive communication Scaled score, mean (SD)	10.96 (2.85)	10.13 (2.49)	11.76 (2.99)	0.043
Expressive communication Scaled score, mean (SD)	10.94 (2.04)	10.5 (2.06)	11.36 (1.96)	0.14
Composite score, mean (SD)	105.92 (12.28)	102.29 (10.49)	109.4 (13.06)	0.041
Motor Subscale				
Fine motor, scaled score (SD)	10.78 (1.39)	10.46 (1.35)	11.08 (1.38)	0.12
Gross motor, scaled score (SD)	10.24 (1.65)	10.42 (1.44)	10.08 (1.85)	0.48
Composite score, mean (SD)	103.31 (7.34)	102.88 (6.43)	103.72 (8.23)	0.69

BISD-III – Bayley Scales of Infant and Toddler Development, Third Edition.

perform equally well at 24 months of age compared with HUU children (Chaudhury et al., 2017). Contrasting this, as well as our results, Van Rie et al. reported HEU pre-school children in the Democratic Republic of Congo, median age 33.4 months as having higher frequencies of delay in mental, language expression and motor subscales when assessed using the BSID-II (Van Rie et al., 2008). Furthermore, a study of older HEU Thai children (mean age 7.7 years, SD 3.2) showed measurable differences in neurodevelopment compared with HUU children after adjusting for caregiver education, parent as caregiver, household income, age, and ethnicity (Kerr et al., 2014). A recent meta-analysis of neurodevelopment in young HEU children concluded that this group may have lower mental and motor scores (McHenry et al., 2018).

Poverty and childhood stunting are used as proxy markers for poor neurodevelopmental outcomes (Lu et al., 2016). In this short-term follow-up we found no significant associations between maternal or infant health indicators and Bayley-III scores. However, mothers with possible indicators of poorer health – lower CD4 count and smaller MUAC – were more likely to default follow-up before one year. Adult morbidity is closely linked with the child's wellbeing (Gray et al., 2006). These indicators should prompt greater effort in keeping these families in care.

In utero and post-natal exposure to ARVs has not been shown to have deleterious effects on neurodevelopment in HEU children (Alimenti et al., 2006; Chaudhury et al., 2018; M. L. Nozyce et al., 2014; Williams et al., 2010). Children in our study were all exposed to the same maternal ART regimen in utero and some to post-natal AZT in addition to NVP. No differences in Bayley scores were found in children exposed to maternal ART from conception compared with children where maternal ART was initiated during the pregnancy. Infant AZT exposure did not result in negative outcomes, although the numbers are small.

Language skill acquisition develops with age and evidence shows girls to be ahead of boys in the development of early communication skills (Barbu et al., 2015; Eriksson et al., 2012). Our findings correspond with this as males scored lower on both receptive and expressive communication skills. SES also influences childhood language development (Pace et al., 2017; Pungello et al., 2009). Mothers of children in our cohort with a greater BMI and MUAC – which could possibly be used as proxy of maternal wellbeing and higher SES – achieved higher Bayley language subscale scores.

Numerous interconnected factors affecting early childhood development (ECD) have been described (Ali, 2013). Apart from exposure to HIV, HEU infants face a plethora of health problems including those arising from social and environmental complications of HIV-infection in the family (Desmonde et al., 2016; Filteau, 2009). It may not be possible to widely extrapolate developmental outcomes of HEU infants because of the heterogeneous nature of the populations studied.

Limitations

A single developmental assessment conducted at 12 months of age may not interpret a child's ability accurately and further assessments would provide more holistic data. Bayley-III composite scores have been described to decrease with age (Rademeyer & Jacklin, 2013) and further assessments would provide data more indicative of long-term abilities. Inclusion of an HUU control group would have allowed us to control for confounders known to influence ECD. Despite being provided with appointment cards and travel reimbursement, as well as telephonic visit reminders, we experienced high loss to follow-up numbers which are fairly typical of longitudinal studies conducted in this setting (Jones et al., 2005).

Conclusion

Young ART-exposed HEU children assessed with the BSID-III at 12 months of age performed well in the cognitive, language and motor subscales. Longitudinal follow-up and comparison to HUU children is needed to contextualise our findings.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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CHAPTER SIX

NEURODEVELOPMENT IN EARLY-TREATED CHILDREN INFECTED WITH HIV

6.1. Publication Details

Chapter Six is presented as a manuscript which has been submitted to, and accepted by, the journal *Child: care, health and development,* for publication. This manuscript addresses one of the main objectives of this research, namely: differences in neurodevelopmental outcomes between early-treated infants infected with HIV receiving a year-long ECD stimulation programme and a comparator group of early-treated infants infected with HIV receiving only the standard of care and no additional developmental stimulation intervention.

6.2. Journal Details

Table 6. 1 Publication Specifics

Title of publication	Neurodevelopment in early treated HIV-infected infants participating in a developmental stimulation program compared with controls
Authors	Renate Strehlau, Megan Burke. Tamryn van Aswegen, Louise Kuhn and Joanne Potterton
Journal name	Child: care, health and development
ISSN	0305-1862 (print); 1365-2214 (online)
Publication Date	Pending
Page number	Pending
DOI number	Pending

The journal *Child: care, health and development* is an international, peer-reviewed journal. The journal publishes quantitative and qualitative research papers from multiple disciplines working with child health. The journal encourages the submission of studies related to children with difficulties – physical, developmental, social and emotional.

6.3. Author Contributions

Author contributions are listed based on the CRediT author statement which was developed to recognise individual author contributions [1]. Definitions of each term can be found in Appendix B. For ease of reference the roles are listed as a table with individual author contributions shaded.

Table 6. 2 Details of Author Contributions

	Strehlau	Burke	van Aswegen	Kuhn	Potterton
Conceptualisation	■				■
Methodology	■				■
Validation	■				■
Formal analysis	■				
Investigation	■	■	■		
Resources	■				■
Data Curation	■	■	■		
Writing - Original Draft	■				
Writing - Review & Editing	■	■	■	■	■
Visualisation	■				
Supervision					■
Project administration	■				
Funding Acquisition	■				

6.4. Rights and Permissions

The manuscript has been accepted by the journal for publication and the reviewer's comments have been addressed. At the time of printing this thesis the final publication proofs have not yet been received from the journal, hence the manuscript as submitted to the journal after addressing the reviewer's comments has been included in this chapter.

6.5. Summary of Findings

Children with perinatal HIV infection, who started ART within the first two weeks of birth, and participated in a year-long home-based early developmental stimulation programme were assessed at 12 months of age using the BSID-III developmental assessment tool. A comparator cohort of children with perinatal HIV infection also starting ART within the first two weeks of birth but not participating in the developmental stimulation programme was also assessed with the BSID-III at 12 months of age. In addition, older CLHIV who had aged beyond 12 months were assessed with the BSID-III at their next birthday – either 24 or 36 months of age.

The BSID-III assessment results at 12 months of age in the stimulation group were encouraging. The group participating in the ECD programme achieved higher scaled and composite scores in each of the assessment domains – apart from the gross motor scaled score – compared with the group not receiving the intervention. BSID-III scores in the older children decreased with age indicating that there exists a need for continued monitoring of neurodevelopment with increasing age in CLHIV despite the early start and continued use of ART.

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1. Allen L, O'Connell A, Kiermer V. How can we ensure visibility and diversity in research contributions? How the Contributor Role Taxonomy (CRediT) is helping the shift from authorship to contributorship. *Learned Publishing*. Jan 2019;32(1):71-74. doi:org/10.1002/leap.1210

NEURODEVELOPMENT IN EARLY TREATED HIV-INFECTED INFANTS PARTICIPATING IN A DEVELOPMENTAL STIMULATION PROGRAM COMPARED WITH CONTROLS

Neurodevelopment in early treated HIV-infected infants participating in a developmental stimulation program compared with controls

Journal:	*Child: Care, Health & Development*
Manuscript ID	CCH-2020-0237.R1
Manuscript Type:	Research Article
Keywords:	Child Development, Early Intervention, Perinatal HIV infection

ABSTRACT

Background: Neurodevelopmental stimulation programmes can improve developmental outcomes. Antiretroviral therapy (ART) started soon after birth potentially limits the invasion of HIV into the central nervous system. A combination of developmental stimulation and early ART initiation may reduce developmental delays in children with perinatally-acquired HIV infection.

Methods: At a single site in Johannesburg, South Africa, we enrolled 36 HIV-infected neonates on ART into an intervention group (IG) participating in a yearlong home-based, neurodevelopmental stimulation program. Bayley Scales of Infant and Toddler Development-3rd Edition (BSID-III) assessments were conducted at 12 months. Scores were compared with 24 early-treated HIV-infected infants in an observational group (OG). BSID-III assessments were also conducted for older children in an observational group at 24 or 36 months. Cognitive, language and motor scaled and composite scores were analysed.

Results: BSID-III scaled and composite scores were all higher in the IG apart from the gross motor scaled score (9.25 vs. 10, p=0.1954). Receptive communication scaled score was significantly higher in the IG (10.96 vs. 9, p=0.0331). IG composite scores were all higher than OG scores. OG children assessed at 24 or 36 months had lower composite scores in all subscales than 12 month OG scores.

Conclusions: Early-treated HIV-infected children participating in a neurodevelopmental stimulation programme achieved higher BSID-III scores at 12 months compared with early treated HIV-infected children who did not receive the programme.

Introduction

The period of early childhood is critical for the development of the brain and central nervous system (CNS) with the immature CNS being at high risk of adverse developmental outcomes from a variety of causes.

The propensity of HIV to invade the CNS, has been documented in early reports from untreated HIV-infected infants as a progressive encephalopathy with an invariably fatal outcome [1, 2]. The use of antiretroviral therapy (ART) has significantly reduced the incidence of overt HIV-related CNS manifestations in paediatric populations [3] especially when treatment is started at a young age [4-6]. In the ART era HIV-related neurocognitive impairment and neurodevelopmental delays in children tend to have an overall more subtle presentation, often affecting school performance and behaviour [7-9].

Early childhood developmental (ECD) programmes can positively influence developing brain architecture and long-term health outcomes, even into adulthood [10, 11]. Childhood HIV management programmes do not, however, uniformly emphasise developmental stimulation nor screening for developmental delays. Reported developmental interventions utilised for HIV-infected children differ widely in their approach, duration, intensity and timing [12]. Consequently, results may not be comparable.

In this study, we investigated whether early-treated HIV-exposed infected (HEI) children partaking in a parentally-driven, home-based developmental stimulation programme started at birth through the first year of life, achieved higher scores on the Bayley Scales of Infant and Toddler Development-3rd Edition (BSID-III) at 12 months of age compared with an early-treated HEI control group who did not receive this intervention. In addition, we describe BSID-III scores in a separate group of early-treated HEI children not participating in an ECD programme, at 24 and 36 months of age.

Methods

Study population

Enrolment into this neurodevelopmental assessment trial began in September 2017. Newborn HEI infants were enrolled into an intervention group (IG) and, in addition to starting ART as soon as the HIV diagnosis had been confirmed, took part in a 12-month programme designed to stimulate infant development. Most of the infants in the IG were co-enrolled in an existing early treatment trial – Latency and Early Neonatal Provision of Antiretroviral Drugs (LEOPARD) – which began enrolling in March 2015 [13]. Children in follow-up on the LEOPARD trial having also started ART at an early age but not participating in the developmental stimulation program, made up the pre-intervention observational group (OG). Developmental assessments were done during the period September 2017 through December 2019. All follow-up was conducted at Rahima Moosa Mother and Child Hospital (RMMCH), Johannesburg, South Africa.

Study procedures

HIV-exposed neonates born at RMMCH were routinely tested for HIV infection prior to discharge. Infant blood samples were sent to the national laboratory for HIV-1 total nucleic acid (TNA) testing (COBAS TaqMan HIV-1 Qualitative Test Version 2·0 Roche Molecular Systems, Inc., Branchburg, NJ). In order to obtain a more immediate diagnosis, a sample from the same blood draw was tested concurrently using the on-site point-of-care (POC) Cepheid Xpert® HIV-1 Qualitative assay (Cepheid, Sunnyvale, CA). Newborn infants with two positive Xpert results were considered HIV-infected and same-day ART started where possible.

The ARV regimen at treatment initiation for most HEI infants comprised twice daily nevirapine (NVP), zidovudine (AZT) and lamivudine (3TC) syrups. At 42 weeks post-menstrual age lopinavir-ritonavir replaced nevirapine and abacavir replaced zidovudine when the infant was ≥3 months of age. Daily prophylactic cotrimoxazole was started at 4-6 weeks of age and discontinued when infants were >12 months of age with a CD4% >25 and had achieved virological suppression. Infants were monitored for drug-related toxicities.

Infants in both groups were seen at weeks 1, 2 and 4 after diagnosis, every month until 6 months, and then twice monthly until 12 months. Two-monthly follow-up continued until 24 months after which children were seen every three months.

After birth, infants enrolled into the IG of the neurodevelopmental study received a standardised set of age-appropriate developmentally stimulating toys and books, as previously described [14]. Starting at birth, every three months the caregiver was provided with an age-specific information card along with pre-specified toys and items to help stimulate infant development. The information cards contained details, along with pictures, explaining what the infant should achieve in terms of motor development; learning, thinking and solving problems; language and communication; and social and emotional skills during the coming months. The card also detailed play activities and responsive, nurturing parenting ideas. Caregivers were encouraged to work through the play activities, at least one activity per day, in addition to reading to the child daily. At follow-up visits a verbal report was obtained from the parent/caregiver on whether they were making use of the stimulation programme. The items provided were aimed at stimulating the various developmental domains, for example in terms of cognitive development, a mirror was provided to stimulate information processing, a rattle for cause-and effect reasoning, and a blanket and toy for playing peek-a-boo to stimulate development of object permanence. At 12 months chronological age, with a window of ± 4 weeks, children in the IG were assessed using the BSID-III. Three developmental domains, namely, cognition, motor skills and language development were evaluated. The BSID-III has been used extensively in the South African setting with scores from 12-month-old black South African infants being comparable to scores from infants in the United States [15, 16].

Two trained assessors conducted the assessments – a physician and a physiotherapist. The child's caregiver remained with the child throughout the assessment. The BSID-III was conducted in English, and parents translated instructions to their children when needed.

Children enrolled in the pre-intervention OG were also assessed using the BSID-III. The assessment was done at their soonest birthday (12, 24 or 36 months) after the start of the neurodevelopmental trial. The OG did not receive the stimulatory toys or parental information.

Written informed consent was obtained from the child's caregiver prior to conducting study-related procedures. Study participation was voluntary and non-participation in the neurodevelopmental trial did not preclude participation in the main trial. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M170653), registered with the Pan African Clinical Trial Registry (PACTR201801002967587), and study protocol published [14].

Statistical Analysis

Raw scores, the initial test score obtained in each developmental subscale – cognition, expressive and receptive language and fine and gross motor – were converted into scaled scores with a reference mean of 10 (range 1-19, SD 3). Scaled scores are further converted into three composite scores for the cognitive, language and motor subscales with a reference mean of 100 (range 40-160, SD 15) [17]. Scores for premature infants (<37 weeks gestational age) were calculated using their corrected age until 24 months.

Score interpretation for the BSID-III classifies developmental delay as a composite score 1.5 standard deviation units below the mean in two or more subscales, or two standard deviation units below the mean in one subscale [17].

We describe mean scaled and composite scores obtained for each subscale in the two groups (IG and OG) in relation to the test reference mean, as well as interpreting scaled and composite scores in relation to standard deviation units below the reference mean for each subscale.

Anthropometric z-scores were calculated using the World Health Organization Anthro software v3.2.2 [18]. Normally-distributed continuous variables are reported as means with a 95% CI. Chi-squared or Fisher's exact tests were used to compare categorical and frequency data and t-tests to compare means. Spearman correlation coefficients were used to assess correlations on a continuous scale. Statistica software version 13.5.0.17 (TIBCO Software Inc.) was used for data analysis.

Results

Study participants

A total of 161 HEI infants were enrolled for follow-up – 36 in the IG and 125 in the OG. Assessments using the BSID-III were conducted on 28 (77.8%) children from the IG, and 65 (52%) from the OG. In the OG, 24 (36.9%) were assessed at 12 months, 20 (30.8%) at 24 months and 21 (32.3%) at 36 months of age. Of those not assessed in the IG, 5 (13.9%) were lost to follow-up (LTFU), 2 (5.6%) transferred out, and 1 (2.8%) died. Reasons for non-assessment in the OG included: LTFU (15, 12%); transferred out (13, 10.4%); indeterminate HIV diagnosis (14, 11.2%), missed appointment (7, 5.6%); died (4, 3.2%); and other (7, 5.6%) (**Figure 1**). No child was assessed at more than one timepoint.

Birth characteristics of all children with confirmed HIV infection in the IG (n=36) and OG (n=111) combined showed 46.9 % (69) of the group to be male, with a mean gestational age of 38.5 ± 2.92 weeks and 19.7% (29) being born prematurely at <37 weeks. Just over two thirds of the births were normal vaginal deliveries (71.9%) and 81.4% were ever breastfed. The average anthropometric z-scores at birth all fell below the expected means: weight-for-age (WAZ) -1.34 (SD 1.59), length-for-age (LAZ) -1.21 (SD 1.91), weight-for-length (WLZ) -0.82 (SD 2.09), head circumference-for-age (HCZ) -0.46 (SD 1.95).

AZT/3TC/NVP was started in 75.7% at a median age of 4 days (IQR 1-11.75). Median CD4% at the time of ART start was 39.9 (IQR 31.2-49.1).

Comparing birth characteristics of neonates in the IG and those in the OG assessed using the BSID-III at 12 months of age (**Table 1**), showed the groups to have a similar mean gestational age (38.4 vs. 38.8 weeks, p=0.56). In both groups some breastfeeding was initiated by over 80% of mothers and 13 (21.7%) neonates were classified as low birth weight i.e. birth weight <2499g, 7 in the IG and 6 in the OG. No significant differences in birth anthropometry were seen between groups. For the groups combined, the median age at ART initiation was 3 days (IQR: 1-9) and most children (85%) started a regimen of AZT/3TC/NVP. There were no significant differences in CD4 and VL results between groups at birth.

At 12 months of follow-up 61.5% and 50% of the infants in the IG and OG respectively, were still being breastfed, p=0.41. WLZ fell below the mean in the IG (-0.34) but was just greater than the mean in the OG (0.16), p=0.15. HCZ in both the IG and OG was just above the expected mean for age (0.29 vs. 0.36, p=0.81). Infants in the IG had been on ART for an average of 346.1days (SD 28.9) and 45.5% of the IG had an HIV RNA VL of <20 copies/ml and median CD4% of 32.62 (IQR 30.2-38.3) (**Table 2**).

Birth characteristics of the OG (n=65) assessed with the BSID-III at one of the three follow-up time points i.e. 12, 24 or 36 months of age, showed a significant difference in mean gestational age (weeks) of 38.8 (SD 1.64) vs. 37.3 (SD 3.50) vs. 39.71 (1.93), p=0.0089, respectively, as well as a difference in the number of normal vaginal deliveries vs. caesarian section births – 18 (75%) vs. 10 (50%) vs. 18 (85.71%), p=0.0361, respectively. There were no other significant differences in terms of birth anthropometry, age of ART start, birth HIV RNA VL, or birth CD4%.

At each of the OG follow-up time points, mean anthropometric z-scores worsened, and the number of children with anthropometric z-scores falling below the mean projected for age was greatest at month 36 (**Table 3**). No differences between WHO disease stage, mean HIV RNA VL or mean CD4% were demonstrated.

Bayley-III Results

IG and OG at 12 months of age

At 12 months of age the Bayley-III assessment was conducted on 28 children in the IG (mean age 345.5 days, SD 66.2) and 24 (mean age 352 days, SD 27) in the OG. For both groups the mean composite scores for the cognitive, language and motor subscales were within the test reference average range of 100 (SD 15), with higher composite scores in the IG on all subscales, although differences were not statistically significant (**Table 2**). Within the language subscale, the mean receptive communication scaled score was significantly higher in the IG than in the OG (10.96, SD 2.35 vs. 9, SD 4, p=0.03).

One child in the OG was classified as showing developmental delay on the language subscale, achieving a composite score of 65 i.e. less than 2 SD subunits below the mean.

For the IG and OG no associations between categorical variables (sex, prematurity, method of delivery, low birth weight, or breastfeeding status) or continuous variables (time on ART, anthropometric Z-scores, VL or CD4%) at birth and at 12 months, and cognitive, language and motor subscales scores were found.

OG at 12, 24 or 36 months of age

At each of the three time points the average scaled and composite scores for each subscale fell within the test mean of 10 (SD 3) and 100 (SD 15), respectively. However, mean composite scores for each subscale decreased significantly with age (**Table 3**) as did mean scaled scores apart from the receptive communication score which increased with age, and the fine motor score which showed a non-significant decrease. At month 24 and 36 no children were classified as displaying developmental delay.

In the groups assessed with the BSID-III at 12 and 24 months of age, no correlations were found between BSID-III composite scores and demographics, growth or disease characteristics such as VL and CD4 counts. However, a positive correlation was found in children assessed at 36 months of age between cognitive composite scores and CD4% and absolute counts, r=0.65, p=0.0015 and r=0.59, p=0.0049, respectively. Positive correlations were also found between composite scores in the language subscale and HAZ-score (r=0.45, p=0.0425) and CD4% and absolute counts, r=0.56, p=0.0090 and r=0.44, p=0.0433, respectively.

Discussion

In a cohort of birth-identified HEI infants started on ART within the first week of life in conjunction with a yearlong home programme designed to stimulate neurodevelopment, we observed higher cognitive, language and motor composite score results when assessed using the BSID-III at 12 months of age as compared with a cohort of early-treated HEI infants not receiving the stimulation programme.

Interventions aimed at improving developmental outcomes in HEI children have been employed but differ widely in their approach [12] and effectiveness [19]. Programmes aimed at improving childhood developmental outcomes have shown substantial and sustainable results [20]. Prior to the use of early infant ART, significant improvements in cognitive and motor outcomes were reported in HEI children receiving a home-based stimulation programme [21]. Although improvements may be more subtle with the use of early ART, interventions are as important to address developmental shortfalls through childhood and into adolescence.

The IG showed significantly better receptive communication results. Language development of at-risk infants e.g. preterm or low birth weight, benefit from stimulatory interventions [22]. Daily reading of books and informal play opportunities, as encouraged in the IG, are reportedly protective factors for language delay [23].

At 12 months of age children in the OG achieved good BSID-III scores which were all within 1 SD of the test reference mean. Similar results, from a 2019 South African cohort of HEI infants starting ART within 3 weeks of life and assessed using the Griffiths Mental Development Scale at a mean age of 11.5 ± 0.8 months, reported infants to achieve scores within the normal range [24].

However, BSID-III composite scores decreased with age as seen in the older children in the OG assessed at 24 or 36 months of age. This may result from factors associated with underlying disease processes as even when on suppressive ART children may continue to display evidence of neurocognitive impairment [25]. Linguistic bias may have affected language scores as many children in the cohort were learning two languages – their non-English mother tongue in conjunction with English as a second language which may be interpreted on testing as a specific language impairment [26]. Culturally diverse child rearing

practices may emphasise different abilities at different ages. The BSID-III test scores were standardised on North American children and cross-cultural bias may have played a role in the lower scores obtained by the OG tested at 24 or 36 months of age. Furthermore, child development is influenced by a myriad of socio-environmental factors affecting children raised in families affected by HIV which may become more evident as the child ages. An African multi-site study of HEI school-age children on suppressive ART initiated in early childhood, concluded the children as being at significant neuropsychological risk, even with ART and medical support [27].

Our study has some limitations and would have been strengthened with a socio-demographically matched HIV-uninfected comparator group. A longer follow-up period for the IG, with repeat BSID-III assessments, would be necessary to truly depict the developmental trajectory and whether good test scores are maintained as the child ages. Assessor bias may have influenced testing of children in the IG or OG as assessors were not blinded. The small sample size of the groups limits the generalisability of the results to other populations as well as the ability to draw conclusions.

In conclusion, we found that young, early-treated HEI children participating in a neurodevelopmental stimulatory programme obtained superior results on developmental testing compared with a control group. Compared with children assessed at 12 months of age, lower BSID-III subscale scores were evident in early-treated HEI children assessed at 24 and 36 months of age indicating that these children need to be monitored for developmental delays which may only become evident with increasing age. A proactive approach in which an ECD programme is prioritised and started alongside paediatric ART should be employed in an attempt to mitigate adverse HIV-related developmental outcomes and diminish the risk of future educational delays.

Key Messages:

- Paediatric HIV infection can result in neurodevelopmental delay.
- Early childhood development programmes in conjunction with antiretroviral therapy may improve developmental outcomes.
- We found 12-month-old early-treated HIV-infected infants performed well on developmental testing.
- Participation in a stimulation programme further improved developmental scores in early-treated HIV-infected infants.
- Comprehensive HIV care ought to include a developmental stimulation programme.

Table 1. Characteristics at birth of all infants enrolled in the intervention group compared with characteristics at birth of infants enrolled in the observation group and having had a BSID-III assessment at 12 months of age

		Intervention and observation group combined		Intervention Group		Observation Group	P value
	N	60	N	36	N	24	
Male, n (%)		29 (48.3%)		17 (47.2%)		12 (50%)	0.8329
Gestational age (weeks), mean, (SD)		38.57 (2.45)		38.42 (2.88)		38.8 (1.64)	0.5607
Gestational age ≤37 weeks, N (%)		13 (21.67%)		10 (27.8%)		3 (12.5%)	0.1593
Vaginal Delivery, N (%)	59	41 (68.33%)	35	23 (65.71%)		18 (75%)	0.4467
Breastfeeding initiated at birth, N (%)	58	51 (85%)	34	30 (88.2%)		21 (87.5%)	0.9325
Birth Anthropometry, mean (SD)							
Weight (kg)	59	2.82 (0.56)	35	2.74 (0.71)		2.86 (0.58)	0.4959
Length (cm)	59	48.63 (4.73)	35	48.74 (4.35)		48.67 (5.32)	0.9560
Head circumference (cm)	59	33.93 (2.46)	35	33.69 (2.14)		34.38 (2.87)	0.2945
Birth weight < 2499 (g), N (range)		13 (1 290-2 410)		7 (1 290-2 410)		6 (1 710-2 400)	0.6088
Birth Z-scores, mean (SD)							
Weight-for-age Z-score	59	-1.25 (1.41)	35	-1.12 (1.32)		-1.36 (1.54)	0.5241
Length-for-age Z-score	57	-0.29 (1.84)	34	-0.09 (1.66)	23	-0.45 (2.14)	0.4781
Weight-for-length Z-score	53	-1.52 (2.04)	33	-1.37 (2.00)	20	-1.58 (2.21)	0.7232
Head circumference-for-age Z-score	59	-0.43 (1.73)	35	-0.38 (1.74)	24	-0.42 (1.81)	0.9323
Age ART start (days), median (IQR)	59	3 (1-9)	35	2 (1-9.5)	24	3 (1-7)	0.7188
ART regimen initiated, N (%)	59		35		24		
AZT/3TC/NVP		51 (85%)		31 (88.6)		20 (83.3)	0.5637
ABC/3TC/NVP		3 (5%)		0		3 (12.5)	
AZT/3TC/LPV/r		3 (5%)		2 (5.7)		1 (4.2)	
ABC/3TC/LPV/r		2 (3.33%)		2 (5.7)		0	
HIV RNA VL (copies/mL) at time of ART start, median (range)	50	43 225 (100-10 million)	28	74 950 (105-10 million)	22	24 700 (100-1.74 million)	0.7974
CD4+ T-cell count at time of ART start, median (range)	55	1 987 (215-5 000)	33	1 990 (296-4 112)	23	1 823 (215-5 000)	0.9045
CD4+ T-cell percentage at time of ART start, median (range)	55	44.27 (9.16-69.05	33	42.74 (9.16-69.05)	23	44.94 (18.29-62.96)	0.6312

BSID-III – Bayley Scales of Infant and Toddler Development, 3rd Edition, ART – antiretroviral treatment, AZT-zidovudine, 3TC- lamivudine, NVP-nevirapine, ABC-abacavir, LPV/-lopinavir/ritonavir, VL- viral load

Table 2. Characteristics of the intervention (n=28) and observation (n=24) groups at 12 months of age and BSID-III assessment scaled and composite scores for the cognitive, language and motor subscales

	Intervention Group		Observation Group		P value
	N		N		
Male, n (%)	28	16 (57.14)	24	12 (50)	0.6065
Z-scores, mean (SD)					
Weight-for-age Z-score	27	-0.81 (0.93)	24	-0.55 (1.25)	0.4002
Length-for-age Z-score	27	-1.10 (1.24)	24	-1.30 (1.19)	0.5606
Weight-for-length Z-score	27	-0.34 (1.26)	24	0.16 (1.14)	0.1456
Head circumference-for-age Z-score	26	0.29 (0.95)	24	0.36 (1.07)	0.8075
Mid upper arm circumference-for-age Z-score	26	0.44 (0.99)	24	0.48 (1.10)	0.8929
Still breastfeeding	26	16 (61.54)	24	12 (50)	0.4116
Duration on ART (days), mean (SD)	27	346.12 (28.85)	24	348.67 (23.69)	0.7318
WHO staging, N (%)	27		24		
1		25 (92.59)		22 (91.7)	0.9323
2		1 (3.7)		1 (4.2)	
3 or 4		1 (3.7)		1 (4.2)	
HIV RNA VL (copies/mL), N (%)	22		23		
<20		10 (45.45)		9 (39.13)	0.4895
<1 000		9 (40.91)		6 (26.09)	
1 000-100 000		2 (9.09)		7 (30.44)	
>1 million		1 (4.55)		1 (4.35)	
HIV RNA VL (copies/mL), median (IQR)	22	36.5 (0-278.75)	23	54 (0-3 330)	0.3371
CD4+ T-cell count, median (IQR)	19	2 155 (1 889.5-2 901.5)	22	2 521 (2080-2843.25)	0.3269
CD4+ T-cell percentage, median (IQR)	19	32.88 (30.18-38.26)	22	32.88 (30.18-35)	0.6767
Age at time of BSID-III assessment (days), mean (SD)		345.47 (66.2)		352 (27)	0.6535
BSID-III Cognitive subscale scores, mean (SD)					
Scaled score		11 (2.57)		11 (2)	1.0000
Composite score		105 (12.84)		103 (9)	0.5252
BSID-III Language Subscale scores, mean (SD)					
Receptive Communication Scaled score		10.96 (2.35)		9 (4)	**0.0331***
Expressive communication Scaled score		10.75 (2.08)		10 (2)	0.1931
Composite score		105.21 (11.07)		100 (17)	0.1904
BSID-III Motor Subscale scores, mean (SD)					
Fine motor		10.5 (2.08)		10 (2)	0.3833
Gross motor		9.25 (2.10)		10 (2)	0.1954
Composite score		99.46 (9.24)		99 (11)	0.8705

BSID-III – Bayley Scales of Infant and Toddler Development, 3rd Edition, ART – antiretroviral treatment, AZT-zidovudine. ***** statistically significant

Table 3. Demographics, anthropometry, disease characteristics and BSID-III results for children in the Observation Group assessed at 12, 24 or 36 months of age

		M12 group		M24 group		M36 group	p
	N		N		N		
Male, n (%)	24	12 (50)	20	7 (35)	21	6 (28.57)	0.3136
Age, mean (SD)		352 days (27)		104.2 weeks (2.27)		36.72 months (6.94)	
Duration on ART, mean (SD)	24	348.67 days (23.69)	20	98.85 weeks (12.3)	21	35.03 months (3.49)	
Z-scores, mean (SD)	24		20		21		
Weight-for-age Z-score		-0.55 (1.25)		-0.96 (1.05)		-1.23 (0.93)	0.1192
Length-for-age Z-score		-1.30 (1.19)		-1.77 (1.24)		-1.82 (0.79)	0.2198
Weight-for-length Z-score		0.16 (1.14)		-0.06 (0.91)		-0.30 (1.14)	0.3761
Head circumference-for-age Z-score		0.36 (1.07)		0.15 (1.45)		-0.09 (1.08)	0.4717
Mid upper arm circumference-for-age Z-score		0.48 (1.10)		0.34 (0.85)		-0.14 (0.83)	0.0872
Number with a z-score less than the mean for age, N (%)							
Weight-for-age Z-score		17 (70.83)		14 (70)		18 (85.71)	0.4090
Length-for-age Z-score		20 (83.33)		18 (90)		21 (100)	0.4340
Weight-for-length Z-score		13 (54.17)		10 (50)		14 (66.67)	0.5278
Head circumference-for-age Z-score		8 (33.33)		10 (50)		11 (52.38)	0.3709
Mid upper arm circumference-for-age Z-score		5 (20.83)		6 (30)		13 (61.9)	**0.0129***
Still breastfeeding	24	12 (50)	20	5 (25)	21	0	
WHO disease stage, N (%)	24		20		21		
1		22 (91.7)		20 (100)		20 (95.23)	
2 and 3		2 (8.3)		0		1 (4.76)	
HIV RNA VL (copies/mL), N (%)	23		20		21		
<20		9 (39.13)		13 (65)		14 (66.67)	0.2530
<1 000		6 (26.08)		7 (35)		5 (23.81)	
≥1 000		8 (34.78)		0		2 (9.52)	
HIV RNA VL (copies/mL), median (IQR)	23	54 (0-3 330)	20	0 (0-51.75)	21	0 (0-48)	
CD4+ T-cell percentage, median (range)	22	32.17 (29.88-35.66)	20	33 (15-41)	21	33.79 (18.55-45.92)	0.3572
BSID-III Cognitive subscale scores, mean (SD)							
Scaled score		10.58 (1.69)		9.10 (1.45)		9 (1.48)	**0.0013***
Composite score		102.92 (8.46)		95.5 (7.24)		94.95 (7.49)	**0.0013***
BSID-III Language Subscale scores, mean (SD)							
Receptive Communication Scaled score		8.71 (1.62)		8.35 (2.08)		10.29 (3.33)	**0.0273***
Expressive communication Scaled score		10.71 (2.18)		8.65 (1.57)		8.24 (1.3)	**<0.0001***
Composite score		103.08 (13.45)		91.25 (8.83)		91.14 (7.00)	**0.0002***
BSID-III Motor Subscale scores, mean (SD)							
Fine motor Scaled score		10.25 (1.96)		9.2 (2.09)		9.48 (1.40)	0.1507
Gross motor Scaled score		9.5 (2.27)		8.10 (0.91)		9.52 (2.60)	**0.0486***
Composite score		99.33 (10.20)		91.9 (7.67)		97.00 (8.75)	**0.0277***

ART-antiretroviral treatment, WHO-World Health Organization, VL-viral load, BSID-III- Bayley Scales of Infant and Toddler Development, 3rd Edition *statistically significant

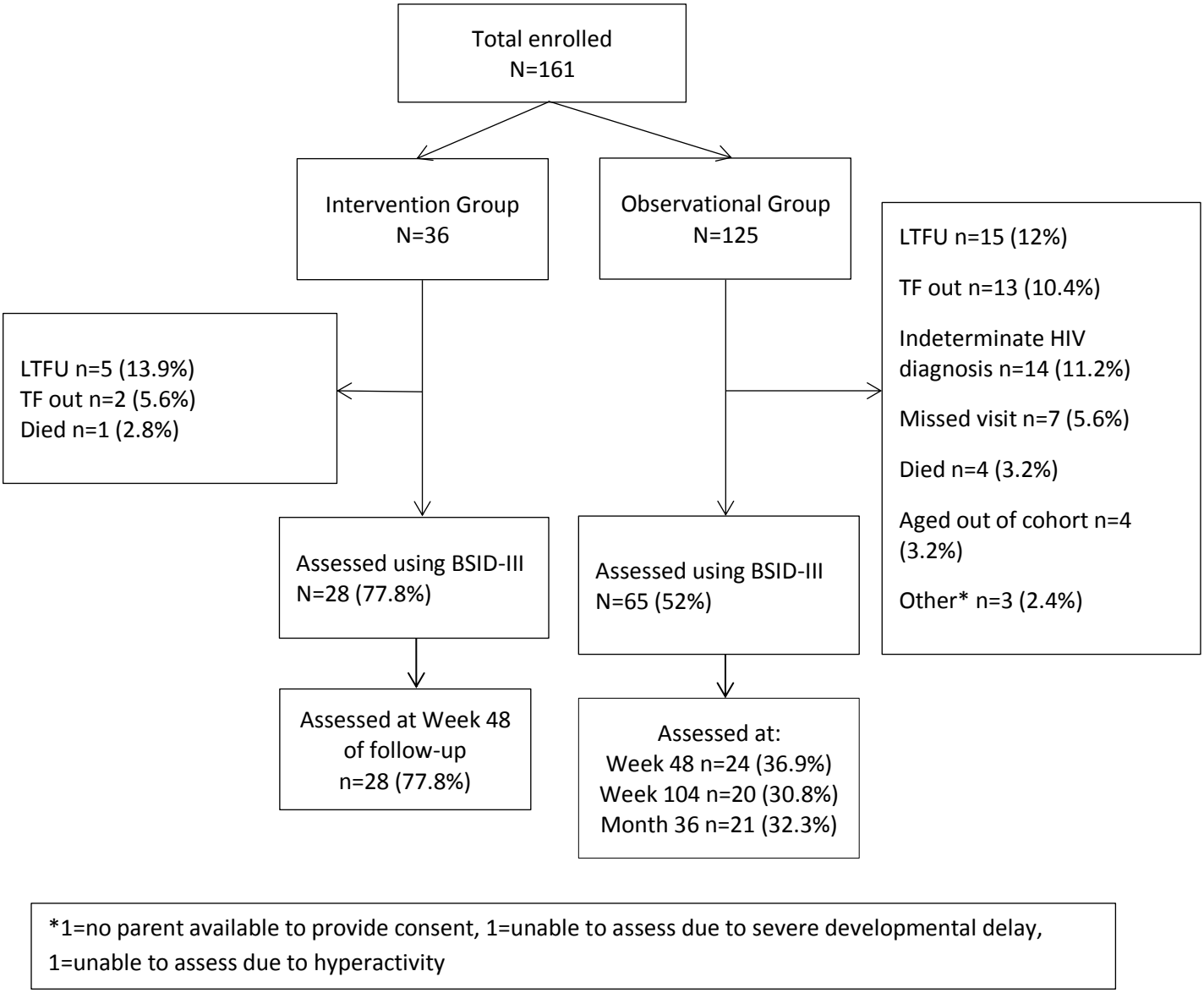

Figure 1. Population of HIV-exposed infected neonates enrolled in follow-up in the intervention and observation groups

Supplementary Table 1: Characteristics at birth of all infants diagnosed with HIV infection and enrolled for follow-up in the intervention groups compared with the observation group

		Intervention Group		Observation Group	P value
	N		N		
Male, n (%)	36	17 (47.2)	111	52 (46.85)	0.9687
Gestational age (weeks), mean, (SD)	36	38.42 (2.88)	111	38.50 (2.94)	0.8868
Gestational age ≤37 weeks, N (%)	36	10 (27.8)	111	19 (17.12)	0.1625
Vaginal Delivery, N (%)	35	23 (65.71)	111	82 (73.87)	0.2492
Breastfeeding initiated at birth, N (%)	34	30 (88.2)	111	88 (79.3)	0.5953
Birth Anthropometry, mean (SD)					
Weight (kg)	35	2.74 (0.71)	111	2.72 (0.67)	0.8796
Length (cm)	35	48.74 (4.35)	111	47.92 (4.73)	0.3638
Head circumference (cm)	35	33.69 (2.14)	111	33.42 (2.75)	0.5957
Birth weight < 2499 (g), N, % (range)	36	7, 19.44% (1 290-2 410)	111	32, 28.83% (865-2 425)	0.2678
Birth Z-scores, mean (SD)					
Weight-for-age Z-score	35	-1.12 (1.32)	109	-1.40 (1.67)	0.3672
Length-for-age Z-score	34	-0.09 (1.66)	103	-0.47 (2.03)	0.3253
Weight-for-length Z-score	33	-1.37 (2.00)	85	-1.62 (1.85)	0.5208
Head circumference-for-age Z-score	35	-0.38 (1.74)	110	-0.62 (2.09)	0.3598
Age ART start (days), median (IQR)	35	2 (1-9.5)	111	4 (1-12)	0.3789
ART regimen initiated, N (%)	35		111		
AZT/3TC/NVP		31 (88.6)		80 (72.07)	0.3030
ABC/3TC/NVP		0		3 (2.07)	
AZT/3TC/LPV/r		2 (5.7)		8 (7.21)	
ABC/3TC/LPV/r		2 (5.7)		20 (18.02)	
HIV RNA VL (copies/mL) at time of ART start, median (IQR)	28	74 950 (2 263.75-303 531.25)	111	16 077 (1 720 - 224 515)	0.4009
CD4+ T-cell count at time of ART start, median (range)	33	1 990 (296-4 112)	89	2 136 (846 – 5 223)	0.5619
CD4+ T-cell percentage at time of ART start, median (range)	33	42.74 (9.16-69.05)	89	39.28 (16.65-67.16)	**0.0285***

BSID-III – Bayley Scales of Infant and Toddler Development, 3rd Edition, ART – antiretroviral treatment, AZT-zidovudine, 3TC- lamivudine, NVP-nevirapine, ABC-abacavir, LPV/-lopinavir/ritonavir, VL- viral load *Statistically Significant

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CHAPTER SEVEN

The final chapter of this thesis provides a brief overview of the research conducted, bringing together the findings as presented in the published manuscripts and linking them to the study objectives. The practical application of the study findings in terms of patient care is discussed as well as the limitations encountered during the execution of the study. Recommendations for future research are included before a concise concluding paragraph.

7.1. DISCUSSION

The ultimate goal of medical professionals working in the field of paediatrics is to not only provide treatment and management for immediate health problems, but also to see the growing child thrive and become a competent contributing adult in society. Perhaps this is a lofty goal, but arguably one that is worth striving for when considering the developmental potential within each child. This research was aimed at harnessing the developmental potential of a group of children with a particular vulnerability, namely HIV infection, by using a developmental stimulation programme in conjunction with life-saving ART, both initiated within the first month of life.

The natural history of the devastating outcomes of paediatric HIV infection has been well described [1]. Although the progression of the disease has been vastly altered following the introduction of paediatric ART [2, 3], access to early infant diagnostic services and the subsequent initiation of treatment remains inadequate, especially in high-burden countries within SSA [4]. Consequently, children continue to be impacted negatively by delayed HIV diagnosis and older age at ART start [5].

Apart from CLHIV, the other children of concern in the HIV epidemic are those who remain HIV uninfected – mainly through the successful use of maternal ART – but who are at risk of the negative effects of being exposed to HIV as well as maternal ARVs whilst *in utero* [6]. The successful scale-up of the use of ART in pregnancy has resulted in an increasing population of HEU children [7].

7.1.1. Synopsis of the Scoping Review and the Stimulation Programme used in this Study

Taking into account the particular vulnerabilities of infants diagnosed with, or exposed to, HIV infection in conjunction with published data describing the components required for comprehensive, effective ECD programmes, we conducted a scoping review – presented in Chapter Three – investigating interventions aimed at mitigating and/or preventing neurodevelopmental delay specifically in CLHIV and HEU children.

ECD programmes should ideally be delivered to the child within an environment fostering the ideals of nurturing care, namely: good health, adequate nutrition, responsive caregiving, and safety and security [8]. The stimulatory intervention employed in this study took into account the components of the nurturing care model, combined with concepts from interventions identified in the scoping review.

The scoping review identified a lack of research investigating ECD stimulatory interventions developed for and directed at improving developmental outcomes in CLHIV and HEU pre-school children. Only one study which employed an intervention directed specifically at stimulating neurodevelopment was identified – the RCT study was conducted in Soweto, South African by Potterton *et al.*, in which CLHIV between the ages of 10-30 months were given individualised home programmes utilising activates which could be incorporated into everyday happenings such as bathing, dressing and feeding [9]. Caregivers were also encouraged to spend

time daily with the child looking at a picture book which was provided and within all of the activities there was an emphasis on play. Even though not all of the children in the intervention group had started ART, BSID (II edition) motor and cognitive scores in the intervention group showed significant improvement after 12 months of follow-up compared with control group scores [9].

Numerous publications from a group in Uganda have reported improvements in ability assessments for pre-school CLHIV whose caregivers participated in a MISC programme [10]. Although, the programme did not incorporate an intervention focusing specifically on stimulating ECD, the MISC programme focuses on training caregivers on aspects of responsive caregiving, e.g. engaging the child's attention and assisting the child to focus on the learning experience, and communicating emotional excitement, appreciation, encouragement and affection [11].

The ECD stimulation programme which was used in the research presented in this thesis can be evaluated according to the components of nurturing care and elements required for a successful ECD programme – both of which have been extensively discussed in the introduction and literature review (Chapter Two).

Good health and responsive caregiving are two components of nurturing care which were well addressed in this study population. The children followed an intensive schedule of visits during which they consulted with a study physician, this included taking a full history and conducting a full physical examination; monitoring and plotting of anthropometric measurements on growth charts; adherence monitoring regarding use of the ART; provision of ART, cotrimoxazole prophylaxis, multivitamin syrup, outstanding vaccinations, vitamin A supplementation and deworming medication; and the investigation of and referral for further management of underlying health problems. Follow-up for the clinical trial occurred more frequently than if children had been attending a routine standard of care clinic. In terms of responsive caregiving, at each follow-up visit the health of the mother was also enquired after and, if needed,

management of simple health complaints or referral for more complex matters was provided. Ensuring the good health of the caregiver is pivotal in ensuring their ability to provide care and stimulation needed by the child. The caregiver played a central role in administering the home-based stimulation programme. At each follow-up visit the importance of the caregiver's role in stimulating the child and participating in responsive parenting was emphasised. The caregiver was praised for continuing the stimulation programme in the home and encouraged to continue to do so on a daily basis.

Two components of the nurturing care model which we were unable to see to in a holistic manner were: adequate nutrition and safety and security. Although the growth of the CLHIV and HEU children in follow-up at the clinic was closely monitored and children displaying growth faltering secondary to inadequate nutritional intake were referred to the dietician and to the social worker if needed, the inadequate provision of nutritional requirements is a problem affecting vast numbers of children within the urban community in which the children live [12]. Similarly, even though children and their caregivers were assisted on an individual basis if safety concerns were raised, the safety and security of children in South Africa is a problem which exists on a societal level well beyond the scope of this project.

Considering the ECD programme and the manner in which it was implemented in this group of CLHIV, a number of components were shown to be effective, while others should perhaps be reconsidered when using the programme in a similar population. Components which were thought to aid in the effectiveness and feasibility of the programme included: the activities could be carried out in the home environment and incorporated into activities of daily living thereby becoming an integral part of the child care routine e.g. playing with stacking cups while bathing; the caregiver was included with an essential participatory role, therefore allowing them feel included; there was an emphasis on play which made the programme enjoyable and workable for both the caregiver and the child; the ECD information cards which were provided contained clear pictures for easy reference; and the caregivers incurred no expense when participating in the programme. Elements in the provision and implementation of the ECD programme which should

be carefully considered in future work include: families in which there are several caregivers the ECD programme should ideally be presented and explained to all those involved with the care of the child; similarly for caregivers who return to work, the ECD programme needs to be explained to child's new primary caregiver to ensure continuation with the programme e.g. the child's father [13]; activities within the programme and the toys provided should be presented in a manner which is sensitive to cultural practices e.g. children's picture books should ideally represent cultural norms and practices [14]; a home visit would provide opportunity to assess the context in which the child is being raised and perhaps allow for adaptation of the suggested activities if required; follow-up on implementation of the ECD programme by community health workers in the child's home may aid adherence to the programme and allow to knowledge transfer in a safe and unhurried environment [15, 16]; lastly, the cost involved in the provision of toys as part of the ECD programme is not sustainable at scale.

7.1.2. BSID-III Assessment Scores in Early-Treated Children Infected with HIV

One of the goals of starting ART in a neonate within days of birth is to try and reduce the amount of virus invading the central nervous system and thereby hopefully prevent or lessen the detrimental neurodevelopmental outcomes which have been attributed to this neuro-virulent virus [17, 18]. The neurodevelopmental outcomes of CLHIV have been described at various stages of the epidemic. We aimed to describe the BSID-III scores from a cohort of children who had been started on ART as soon as possible after the birth HIV diagnosis had been confirmed, and compare the scores to the BSID-III test reference means. To achieve this aim children already enrolled into the LEOPARD clinical trial, prior to the start of the neurodevelopmental intervention study, were assessed at a single time-point according to age at next birthday, i.e.12, 24 or 36 months of age, using the BSID-III. The results are included in the manuscript contained in Chapter Six.

The first finding directly related to the research question was that the group of early-treated CLHIV assessed at 12, 24 and 36 months of age achieved mean scaled and composite BSID-III

test scores within the range of the test reference mean of 10 (SD 3) and 100 (SD 15), respectively. However, as the children aged, the BSID-III composite scores for the three subscales – cognition, language and motor – showed a significant decline in comparison with the scores achieved by the children at 12 months of age. Only the receptive communication scaled score improved by 36 months, and the fine motor scaled score showed some improvement after the decrease seen from 12 to 24 months.

A second, and important, finding in this group of CLHIV was that despite ART having been started within the first week of life, and most children demonstrating a good response in terms of viral load reduction, CD4 T-cell count increase and absence of HIV-related opportunistic infections, the weight-for-age (WAZ) and height-for-age (HAZ) did not normalise according to expected mean anthropometric z-scores for age. At birth, mean anthropometric z-scores for the group fell below the expected means and despite the children having started ART within days of birth, at 36 months all z-scores fell below the expected mean for age. Our data showed a positive correlation at 36 months of age between the composite score obtained on the language subscale and HAZ. Childhood HIV infection has been shown to result in growth faltering, and even on ART growth recovery is not comparable with uninfected children [19]. As discussed in the Chapter Two, growth failure can be considered as a proxy marker of poverty. It is likely that despite the provision of suppressive ART, growth in this group of at-risk CLHIV was negatively affected as a result of the interplay between child, household and community factors as described in the WHO's conceptual framework on childhood stunting [20].

Although ART is life-saving for infants diagnosed with HIV infection, successful treatment and management of the child cannot rely solely on the provision of ART. Care provided to CLHIV needs to be holistic in order to mitigate the multitude of factors affecting the immediate health as well as the long-term outcomes of the child. In CLHIV who display no signs or symptoms of active HIV infection and present with laboratory parameters indicating successful treatment such a suppressed viral load and CD4 T-cell count within the expected range for age, healthcare practitioners should not be complacent in terms of screening for underlying developmental delays which may only become evident as the child ages.

7.1.3. BSID-III Assessment Scores in HIV-Exposed Uninfected Children

Concern has been expressed for the developmental outcomes of HEU children [21]. Poor outcomes may be attributed to numerous adverse psycho-social factors which may be more abundant in families affected by HIV, compounded by the direct effects of exposure to HIV and ART [22]. Wedderburn et al. propose that maternal HIV infection and subsequent *in utero* and postnatal HIV exposure may amplify a range of universal risk factors, which may possibly negatively influence neurodevelopment. Augmented risk factors include increased exposure to intrauterine infections and toxins; adverse birth outcomes; suboptimal breastfeeding practices; poor maternal mental and physical health resulting in a greater risk of poverty and neglect [22]. A control group of HEU children was included in this study with the aim to describe early neurodevelopmental ability and explore factors associated with scores achieved on the BSID-III assessment.

At 12 months of age the HEU children assessed in this study achieved BSID-III assessment scores for the cognitive, language and motor subscales above the test reference means. A comparable South African study reported that breastfed HEU children achieved average BSID-III scores at the end of the first year of life similar to scores achieved by their HIV-unexposed counterparts, however, the authors found an excess of minor deficits in the HEU children [23]. This may indicate that perhaps these children need careful monitoring as potential developmental deficits may be missed. Additionally, reports of delays in cognition, language expression and motor abilities which have been described in HEU children, have emerged from older cohorts of pre-school and school-aged children [24, 25].

Considering this, although the assessment scores obtained by the HEU children in this study were reassuring, these children should ideally be closely monitored in long-term care and regularly assessed for subtle developmental deficits using appropriate screening and assessment tools. Realistically, with an estimated 1.25 million HEU children born annually [6], children are unlikely to receive the careful, long-term follow-up necessary under the existing healthcare services.

7.1.4. BSID-III Assessment Scores in Early-Treated Children Infected with HIV Participating in a Developmental Stimulation Programme

Central to this study was the provision of a developmental stimulation programme used in conjunction with ART, both started in the neonatal period. Starting at birth, we initiated a home-based stimulatory programme emphasising responsive caregiving and opportunities for early learning through play. At three monthly intervals caregivers were provided with age-appropriate toys alongside an information card containing details of expected motor, language and cognitive milestones. Ideas for play activities and responsive parenting were also provided. Caregivers played a central role in carrying out the programme and were encouraged to incorporate the suggested activities into activities of daily living.

Substantial evidence exists that ECD programmes are an effective means of preventing the loss of childhood developmental potential and increase a child's chances of success throughout the life course [26]. However, when conducting the scoping review for this thesis, a paucity of published research investigating interventions aimed specifically at improving the developmental outcomes of CLHIV and HEU children, was found. Interventions which were identified differed widely in content, duration and intensity [27]. A systematic review investigating the effectiveness of interventions in reducing cognitive delay in CLHIV and HEU children reported effective interventions to be available but highlighted the need for evidence-based interventions to be initiated and complex interventions studied further [28].

The BSID-III assessment scores at 12 months of age in the group of CLHIV who had participated in the stimulatory programme – the IG – and those in the OG were encouraging. The scaled and composite scores for each of the subscales assessed – cognition, language and motor – fell within range of the test reference means. Similar neurodevelopmental assessment results were reported from a recent study conducted in Cape Town, South Africa, which assessed neurodevelopment in infants with HIV infection starting ART within the first three weeks of life. Infants assessed at a mean age of 11 ± 0.8 months achieved mean quotients on the GMDS within

the average range [29]. The findings are encouraging and suggest that early-ART allows for typical neurodevelopment through the first year of life.

Even though both the IG and OG achieved good scores at 12 months of age, when compared with the OG which received only early ART and not the developmental stimulation programme, there was a trend towards higher composite scores for each subscale in the IG. There is limited published data from studies investigating the use of ECD programmes in infants with HIV infection. Results of the scoping review reported here showed only one trial by Potterton *et al.* which initiated a specific child-directed home stimulation programme within the first year of life [9]. The interventions reported in the Ugandan trials were started in CLHIV ranging in age from 16 months-5 years, and used a parent-directed intervention [30, 31].

Although not formally measured in terms of a feedback questionnaire, the caregivers displayed positive responses towards the home programme, expressing interest in the information provided which detailed expected milestones as well as in the toys and ideas for play. At follow-up visits, reports were often given by the caregiver about what the children had learnt to do. One of the infant's mothers excitedly showed the researcher photographs taken with her cellular telephone of her young child paging through the story book which had been provided to them. Responsive caregiving – one of the components of the Nurturing Care Framework – is an essential element which needs to play a central role in ECD programmes in LMIC. Interventions integrating components of nurturing care such as: caregiver behaviours and knowledge regarding caregiving; child stimulation; and early bonding, secure attachment and trust through responsive caregiving, can target multiple risks to developmental potential [32].

Despite the improved availability of, and access to, paediatric ART, numerous harmful biopsychosocial factors can threaten the well-being of CLHIV and place these children at an increased risk of not reaching their developmental potential [33]. Healthcare practitioners should remember that suppressive ART is not the great panacea for CLHIV as these children continue to

display subtle developmental delays [34] suggesting the need for careful monitoring, regular developmental ability screening and early effective interventions as part of holistic management.

7.2. PRACTICAL APPLICATION & RECOMMENDATIONS

Clinical research involving human participants has the ability to bring about positive changes and improvements in the specific fields to which the research relates. The research results presented in this thesis showed that although the initiation of ART in the neonatal period is an important measure to limit the early complications of HIV infection during infancy, this vulnerable group of CLHIV demonstrated improved neurodevelopmental outcomes when adding a home-based, developmental stimulation programme to their management plan.

7.2.1. Health Practitioner Education

The results of this research have brought about an awareness of the possibility of the existence of subtle, long-term developmental deficits in CLHIV. Increasing knowledge among healthcare practitioners about the risks CLHIV face which can result in lost developmental potential, and the possibility of subtle developmental delays manifesting over the course of the early years through into adolescence, is a vital starting point.

Colleague healthcare practitioners including doctors, nurses, physiotherapists and counsellors at RMMCH expressed a great deal of interest when exposed to the content of this research. The research fostered discussions about the importance of development during the early childhood period; how developmental outcomes can be improved; and the inclusion of developmental screening and assessment procedures as part of routine clinic follow-up visits. Sharing information and educating healthcare workers caring for CLHIV is a vital first step in creating awareness, stimulating interest, and encouraging knowledge transfer about the importance of childhood development.

The research findings and discussions around early development should not be limited only to RMMCH staff, but information dissemination and healthcare worker training should include staff from local clinics which provide healthcare services to children. Inclusion of ECD as a topic in the undergraduate curriculum of various healthcare workers would perhaps underline the importance of the subject field and foster an awareness of ECD in vulnerable populations.

7.2.2. Use of Developmental Screening Tools

Developmental screening tools have not been routinely used during clinic follow-up visits at the RMMCH clinic for CLHIV. As this research study progressed and the interest in childhood development increased, knowledge was shared and discussions held regarding implementing developmental screening as part of routine patient care. The use of age-appropriate parent/caregiver- or practitioner-completed developmental screening tools as part of patient follow-up visits has since been included as a part of patient follow-up visits. The use of screening tools may increase the detection of developmental delays in CLHIV. These children can then be referred for formal developmental assessments within the services offered by the hospital.

7.2.3. Home-Based Developmental Stimulation Programmes

Learning and knowledge acquisition is a continual process which starts at birth. Thus programmes aimed at maximising a child's developmental potential should ideally be incorporated into daily activities within everyday surroundings. The ECD stimulation programme used in this research suggested easy-to-follow ideas which encouraged learning through play, making use of items found in most households. The idea that the development of the child need not depend on the provision of expensive toys was shared with the caregivers participating in the study who were empowered to actively participate in play activities with their child using available objects.

When evaluating the home stimulation programme used in this study in terms of the ideal components of ECD programmes detailed in Chapter 2, Section 2.7, the programme met the following requirements: participation in the programme included all caregivers involved with the rearing of the child; starting the programme as soon as possible after birth; inclusion of the programme in activities of daily living and incorporation of the activities into the family's daily lives; and having an emphasis on play. The utilisation of local knowledge and child rearing practices as well as more regular follow-up to ensure the programme was being correctly carried out, could possibly have strengthened the programme.

The transfer of information and ideas about stimulating the child's development in the home environment through activities of daily living and play can easily occur alongside health education e.g. the importance of childhood immunisation, which is already being provided during clinic visits.

7.3. LIMITATIONS & CHALLENGES

Throughout the course of conducting this research a number of limitations and challenges were encountered. It is important to recognise limitations as they occur during the research process in order to understand how the research outcomes could potentially be affected by these limitations. Recognising study limitations will also help when planning future research. Limitations specific to study objectives have been detailed in the published manuscripts included in the chapters of the thesis and will not be repeated here. Overarching limitations encountered will be briefly discussed in the ensuing paragraphs.

Initially it was decided to include the Parenting Stress Index-short form (PSI-SF) as a data collection tool. It was hypothesised that the data collected on parental stress would be useful when interpreting BSID-III assessment scores and examining associations between PSI-SF scores. The completion of the PSI-SF was initially carried out by the study investigator together

with the child's mother. The interview was conducted in English and an English version of the PSI-SF was used. Often times when obtaining the clinical history a variety of stressors were reported by the mother, however, the researcher found that when completing the PSI-SF with the mother later on during the consultation process, the mother's answers on the PSI-SF did not seem to echo what she had previously reported. It was proposed that perhaps the PSI-SF be completed by a study counsellor able to converse with the mother in her home language; however, the validity and reliability of the screening tool could not be ensured.

As parenting and life stressors change over time it would have been useful to complete the PSI-SF at numerous time points during the period of study follow-up as collecting information at a single time-point provided only cross-sectional data. Similarly, collecting information on the Household Survey form would have provided more informative data if completed at numerous time points through the study follow-up period, perhaps, then capturing changes in living conditions and parental employment status. Further analysis of the PSI-SF data collected as part of this study is planned, but due to the quality of the data collected it may not be possible to deduce associations between reported parental stress and childhood developmental outcomes.

The inclusion of a further comparison group of socio-demographically matched HUU children would have provided further depth to the current analysis. As discussed in Chapter Two, HEU children have been shown to perform less well on developmental testing when compared with their HUU-matched peers.

Mothers of children receiving the developmental stimulation programme were provided with toys and information sheets to use at home. The use of the programme in the home was not monitored, for example with a daily diary entry, and we relied on parental self-report regarding the use of the stimulatory programme in the home. One also needs to be sensitive when providing toys for a child living in a home in which poverty prevents the provision of toys for the children. Anecdotal reports were given by the mothers of other children in the household playing with the toys and we were thus unable to monitor specifically participation of the index child.

Although the study follow-up period was emphasised during the enrolment visit, participant attrition resulted in a reduced final sample size. A review of RCTs published in major medical journals found 89% to have missing outcomes data [35] . Missing data could bias results if the data from participants LTFU are associated with the outcome events [36] and a small sample size limits generalisability of findings. Power and sample size estimations calculated during the planning phase of the study suggested 45 children be included in each of the groups to power the study to 90%. Smaller numbers were enrolled into both groups and those LTFU during the first 12 months further reduced the final sample size. The reduced size of the cohort may affect the interpretation of the results. Reasons for ART patients defaulting follow-up have been investigated. Results from ART clinics in South African report patient death, clinic transfer, relocation, transport costs, time required to attend the clinic, and logistical challenges as reasons for defaulting clinic follow-up [37, 38]. Studies conducted in SSA reported women attending PMTCT programmes to default follow-up due to the fear of stigma, discrimination, household conflict, clinic waiting times and transport costs [39].

Initial planning for potential lost-to-follow-up during a longitudinal study is important when considering the time invested during follow-up and the impact of participant attrition on data collection and analysis. Initiatives which could be employed in future studies in an attempt to reduce the rate of LTFU include: the use of community healthcare workers to conduct follow-up visits in the patient's home; study follow-up conducted at local clinics linked to the well-baby checks and immunisation schedule; provision of transport money prior to the scheduled visit by means of acellular telephone money transfer; and linking follow-up with added services such as a supplemental nutrition programme.

As developmental maturation is a dynamic process with delays sometimes becoming more apparent as the child ages, our study would have been strengthened by gathering more data from multiple BSID-III assessments over the study period. A longer follow-up period beyond 12 months of age would provide additional data to confirm or refute our initial findings indicating an age-related decline in BSID-III scores.

The English version of the BSID-III assessment tool was used in this study and assessments were conducted by English language speaking assessors. The use of a language other than the primary home-language of the caregiver and child raises the issue of linguistic bias in both the examiner and the testing materials. Linguistic bias can be defined as "a systematic asymmetry in word choice that reflects the social-category cognitions that are applied to the described group or individual(s)" [40]. According to the American Speech-Language-Hearing Association, when completing the language assessment component of a developmental assessment tool with a linguistically diverse child, the assessor should ideally show native or near-native proficiency in the language(s) being used [41]. Linguistic bias may affect the validity of the assessment and additional clinical observations, further assessment and parental reports should be taken into consideration before diagnosing speech and/or language delay [42].

Two trained assessors conducted all of the BSID-III assessments for this study. However, due to staff constraints, the assessors were also involved with the clinical management of the children and were thus not blinded to the child's HIV status, nor to the group (IG vs. OG) into which the child had been assigned. Although the clinical management between groups did not differ assessor bias may have influenced the developmental testing procedures as assessors may have unknowingly overestimated the effects of the home stimulation programme. Ideally, to eliminate assessor bias, an independent, blinded assessor should have conducted the BSID-III assessment. When interpreting the results from an unblinded clinical trial one needs to consider whether the methodologies employed may have influenced the results.

7.4. RECOMMENDATIONS FOR FUTURE RESEARCH

Working within a clinical setting and conducting a research study oftentimes spurs on ideas and discussions which give rise to new proposals for further research! Listed here are suggested research questions for which there may be a paucity of published data and/or research ideas to further expand on work which has been done.

There is a need for the comprehensive evaluation of ECD stimulation programmes – both existing programmes and newly developed ones – for CLHIV and HEU children within the South African context. Programmes need to be evaluated in terms of timing of initiation, intensity, duration, content and outcomes as well as cultural acceptability and feasibility. Ideally, evaluation of programmes should take place across the many diverse settings found in South Africa, taking into account geographical location, cultural groupings, and socioeconomic distinctions.

Further research into the scale-up of effective ECD programmes, monitoring feasibility and effectiveness, needs to be conducted. The role of community health workers in working with families in the home environment to educate about the developmental needs of CLHIV and assisting the caregiver with carrying out ECD stimulation activities needs to be investigated. Implementation research necessitates long-term, longitudinal follow-up monitoring developmental achievement from early childhood through adolescence. The holistic development – cognitive, language, motor, social, psychological and behavioural – of CLHIV and HEU children exposed to comprehensive ECD programmes ought to be carefully monitored.

The monitoring of developmental outcomes of CLHIV and HEU children needs to continue as adult ARV regimens change and so to the *in utero* and breastmilk exposure of infants to these new agents. The use of dolutegravir during pregnancy and breastfeeding and the potential impact on neurodevelopment in both CLHIV and HEU children is a currently relevant and important research question.

The need certainly exists within the South African population for further longitudinal research, scale-up and development of ECD programmes, outcomes monitoring and possible interventions for the large number of CLHIV and HEU children who are exposed to a multitude of risk factors which will prevent them from attaining their developmental potential.

7.5. FINAL CONCLUSION

The developmental potential within each child must be harnessed during the early childhood years or it will potentially be lost, resulting in life-long detrimental consequences. Infection with, or exposure to HIV places children at particular risk of poor neurodevelopmental outcomes. Additionally, development in this vulnerable group of children is also threatened by a multitude of biopsychosocial risk factors to which they are exposed. ECD stimulation programmes can vastly improve developmental outcomes but their use has yet to be incorporated into the holistic management of CLHIV.

The research presented in this thesis includes a scoping review which investigated interventions aimed at mitigating adverse HIV-related neurodevelopmental outcomes in young children. The research project then described neurodevelopmental assessment scores obtained on the BSID-III in a cohort of early-treated CLHIV receiving an age-appropriate, home-based stimulation program compared with CLHIV and HEU children from similar socioeconomic backgrounds receiving only the standard of care.

The scoping review identified a lack of research investigating best practice for child-directed, early developmental stimulation programmes aimed specifically at CLHIV. In the cohort of children in follow-up we found HEU children at 12 months of age to achieve BSID-III scores comparable with the test reference population however, of concern were the CLHIV, who despite being initiated on ART within weeks of birth, attained lower assessment scores. Encouragingly, the cohort of CLHIV receiving early ART in conjunction with a year-long ECD stimulation programme demonstrated better outcomes in certain developmental domains. BSID-III scores from an older cohort of early-treated CLHIV were lower than scores achieved by the children at one year of age.

In order to make it possible for CLHIV to thrive, the holistic management of these children should ideally be expanded to include screening for developmental delays, appropriate referral for developmental assessment and age-specific ECD stimulation programmes within the sphere of nurturing care. Further work needs to be done to understand which interventions lead to the best outcomes and how to incorporate effective interventions into existing services and scale-up their use to benefit all CLHIV.

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APPENDICES

A. Early Childhood Developmental Stimulation Programme

This Appendix includes the developmental stimulation programme (used with permission) which was provided to mother-infant dyads enrolled into the intervention group of the study from birth through 12 months of age.

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

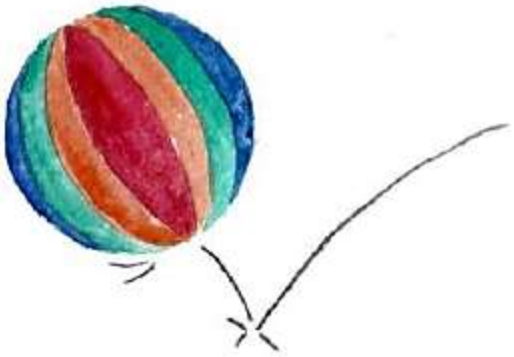
UFS UV

UNIVERSITY OF THE FREE STATE

DEPARTMENT OF CARDIOLOGY AND PHYSIOTHERAPY

DEVELOPMENTAL ACTIVITY PROGRAMME:

A GUIDELINE FOR PARENTS



ACTIVITY GUIDELINE FOR INFANTS AND TODDLERS

0-3 MONTHS

WHAT BABIES SHOULD DO AT THIS AGE:

Physical development:

- When lying the baby moves arms and legs actively and the movements are smooth and rhythmical.
- When held upright over your shoulder baby can lift their head for a moment.
- When lying on their tummy baby can turn their head to both sides.
- Is able to watch your face or a toy with their eyes when it is moved in front of their face.
- Is able to bring both their hands to their mouth.

Learning, thinking and solving problems:

- Pays attention to faces and recognises you.
- Looks around.
- Turns their eyes and head towards the side of the sound when a rattle is or someone speaks loudly.

Language and communication:

- Smiles at the person speaking to them.
- Coos and makes gurgling sounds.

Social and emotional skills

- Can calm themself by bringing their hands to their mouth.
- Will begin to smile.

You should be worried if your baby <u>does not</u>:

- Does not respond to loud noises.
- Does not bring hands to their mouth.
- Does not watch things as they move, or smile at you.
- Does not lift up their head when placed on their tummy, and dislikes the position.

If you noticed any of the above problems immediately tell a nurse at your local clinic, a doctor, physiotherapist or occupational therapist.

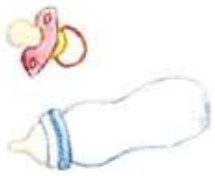
***

Things you can do to help your baby's development:

- Talk, read, sing and play with your baby during feeding, dressing, and bathing.
- Help your baby learn to calm herself. It's okay for them to suck on their hand and fingers to soothe themselves.
- Begin to help your baby get into a routine, such as sleeping at night more than in the day.
- Act excited and smile when your baby makes sounds. Copy your baby's sounds sometimes, but also talk normally to them using clear understandable language.
- Let baby practice watching a small toy by holding it up above their face and moving it up and down and to the left and right.
- It is important to hold your baby in an upright position over your shoulder allowing them to start lifting up their head off your shoulder. This will help to strengthen the neck muscles. Support the neck with your hand as needed.
- It is important to allow your baby to lie on their tummy when awake and during play, put toys nearby them when doing so. Encourage your baby to lift their head up when lying on their tummy by holding toys at eye level for them to look at.
- If your baby is not comfortable lying on its tummy on the floor you can let them lie on your chest while you lean back in a comfortable chair.
- It is best not to let your baby sleep on their stomach but rather on their back or side.

Toys and items you can use at home:

- Rattles (If you do not have a rattle use an empty pill container and fill with rice grains or maize pips- make sure container is sealed tightly).
- Hand held mirror for baby to look at themselves in (if you don't have a hand held mirror sit with your child in front of a large mirror).
- Bangle or plastic ring hung on a shoe lace or piece of string to encourage following with the eyes.
- Make sure toys do not have small loose parts which can be swallowed and cause your baby to choke.
- Make sure toys are small and light enough for baby to hold easily. Keep plastic toys clean by regularly washing them in warm water and dishwashing liquid.



ACTIVITY GUIDELINE FOR INFANTS AND TODDLERS

4-6 MONTHS

WHAT BABIES SHOULD DO AT THIS AGE:

Physical development:

- Can hold their head steady, without support when held in an upright position.
- Rolls from lying on their side back onto their back.
- Lying on their tummy, is able to push up on their arms and lift the head and upper body up off the ground.
- Sits with some support at the hips and back.

Learning, thinking and solving problems:

- Responds to the attention given by parent(s) or caregivers.
- Looks at their own hands.
- Explores objects by shaking them it or by putting them in their mouth.
- Approaches his/her image in a mirror with their body and/or touches the mirror.
- Always tries to reach for objects to get hold of them.

Language and communication

- "Babbles" or makes baby noises.
- Cries in different ways when they are hungry, wet or tired.
- Put sounds together like "ah", "eh" and "oh".

Social and emotional skills:

- Knows familiar faces and may not like strangers.
- Clearly responds to sounds and voices.
- Responds to others emotions and is often happy.
- Like to look at themself in a mirror.

You should be worried if your baby <u>does not</u>:

- Does not try and get objects that are within reach.
- Does not to respond to the sounds around them.
- Does not show affection towards you.
- Cannot bring objects to their mouth to explore.
- Does not make sounds or respond to you.
- Does not roll over to the sides.
- Dislikes being placed on their tummy.
- Has difficulty calming down or getting into a routine.
- Does not smile or laugh.
- Feels very floppy or very stiff.
- Only uses one side of the body.

If you noticed any of the above problems immediately tell a nurse at your local clinic, a doctor, physiotherapist or occupational therapist.

***

Things you can do to help your baby's development:

- Talk, read, sing and play with your baby during feeding, dressing, and bathing.
- Set a routine for sleeping and feeding.
- Act excited and smile when your baby makes sounds. Repeat your child's sounds and say simple words with those sounds. For example, if your child says "bah," say "baby" or "ball."
- Give age-appropriate toys to play with, such as rattle, ring or a small plastic blocks.
- Allow your baby to lie on a blanket on the floor, providing safe opportunities for your baby to play and reach for toys and explore their surroundings.
- Put toys near your baby so that she can reach for them. This will encourage them to start rolling.
- Put toys or rattles in your baby's hand and help him to hold them and pass them from one hand to the other.
- Hold your baby upright with feet on the floor as they will begin to "stand" with support.
- Place your baby on their tummy when awake and during play, put toys nearby them. This will encourage them to reach out for the toys.
- If your baby finds it hard to play while they are on their tummy, place a small rolled up towel under their chest.
- Use "reciprocal" play—when they smiles, you smile; when they makes sounds, you copy them.
- Read children's story books or picture books to your child every day. Praise them when they babble and "read" too.

Toys and items you can use at home:

- Rattles (if you do not have a rattle use an empty pill container and fill with rice grains or maize pips- make sure container is sealed tightly) or small toys that he/she is able to grasp easily and that are light.
- Small wooden or plastic blocks (if you do not have blocks use small empty match boxes).
- Hand held mirror or sit with your child in front of a large mirror.
- Bangle/plastic ring on a shoe lace or piece of string.
- A small ball e.g. a tennis ball
- Hard cover picture books (if you do not have a picture book you can use a magazine with bright pictures of familiar items. You can also cut pictures out of a magazine and paste in an exercise book to make your own picture book).

ACTIVITY GUIDELINE FOR INFANTS AND TODDLERS

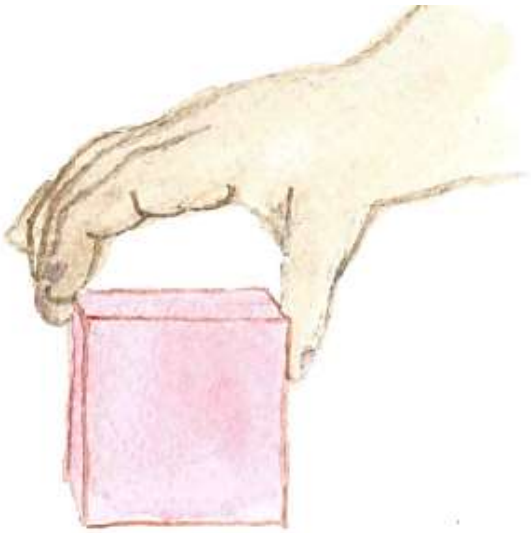
7 - 9 MONTHS

WHAT BABIES SHOULD DO AT THIS AGE:

Physical development:

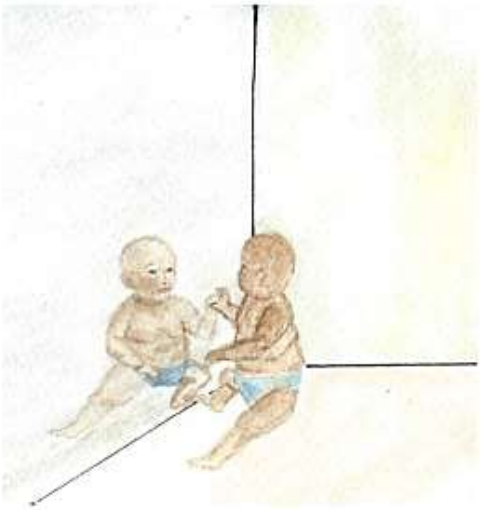
- Sits with slight support and later alone from around 8 months.
- Can roll from the back onto both sides, and later onto the tummy.
- Stands holding on to your hands or stands at a couch or low table.

- Can move frcrylying onto their tummy and up into a crawling position.
- Starts to crawl.
- Picks up a block with one or both hands.
- Able to pick up a small object e.g. cereal "cheerios".
- Can pass a plastic ring or block from one hand to the other.



Learning thinking and problem solving:

- Child plays with their image in a mirror (smiling, touching and mouthing).



- Plays with a string tied to a ring or bangle by pulling or chewing on the string.
- Bangs blocks, spoons during play.
- Looks for a fallen toy when dropped on floor.
- Reaches for toys all the time.

Language skills:

- Turns head towards the side of sounds.
- Recognises and turns head when their name is called.
- Makes sounds and tries use their voice to gain attention.

- Makes sounds like "gaga" "baba", "dada"

Social and emotional skill:

- Responds to others emotions and is often happy.
- Like to look at themself in a mirror.
- Makes noises and laughs in response to speaker's attention.

You should be worried if your baby <u>does not</u>:

- Does not take weight on their legs when you hold them in standing.
- Does not make sounds like "gaga", "mama", "dada" or "baba".
- Does not sit alone or with very little help.
- Does not play games taking turns back and forth.
- Does not roll over to both sides and onto the stomach.
- Does not pass toys from one hand to the other, cannot pick up a small item.
- Seems very floppy or very stiff.
- If the muscles are weak.

If you noticed any of the above problems immediately tell a nurse at your local clinic, a doctor, physiotherapist or occupational therapist.

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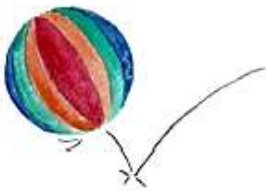

Things you can do to help your baby's development:

- Pay attention to the way they react to new situations and people; try to continue to do things that make your baby happy and comfortable. As they moves around more, stay close so they know that you are near.

- Describe what your baby is looking at; for example, "red, round ball." Copy your baby's sounds and words. But also talk to them using normal language.

- Ask for behaviours that you want e.g. "let's sit down" or "turn onto your tummy".

- Teach cause-and-effect by letting an object fall to the floor and help them look for it.

- Provide lots of room for your baby to move and explore in a safe area on the floor for example on the soft mat or on a blanket.

- Encourage play in sitting, give toys to your child from the front and sides to help develop sitting balance.

- When lying on their tummy put toys out in front of them just out of reach encouraging them to crawl forwards to get to the toy.

Toys and items you can use at home:

- Small plastic or wooden blocks (if you do not have blocks use a small empty match boxes).
- Kitchen spoons (metal or wooden) for banging.
- Cheerios' cereal to develop small hand skills.
- Plastic stack rings or bangle on a string or shoelace.
- Hand held mirror or sit with your baby in front of a large mirror.
- Hard cover picture books (if you do not have a picture book use a magazine with bright pictures and make a picture book).
- Plastic ball.

ACTIVITY GUIDELINE FOR INFANTS AND TODDLERS

10-12 MONTHS

WHAT BABIES SHOULD DO AT THIS AGE:

Physical development:

- Sits alone with good balance, and can turn and reach for toys put to the sides.
- When holding child under their arms in standing they step with their feet.
- Able to move around by crawling.
- Moves from lying to sitting or into a crawling position on their own.
- Stands against furniture for support.

- Able to pull themself up into standing from the ground against the furniture.
- Walks sideways along the furniture.
- Able to pick up a small object e.g. cereal "cheerios"" using thumb and first finger.
- Can pass ring or block from one hand to the other.
- Bangs spoons or blocks together or against surfaces.

Learning thinking and problem solving:

- Child will pick up two small blocks one in each hand.
- Will look at pictures with interest.
- Will pull on a string attached to a ring to bring it closer to grab.

Language skills:

- Turns head and stops playing when their name is called.
- Can start to identify different sounds.
- Tries to get your attention using their voice.
- Child will use gestures to indicate what they want e.g. point to something when

Social and emotional skills:

- Shy and nervous around strangers.
- Cries when mom, dad or a caregiver leaves them.
- Has favourite toys and people.Gets scared in some situations.
- Plays games e.g. hide and seek.

You should be worried if your baby <u>does not</u>:

Does not crawl.

- Cannot stand with support.

Does not search for things that fall.

- Does not point to things.
- Does not use gestures e.g. waving and pointing.
- Does not say any words.

Seems very floppy or very stiff.

- Loses skills that they had.

Struggling to learn to chew food.

- Difficulty seeing or hearing.

If you noticed any of the above problems immediately tell a nurse at your local clinic, a doctor, physiotherapist or occupational therapist.

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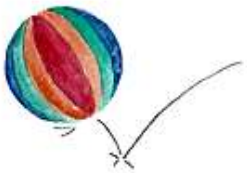


Things you can do to help your baby's development:

- Give your child time to get to know a new caregiver. Bring a favourite toy, stuffed animal, or blanket along to help comfort your child.
- In response to unwanted behaviours, say "no" firmly.
- Give your child lots of hugs, kisses, and praise for good behaviour. Encourage good behaviour.
- Talk to your child about what you're doing. For example, "mommy is washing your face with a cloth."
- Read to your child every day and tell them stories.
- Build on what your child says or tries to say, or what he points to. If he points to a truck and says "t" or "truck," say, "Yes, that's a big, blue truck."
- Play with blocks and other toys that encourage your child to use their hands. Offer them blocks by handing it to them one at a time (up to three blocks).
- Hide small toys and other objects under a facecloth and have your child find them.

Toys and items you can use at home:

- Small wooden or plastic blocks (if you do not have blocks use a small empty match boxes).
- Spoons (metal or wooden), pots and plastic containers.
- Cheerios' cereal rounds to develop fine grasp (safe as it dissolves if swallowed- avoid other small objects as they are choking hazards).
- Hard cover picture and story books (if you do not have a picture book use a magazine with bright pictures and make a picture book).
- Furniture such as low coffee tables, benches, chairs and couches to pull up against and walk alongside.
- Ball.

B. CRediT – Author Contributor Roles Taxonomy

Term	Definition
Conceptualisation	Ideas; formulation or evolution of overarching research goals and aims
Methodology	Development or design of methodology; creation of models
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components
Validation	Verification, whether as a part of the activity or separate, of the overall replication/ reproducibility of results/experiments and other research outputs
Formal analysis	Application of statistical, mathematical, computational, or other formal techniques to analyse or synthesise study data
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse
Writing - Original Draft	Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation)
Writing - Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or post-publication stages
Visualisation	Preparation, creation and/or presentation of the published work, specifically visualisation/ data presentation
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team
Project administration	Management and coordination responsibility for the research activity planning and execution
Funding acquisition	Acquisition of the financial support for the project leading to this publication

Allen L, O'Connell A, Kiermer V. How can we ensure visibility and diversity in research contributions? How the Contributor Role Taxonomy (CRediT) is helping the shift from authorship to contributorship. *Learned Publishing*. 2019;32(1):71-74.

C. Declaration by Student and Co-Authors' Agreement for Write-up with Published Articles

Declaration by student and co-authors' agreement for write-up with published articles

Declaration: Student's contribution to article(s)

I, Renate Strehlau, 9802279Y, declare that this Thesis is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Thesis.

Signature of Student... .....**Date**...16 September 2020....

Name of Primary Supervisor...Joanne Potterton .....

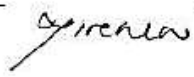
Signature of Primary Supervisor .....**Date**...16 September 2020.....

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Thesis. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for her degree purposes.

Article 1:

Neurodevelopmental assessment of HIV-exposed uninfected and early-treated HIV-infected children: study protocol

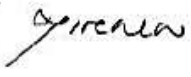
BMC Research Notes. 2018 Apr 6;11(1), p.235. DOI/10.1186/s13104-018-3331-8.

Authors	Name	Signature	Date
1st Author	Renate Strehlau		04 Aug 2020
2nd Author	Tamryn van Aswegen		13 Aug 2020
3rd Author	Joanne Potterton		13 Aug 2020

Article 2:

Interventions addressing neurodevelopmental delay in young children exposed to and infected with HIV: A Scoping Review.

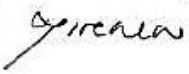
Rehabilitation Oncology. 2019 Jan;37(1), p.7-16. DOI/10.1097/01.REO.0000000000000150

Authors	Name	Signature	Date
1st Author	Renate Strehlau		04 Aug 2020
2nd Author	Tamryn van Aswegen		13 Aug 2020
3rd Author	Joanne Potterton		13 Aug 2020

Article 3:

A description of early neurodevelopment in a cohort of HIV-exposed uninfected children.

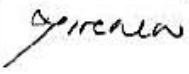
AIDS Care. 2020,p.1-8. DOI/10.1080/09540121.2020.1736257

Authors	Name	Signature	Date
1st Author	Renate Strehlau		04 Aug 2020
2nd Author	Tamryn van Aswegen		13 Aug 2020
3rd Author	Megan Burke		12 August 2020
4th Author	Louise Kuhn		14 Aug 2020
5th Author	Joanne Potterton		13 Aug 2020

Article 4:

Neurodevelopment in early treated HIV-infected infants participating in a developmental stimulation program compared with controls.

Child: care, health and development. 2020, in press

Authors	Name	Signature	Date
1st Author	Renate Strehlau		04 Aug 2020
2nd Author	Megan Burke		12 August 2020
3rd Author	Tamryn van Aswegen		13 Aug 2020

4th Author	Louise Kuhn		14 Aug 2020
5th Author	Joanne Potterton		13 Aug 2020

D. Ethics Clearance Certificate

R14/49 Dr Renate Strehlau

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170653

NAME: (Principal Investigator)	Dr Renate Strehlau
DEPARTMENT:	Paediatrics and Child Health Empilweni Services and Research Unit (ESRU) Rahima Moosa Mother and Child Hospital
PROJECT TITLE:	Neurodevelopmental Assessment of Early-treated HIV-infected Children
DATE CONSIDERED:	30/06/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Joanne Potterton
APPROVED BY:	Professor P. Cleaton-Jones Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/08/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date: 07 August 2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

E. Pan African Clinical Trial Registration

15 January 2018

To Whom It May Concern:

RE: Neurodevelopmental Assessment of Early-treated HIV-infected Children

As project manager for the Pan African Clinical Trial Registry (www.pactr.org) database, it is my pleasure to inform you that your application to our registry has been accepted. Your unique identification number for the registry is **PACTR201801002967587**

Please be advised that your trial is registered under an initiative within our system that allow us to capture data of trials that are already in progress or completed. As such, your trial registration may not adhere to the mandates set forth by the International Committee of Medical Journal Editors for registration requirements, and it is your duty to be transparent to any journal that may ask about the retrospective status of your registration.

Please note you are responsible for updating your trial, or for informing us of changes to your trial. Additionally, please provide us with copies of your ethical clearance letters as we must have these on file (via email or post) at your earliest convenience if you have not already done so.

Please do not hesitate to contact us at +27 21 938 0835 or email epienaar@mrc.ac.za should you have any questions.

Yours faithfully,

Elizabeth D Pienaar
www.pactr.org Project Manager
+27 021 938 0835

THE SOUTH AFRICAN MEDICAL RESEARCH COUNCIL
Cochrane South Africa | PO Box 19070, Tygerberg, 7505
Tel: +27 (0)21 938 0438 | Email: cochrane@mrc.co.za | Web: www.southafrica.cochrane.org

F. Informed Consent Document Signed by Parents of Children Enrolled in the Intervention Group of this Study

Participant Informed Consent:

Neurodevelopmental Assessment of Children

Enrolled on the LEOPARD-CT and LEAOPRD-O trials

Intervention Group

Good day. My name is ……
I am a researcher from the University of Witwatersrand and I work together with the team at Empilweni Services and Research Unit at Rahima Moosa Mother and Child Hospital. You are *invited* to take part in a research study. Taking part is entirely voluntary.

INTRODUCTION
You are being asked to allow your child to take part in this research study because your child is taking part in the LEOPARD clinical trial. Before you decide if you want your baby to participate, we want you to know about the study.

This is a consent form. It gives information about the study. I will talk with you about this information. You are free to ask questions at any time. If you allow your child to take part in the study, you will be asked to sign this form. You will be offered a copy to keep.

Before you decide if you want to be part of this study, it is important that you understand the purpose of the study, the study procedures, benefits, risks, and your right to withdraw from the study at any time.
This information leaflet is to help you to decide if you would like to participate in the study. Take as much time as you need to decide.

- If you have any questions, feel free to ask me.
- If you decide to take part in this study, you will be asked to sign this document to show that you understand the study. You will be given a copy to keep.
- You participate under your own choice. You can choose not to take part and if you join, you may stop at any time. If you decide not to participate or if you decide to stop at any time there will be no disadvantage to you or your baby and we will support your decision and ensure that your baby receives the same care.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to describe how children, who are taking part in the LEOPARD study, are developing in terms of what growing children are expected to do at certain ages. We would like to compare the development of 12 month old children who receive a developmental stimulation box to those who did not receive a box. We would also like to gather information about your family and your home life.

STUDY PROCEDURES

When your baby is born you will be given a box for your baby. The box will contain some items for a new born baby as well as some toys to help your baby learn and develop. An information card will also be included with advice and ideas on how to stimulate babies at different ages through the first year of life. When your baby is 3, 6, 9, and 12 months of age, extra play items will be given to you to add to your box.

Researchers in the clinic will take some extra time during the 12 month LEOPARD study visit to assess your child's development.

The developmental assessment that will be used is called the Bayley Scales of Infant Development (BSID). The assessment is made up of a number of items that checks specific areas of development, namely: thinking, moving and playing, and language. You will be able to stay with your child throughout the assessment, and we encourage you to watch what is done and ask any questions that you may have. The assessment is largely completed by watching the child, seeing what your child is able to do, and how your child reacts to toys. The assessment should take between 30-60 minutes. How your child does on the assessment will be discussed with you after the assessment has been completed. During this visit, we will also ask you to complete the Household Questionnaire which consists of questions about your family and home life, and the Parenting Stress Index which contains questions about how you are coping as a parent.

If the assessment shows that your child needs some extra support in any areas of development, the doctors in ESRU will arrange an appropriate referral as needed.

If your child, or you, is not feeling well at the scheduled visit then we will not do the assessment. We will book a follow-up date when you are both feeling well.

The researchers will also be able to have access to your LEOPARD Study file including results of blood tests. This information is needed to learn important information about your child like details about the birth and how they have been growing. In the same way, LEOPARD study researchers will have access to the information which is collected when you participate in this study.

LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS

We will invite all of the mothers or legal guardians of children newly enrolled onto the LEOPARD trial to participate.

POSSIBLE RISKS

In this study we will only be assessing your child. We will not do anything which will make you or your child feel uncomfortable. It may be upsetting if your child is unable to perform a task which is expected at a certain age. Children all grow and develop at their own pace and we will work together with you if your child needs further follow up.

You may feel uncomfortable about answering questions about your home life and the stressors you may be experiencing as a parent. Please let the interviewer know how you are feeling.

Another risk of taking part in this study is the possibility of a loss of confidentiality. Loss of confidentiality includes having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. All staff members have received training in maintenance of confidentiality and will not disclose your or your child's information to third parties without your consent.

This is not a trial of a new developmental assessment. This is a trial using an existing developmental assessment tool to see how your child is developing and learning new skills.

All information that is collected will only be recorded using a study number. This means that you will not be able to be identified from it. All information that is collected during this study will not be shared with anyone other than the staff from this study. Your records may be reviewed by monitors or officials authorized by the National Institutes of Health, US (who are funding the study), by Columbia University (who are part of the study team) or by the University of the Witwatersrand.

BENEFITS

By taking part in this study you may benefit in the following ways:

- Your child may benefit from being assessed in terms of how he/she is developing, and if there are any problems, the close monitoring may pick them up early.
- If needed, your child will be referred for extra assessments and help to qualified professionals at Rahima Moosa hospital.

IF YOU DO NOT PARTICIPATE

If you decide not to take part in this study you will still be able to continue in the LEOPARD study and receive the best current care from the ESRU study team.

FINANCIAL ARRANGEMENTS

The assessment for this study will be done on the same day as your LEOPARD study visit. Your transportation and inconvenience costs will be covered by the LEOPARD study with R150 per visit. If the assessment needs to be planned for a different day, and it does not coincide with your LEOPARD study visit, you will still receive R150 for transport to and from the clinic because we know how difficult it is to make so many visits to the clinic.

ETHICAL APPROVAL

This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee (certificate number: M170653).

IF YOU NEED MORE INFORMATION DURING THE STUDY

If at any time between your visits, you have any questions about the study or want more research information, please call: (011) 470 9214 (office hours) or 076 474 0632 (emergency contact number) for assistance. You are also welcome to contact the **Human Research Ethics Committee (HREC)** of the University at (011) 717 2301 if you have any questions or complaints about the ethics of the study.

INFORMED CONSENT: Neurodevelopmental Assessment of Children Enrolled on the LEOPARD-CT and LEAOPRD-O trials

- I hereby confirm that I have been informed by the study staff,.....……., about the nature, conduct, benefits and risks of the study involving the neurodevelopmental assessment of children enrolled on the LEOPARD trials.
- I have received and read the consent form and talked about this study, including the purpose, procedures, risks, benefits and alternatives with the researcher. Any questions I had were answered to my satisfaction. I am aware that by signing below, I am agreeing for myself and my child to take part in this research study and that I can stop myself or my child being in the study at any time.
- I am aware that the results of the study, including personal details about me or my child including age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system.
- I may, at any stage, without prejudice, withdraw my consent and my child's participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared for my child to participate in the study.
- I am not giving up any of my or my child's legal rights by signing this consent form. I will be given a copy of this consent form to keep for my records.

Child's Name: _____

Mother/Legal Guardian:

Printed Name	Signature / Mark or Thumbprint	Date and Time

I, ...……, herewith confirm that the above patient has been fully informed about the nature, conduct and risks of the above study.

Person explaining Informed Consent (Designation).....

Printed Name	Signature	Date and Time

Witness (If applicable)**:**

Printed Name	Signature	Date and Time

G. Informed Consent Document Signed by Parents of Children Enrolled in the Observation Group of this Study

Participant Informed Consent:

Neurodevelopmental Assessment of Children

Enrolled on the LEOPARD-CT and LEAOPRD-O trials

Good day. My name is ……
I am a researcher from the University of Witwatersrand and I work together with the team at Empilweni Services and Research Unit at Rahima Moosa Mother and Child Hospital. You are *invited* to take part in a research study. Taking part is entirely voluntary.

INTRODUCTION
You are being asked to allow your child to take part in this research study because your child is taking part in the LEOPARD clinical trial. Before you decide if you want your baby to participate, we want you to know about the study.

This is a consent form. It gives information about the study. I will talk with you about this information. You are free to ask questions at any time. If you allow your child to take part in the study, you will be asked to sign this form. You will be offered a copy to keep.

Before you decide if you want to be part of this study, it is important that you understand the purpose of the study, the study procedures, benefits, risks, and your right to withdraw from the study at any time.
This information leaflet is to help you to decide if you would like to participate in the study. Take as much time as you need to decide.

- If you have any questions, feel free to ask me.
- If you decide to take part in this study, you will be asked to sign this document to show that you understand the study. You will be given a copy to keep.
- You participate under your own choice. You can choose not to take part and if you join, you may stop at any time. If you decide not to participate or if you decide to stop at any time there will be no disadvantage to you or your baby and we will support your decision and ensure that your baby receives the same care.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to describe how children, who are taking part in the LEOPARD study, are developing in terms of what growing children are expected to do at certain ages. We would also like to gather information about your family and your home life.

STUDY PROCEDURES

Researchers in the clinic – who have been seeing your child at the LEOPARD study visits – will take some extra time during the 12 month, or 24 month, or 36 month study visits to assess your child's development.

The developmental assessment that will be used is called the Bayley Scales of Infant Development (BSID). The assessment is made up of a number of items that checks specific areas of development, namely: thinking, moving and playing, and language. You will be able to stay with your child throughout the assessment, and we encourage you to watch what is done and ask any questions that you may have. The assessment is largely completed by watching the child, seeing what your child is able to do, and how your child reacts to toys. The assessment should not take longer than 60 minutes, but may take a little longer in older children as by 36 months (3 years) your child will have a lot of skills and abilities. During this visit, we will also ask you to complete the Household Questionnaire which consists of questions about your family and home life, and the Parenting Stress Index which contains questions about how you are coping as a parent.

How your child does on the assessment will be discussed with you after the assessment has been completed. You will then be provided with an information card which will provide you with ideas on how to stimulate a child at different ages.

If the assessment shows that your child needs some extra support in any areas of development, the doctors in ESRU will arrange an appropriate referral as needed.

If your child, or you, is not feeling well at the scheduled visit then we will not do the assessment. We will book a follow-up date when you are both feeling well.

The researchers will also be able to have access to your LEOPARD Study file including results of blood tests. This information is needed to learn important information about your child like details about the birth and how they have been growing. In the same way, LEOPARD study researchers will have access to the information which is collected when you participate in this study.

LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS

We will invite all of the mothers or legal guardians of every child currently taking part in the LEOPARD trial to participate.

POSSIBLE RISKS

In this study we will only be assessing your child. We will not do anything which will make you or your child feel uncomfortable. It may be upsetting if your child is unable to perform a task which is expected at a certain age. Children all grow and develop at their own pace and we will work together with you if your child needs further follow up.

You may feel uncomfortable about answering questions about your home life and the stressors you may be experiencing as a parent. Please let the interviewer know how you are feeling.

Another risk of taking part in this study is the possibility of a loss of confidentiality. Loss of confidentiality includes having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. All staff members have received training in maintenance of confidentiality and will not disclose your or your child's information to third parties without your consent.

This is not a trial of a new developmental assessment. This is a trial using an existing developmental assessment tool to see how your child is developing and learning new skills.

All information that is collected will only be recorded using a study number. This means that you will not be able to be identified from it. All information that is collected during this study will not be shared with anyone other than the staff from this study. Your records may be reviewed by monitors or officials authorized by the National Institutes of Health, US (who are funding the study), by Columbia University (who are part of the study team) or by the University of the Witwatersrand.

BENEFITS

By taking part in this study you may benefit in the following ways:

- Your child may benefit from being assessed in terms of how he/she is developing, and the close monitoring may pick up problems early.
- If needed, your child will be referred for extra assessments and help to qualified professionals at Rahima Moosa hospital.

IF YOU DO NOT PARTICIPATE

If you decide not to take part in this study you will still be able to continue in the LEOPARD study and receive the best current care from the ESRU study team.

FINANCIAL ARRANGEMENTS

The assessment for this study will be done on the same day as your LEOPARD study visit. Your transportation and inconvenience costs will be covered by the LEOPARD study with R150 per visit. If the assessment needs to be planned for a different day, and it does not coincide with your LEOPARD study visit, you will still receive R150 for transport to and from the clinic because we know how difficult it is to make so many visits to the clinic.

ETHICAL APPROVAL

This clinical study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee (certificate number: M170653).

IF YOU NEED MORE INFORMATION DURING THE STUDY

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INFORMED CONSENT: Neurodevelopmental Assessment of Children Enrolled on the LEOPARD-CT and LEAOPRD-O trials

- I hereby confirm that I have been informed by the study staff,.....……., about the nature, conduct, benefits and risks of the study involving the neurodevelopmental assessment of children enrolled on the LEOPARD trials.
- I have received and read the consent form and talked about this study, including the purpose, procedures, risks, benefits and alternatives with the researcher. Any questions I had were answered to my satisfaction. I am aware that by signing below, I am agreeing for myself and my child to take part in this research study and that I can stop myself or my child being in the study at any time.
- I am aware that the results of the study, including personal details about me or my child including age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system.
- I may, at any stage, without prejudice, withdraw my consent and my child's participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared for my child to participate in the study.
- I am not giving up any of my or my child's legal rights by signing this consent form. I will be given a copy of this consent form to keep for my records.

Child's Name: _____

Mother/Legal Guardian:

Printed Name Signature / Mark or Thumbprint Date and Time

I, ...……, herewith confirm that the above patient has been fully informed about the nature, conduct and risks of the above study.

Person explaining Informed Consent (Designation) .....

Printed Name Signature Date and Time

Witness (If applicable)**:**

Printed Name Signature Date and Time

H. Turnitin Similarity Report for this Thesis

The University of the Witwatersrand requires a Turnitin report to be included to determine originality of the work presented in this thesis.

The published manuscripts included as part of this thesis – Chapters 3, 4 and 5 – were excluded from the Turnitin analysis as including them would have resulted in 100% match.

The report result shows a 22% match between the contents of this thesis and other sources. No matches were greater than 1%. When excluding matches <1% the similarity index was 3%.

As the Turnitin report is a large document of 256 pages the first page of the report has been included as an appendix and the full report submitted as a supplementary file.

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ORIGINALITY REPORT

22%	18%	10%	7%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.scribd.com Internet Source	1%
2	www.tandfonline.com Internet Source	1%
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