The impact of maternal mental health on child cognitive development in the presence of HIV-a study in Zimbabwe

Thesis presented for the degree of

DOCTOR OF PHILOSOPHY

(Global Health and Epidemiology)

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Declaration

I, Helen Mebrahtu, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ACKNOWLEDGEMENTS

First and foremost, my deep and heartfelt gratitude to my supervisor Prof. Lorraine Sherr, whose caring and nurturing style of teaching, guided me through one of the most challenging times in my educational history. Thank you for giving me this opportunity and believing in me. Thank you for always encouraging me to take breaks, to write papers and most importantly for always redirecting me to the bigger picture whenever I seemed to have lost sight.

Secondly, my deep and sincere gratitude to my co-supervisor Prof. Frances Cowan, whose brilliant mind and dedication to research always inspired me to only aim for perfection in every piece of work I produce. Thank you for all the advice, support and guidance provided throughout the course of this research.

Special thanks to Dr. Victoria Simms- her meticulous attention to detail, thorough and prompt feedback for every paper and draft sent through the course of my PhD. Thank you for all the statistical advice and classes you've given me and helping me become a better researcher.

I would also like to thank the CeSHHAR team in Zimbabwe for welcoming me and making me feel part of the team, the LSHTM team (Prof. Helen Weiss & Dr. Andrea Rehman) for all the statistical support and advice provided, the World Education team, and Mavambo- who without the effort and dedication, my PhD and this research would have not been completed successfully.

To my colleagues and friends at Royal Free Manoulis, Kassonde, Kathryn, Sophia, Reynie, Davide- thank you for welcoming me to the department and for the much-needed distractions with endless rounds of cakes to help me get through the days that seemed endless at times. Special thanks to Ada my unofficial mentor for her constant encouragement and advice, and to Sarah and Hibo my support system for helping me navigate through PhD work and life.

To my close friends near and far- thanks for always being understanding of my antisocial antics at times, for encouraging, and pushing me to follow my dreams. Thank you for planning the much-needed holidays which always helped me maintain a balance and not get completely consumed by the hectic PhD life.

Lastly but not least to my family- my siblings Henok, Sara, and Haben - thank you for the moral, emotional, financial and all-round support, without you all I wouldn't have made it this far. Special thanks to my parents Lucia and Mebrahtu who are my motivation for doing this PhD and the reason the love of education and learning new things were instilled in me from a young age. To my mother, thank you for your endless love, care, support, and prayers. To my father, thank you for all the sacrifices you made for me to reach this level, I'm here because of you!

ABSTRACT

Early childhood is a critical period for development. Exposure to factors such as HIV and poor maternal mental health may negatively impact child cognitive development. The evidence points to lack of evaluated interventions in sub-Saharan Africa and Zimbabwe specifically, aimed at enhancing child developmental outcomes in the last nine years.

The aim of this thesis was to investigate the impact of maternal mental health on cognitive development of 0-36 month old children in Zimbabwe in the presence of maternal HIV infection. The research was nested within a large cluster randomised controlled trial (Child Health Intervention for Development Outcomes-CHIDO trial) aimed at enhancing child outcomes. The study focussed on 574 child-caregiver dyads recruited through the HIV exposed clinic registers in two rural districts of Zimbabwe. The cognitive performance of participating HIV positive and HIV-exposed uninfected (HEU) children was investigated using the 5 Mullen child development inventory sub-scales (visual reception, expressive language, receptive language, fine motor, and gross motor), and the mental health of their mothers in the trial (n=562) assessed using the Edinburgh Postnatal Depression Scale, Parental Stress Index-Short Form, and 8-item Shona Symptom Questionnaire. The use of standardised child development tools and the potential for exploring shorter forms was also undertaken as part of this research.

Child cognitive development outcomes pre and post CHIDO intervention roll out were investigated. There was no evidence of a difference in Mullen composite scores after intervention implementation between the trial arms (mean of 88.1 in the intervention arm and 87.6 in standard of care arm; adjusted mean difference (aMD): 0.06; 95% CI: -2.68 to -2.80; p=0.97); thus the caregiver-child data from all arms of the trial were pooled and used for subsequent analyses. Child cognitive development were examined at baseline and there was no evidence of difference in the overall cognitive functioning of the children by HIV status (HIV+ve children 101.3 vs. HEU: 100.0; aMD: -1.18; 95% CI: -9.14 to 6.79; p=0.77).

The prevalence and association of common mental disorders (CMD), depression symptoms and stress, as well as maternal suicidal ideation with child cognitive scores at baseline and 12 months follow-up were examined individually. Chronic maternal

CMD (i.e. over 12 months period) was negatively associated with child receptive vocabulary (aMD: -2.8, 95% CI: -5.1 to -0.6; p=0.05) when compared to those with no CMD. Similarly emerging maternal suicidal ideation was negatively associated with overall poorer child cognition (aMD: -6.1; 95% CI: -10.3 to -1.8; p=0.03), and developmental sub-domains, visual reception (aMD: -4.4; 95% CI: -7.6 to -1.2; p=0.04), and receptive language ability (aMD: -4.2; 95% CI:-7.2 to -1.2; p=0.02). Of importance, children of mothers reporting any emerging mental disorder (either depression symptoms, CMD or suicidal ideation) had lower cognitive scores across all the developmental domains at the end of the trial compared to those without any mental disorders.

The research in this thesis demonstrates the importance of maternal mental health in child language and visual reception development within an HIV affected population. Timely identification of these HEU children, as well as prompt multicomponent interventions which include treatment of maternal mental health, are required to ensure that these children are able to reach their maximum developmental potential.

IMPACT STATEMENT

HIV exposed children in developing countries face multiple and complex stressors associated directly and indirectly with HIV infection. These children are at high risk of developmental delay and impairment particularly in resource-limited settings such as Zimbabwe. Thus, the psychosocial needs of these children must be at the centre of future interventions and policymaking.

Current literature on the effectiveness of interventions to prevent cognitive delay in HIV affected children in sub-Saharan Africa shows that there is an urgent need for evaluated interventions in this population, including in Zimbabwe. The systematic review of the evidence presented in this thesis will be shared with a larger audience and submitted for peer reviewed publication.

The CHIDO trial- which evaluated a comprehensive intervention aimed at mitigating developmental delay which is implemented in rural Zimbabwe (combining early childhood stimulation and parenting skills training elements supported by home visits), was found to have no impact on child cognitive development within a median 4.5 months of completion. The findings here suggest that the benefits of parenting training may need more time to influence child development outcomes. The results from this work can inform design of future intervention studies in Zimbabwe and elsewhere, suggesting the need for longer follow-up to assess the impact of child development interventions in randomised controlled trials.

Importantly the findings from this thesis show high burden of mental health in HIV positive mothers, and the impact this has on their children's cognitive development, particularly in language and visual reception development. The longitudinal studies in this research project add useful insight to the literature on the role of maternal mental health on child development in the Southern Africa context. Findings of this research in addition to illustrating the importance of maternal mental health provide valuable information on the characteristics of HIV positive mothers at risk of common mental disorders and more extreme mental disorders such as suicidal ideation in Zimbabwe. Results from this study can inform programmers and researchers on the importance of multicomponent interventions to address the complexity of challenges faced by mothers with HIV and their children in similar context.

The possibility of developing a simple child cognitive assessment tool usable by lay health workers was investigated in this thesis and shown to be feasible and valid. However, future researchers looking to utilize such tools will need to address copyright and licencing issues of the more complex and validated scales.

Overall, findings from this PhD research were disseminated and shared with a wider audience through peer-reviewed journal publications as well as conference posters and presentations. The take home message was HIV positive mothers in Zimbabwe have high rates of poor mental health and household poverty which need to be addressed along side programmes which aim to improve child cognitive development.

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GLOSSARY OF ACRONYMS AND ABBREVIATIONS

ACASI- Audio computer assisted survey instrument

AMD- Adjusted mean difference

AIDS - Acquired immune deficiency syndrome

ART- Antiretroviral treatment

BRIEF- the Behavior Rating Inventory of Executive Function

CI- Confidence interval

CCW- Case care worker

CHWs- Community health workers

CHIDO- the Child health intervention for developmental outcomes

CMD- Common mental disorders

CNS- Central nervous system

CeSHHAR- Centre for Sexual Health HIV/AIDS Research

COAT- Color-Object Association

ECD- Early childhood development

ECS- Early childhood stimulation

ELC- Early learning composite

EPDS- Edinburgh postnatal depression scale

HEU- HIV-exposed uninfected

HEI- HIV exposed and infected

HIV- Human immunodeficiency virus

HOME- Caldwell Home Observation for the Measurement of the Environment

IQR- Interquartile range

ISALS- Internal savings and lending scheme

K-ABC- Kaufman assessment battery for children

LHW- Lay healthcare workers

LMICs- Low- and middle-income countries

MDAT- Malawi developmental assessment tool

MISC- Meditational Intervention for Sensitizing Caregivers

MoHCC- Ministry of Health and Child Care (Zimbabwe)

MTCT- Mother-to-child transmission

MSEL- Mullen scale of early learning

NVP- Nevirapine

OR- Odds ratio

PCR- Polymerase chain reaction

PEPFAR- U.S. President's Emergency Plan for AIDS Relief

PLWH- People living with HIV

PMTCT- Prevention of mother-to-child transmission

PSI-SF- Parental stress index- short form

RCT- Randomised controlled trial

SD- Standard deviation

SSA- Sub-Saharan Africa

SSQ- Shona symptoms questionnaire

USAID- United States Agency for International Development

WHO- World Health Organization

MY ROLE IN THE CHIDO TRIAL

My PhD project was nested within the infrastructure of the CHIDO trial. This project was a collaboration between University College London, Liverpool School of Tropical Medicine, London School of Hygiene and Tropical Medicine, Centre for Sexual Health HIV/AIDS Research Zimbabwe, World Education Inc./Bantwana Zimbabwe, and other partners, funded by USAID-PEPFAR under the Orphans and Vulnerable Children Special Initiative. Professors Lorraine Sherr and Frances Cowan were the Principal Investigators for this trial and co-supervised this PhD project alongside Dr Victoria Simms.

As the trial was a collaboration between several institutions across different countries, it involved working as part of a larger team as well as strong communication skills. Throughout the trial, I worked closely with the data manager and project co-ordinator in Zimbabwe on the management of the baseline and follow-up data as well as working jointly with the trial statisticians on analysis of the primary and secondary outcomes. I took primary responsibility for Mullen scores data cleaning, maternal mental health measure scoring, and creation of other core variables for my PhD research questions. I produced the guidance documents and metadata of data items/variables collected as part of the trial. I also assisted in designing the qualitative questions for process evaluation purposes at 12 months follow-up data collection.

Over the course of my PhD, I contributed to writing of scientific papers and reports using the trial data. I took the lead role in preparing the CHIDO baseline report which summarized household demographics, child and caregiver demographics and trial outcome measures (pre-intervention) [1]. The report was shared with and presented to our various stakeholders (from trial funders, field team, to implementing partners).

I co-authored several papers relating to this research, with other manuscripts either submitted for publication or in preparation. I first authored the CHIDO trial findings paper which was published by BMJ Global Health journal [2] as well as co-authoring the trial protocol paper (published by BMC Paediatrics) [3], **Appendices 2 and 3**.

Preliminary findings of the trial and my PhD research questions were presented at international conferences. I gave oral presentations on the cognitive profiles of the

children in the study at the 13th AIDSImpact international conference in Cape Town in 2017 [4], and on maternal suicidal ideation and its role on child cognitive development at the 14th AIDSImpact conference in London in 2019 [5]. In addition, I presented a poster on the role of infant nutritional status (stunting) on early cognitive development at the 22nd International AIDS conference, Amsterdam 2018 [6].

Finally, there was a wealth of data collected from children and their caregivers in the CHIDO trial; this enabled me to investigate child development profiles and the link between child development and maternal mental health in depth. Results from these analyses were used to address my thesis questions. My findings on maternal mental health and child cognitive development were published by AIDS Care (AIDS Care) [7], with the following manuscripts under consideration by journals for publication;

1. *Effects of maternal suicidal ideation on child cognitive development: A longitudinal analysis* (under consideration by AIDS and Behaviour journal) [8],
2. *The impact of common mental disorders among caregivers living with HIV on child cognitive development in Zimbabwe* (under consideration by AIDS Care journal) [9].

CHAPTER 1: Background and introduction

This introductory chapter provides a detailed review of published literature on early childhood development, and the different factors that may affect it, with specific focus on cognitive development, the impact of HIV infection and/or exposure as well as several other maternal factors associated with child cognitive performance. The impact of contextual factors including poverty and parenting style on child development are also considered. The HIV epidemic in Zimbabwe and HIV prevention from mother to child transmission are discussed.

1.1 Early Childhood Development

Early childhood is the period of growth from conception through birth that can span up to eight years of age and is a crucial phase of growth and development for humans [10, 11]. Child development is a dynamic process through which children progress from dependence in all areas of functioning towards growing independence from infancy through adulthood [11, 12]. Early childhood development (ECD) is a generic term that refers to the first 3 years of a child's life and describes the gradual unfolding of their sensory-motor, social-emotional, cognitive-language, capacities shaped by interactions between the environment, experience, and genetics [12, 13]. It is a period of rapid physical growth during which an individual acquires a complex set of skills and functional competencies that should facilitate achievement of their potential in life [10, 14]. These early childhood experiences lay the foundation for long-term physical, emotional, and psychological health in children [15, 16].

Child development can be monitored using key developmental milestones. These developmental milestones comprise behaviours, skills, and abilities that are demonstrated at specified ages during infancy and early childhood in typical development. Children grow and develop rapidly across five main areas of development, these developmental domains include cognitive, motor, language, social/ emotional and adaptive behaviour [17] (**Table 1.1**). Development in each domain proceeds through a series of milestones or steps and typically involves mastering simple skills before skills that are more complex can be learned. However, although the stages of child development can have predictable sequence and are measured as such, it is important to note that every child will have a unique course of development [18]. The table below summarises key developmental domains described in the literature which form the basis of numerous assessment and milestone investigations with researchers typically exploring five core domains [17-19].

Table 1.1**:** *Child developmental domains and corresponding description of each domain*

Child developmental domains and subdomains	***Description of domains and subdomains***
Cognitive	Strategies and processes children develop to interpret and respond to their environment and experiences including; memory (ability to encode, retain and recall information over time), and attention (the ability to choose what to focus on for a sustained period).
Language	
Receptive language	Understanding of the spoken word and sentence structure
Expressive language	Spoken vocabulary
Motor	
Fine motor	Ability to manipulate small objects
Gross motor	Ability to walk, run and coordinate complex physical activities
Social and emotional	The ability to identify and understand one's own feelings and to accurately read and comprehend emotional states in others. Ability to regulate one's own behaviour, to develop empathy for others, and to establish and maintain relationships.
Adaptive behaviour	Collection of conceptual, social and practical skills that have been learned by people in order to function in their everyday lives.

Research suggests that, during early childhood, children's brains develop rapidly and can be modified by the quality of the environment they are exposed to [20]. It is hypothesised that this is due to the newly developing brain being highly plastic and very responsive to change as billions of integrated neural circuits are established through the interaction of biology and the social environment influencing the child's ability to learn and develop over time [21-23]. Adversities experienced during this

stage of life can negatively influence child development [24]. Therefore it has been argued that early childhood provides a window of opportunities for early intervention and is the most effective and cost-efficient time to ensure that all children develop their full potential. Investing during this period will have substantial returns [15]. Research has demonstrated that early childhood stimulation could have long-term positive impact on children's health, growth, and cognitive and social development [25-27]. Reduced stimulation is a predictor of poor cognitive performance. A review examining several intervention studies from developing countries that assessed the effect of cognitive stimulation on young children found that, many of the studies reported beneficial effects of cognitive stimulation on child task orientation, social behaviour, self-confidence, and positive affect [28]. In addition to appropriate stimulation, having a consistent, responsive caregiver and a stable environment during these early years of life contributes to promoting optimal development [15, 29, 30].

On the other hand, adversities and multiple risks such as poverty, malnutrition, poor health, and unstimulating home environments throughout the early life can disrupt brain development, attachment, and early learning [20]. If not mitigated, developmental delays may become evident in the first year, worsen during early childhood, and continue throughout life [31].

1.2 Child cognitive development

Cognitive development refers to how an individual perceives, thinks, and gains understanding of their world through the interaction of genetic and learned factors. Among the areas of cognitive development are information processing, intelligence, reasoning, language development, and memory. Recognition and meaning (i.e. reasoning) of symbols (words, objects, images, letters, numbers etc.) are indicators of such learning [32]. Children tend to begin actively learning from birth, by gathering, sorting and processing information from their surroundings, and using the data to develop perception and thinking skills. Curiosity and creativity are two key features of this developmental domain often noted in children [32]. These features are often the driving forces that lead children to explore their surroundings, and in turn provide the necessary sensory inputs and the opportunity to learn from sensory perception. Newborns for instance explore the world by mouthing objects; and later explore the

world by imitating actions, manipulating objects and planning two-step strategies to get what he/she wants. As children get older (from 2 years on) they increase their use of language and start make-believe play [33]. In children aged 3–5 years there is rapid development in information processing (the speed and fluency of response following stimuli), cognitive flexibility (the ability to make and change strategies as required, and to simultaneously process multiple stimuli) and goal setting (the ability to plan strategies in a coherent and efficient order) [33]. These developmental domains are considered to be of great importance for predicting future achievement and reaching one's potential.

1.3 Developmental delays

Developmental delay occurs when a child exhibits a significant delay in the acquisition of milestones or skills acquisition outside of the typical sequence, in one or more domains of development [34] when compared to age matched children. Developmental delays are generally an early warning that the child needs further observation and possibly professional assessment and intervention. These delays can be difficult to recognize particularly when they are not physically evident. For example, severe disorders such as cerebral palsy, and other physically evident conditions can be recognized at birth or by physicians. However, developmental disabilities such as mental, sensory, language and behavioural disorders are difficult to recognize and diagnose in the early years or infancy as they may be considered by parents to be within the limits of normal variation. It is important to identify children with developmental delays early on, ideally during the first three years of life, as they are easier to mitigate during this period using appropriate interventions which can improve long-term outcomes [35]. Nevertheless many children in developing countries with low income and limited resources with developmental delay may never have the opportunity to undergo developmental assessment in the first three crucial years [35].

1.4 Measuring cognitive development

Developmental domains are theoretical concepts that cannot be directly measured but are inferred through the child's performance on a number of observed variables or test items [33]. These domains can be assessed by the child's ability to carry out a

series of complex activities that reflect the expected level of development at a particular age [33]. Some of the most commonly assessed child developmental domains include language, motor, cognitive, social and emotional and adaptive behaviour skills [17]. These domains of childhood development are interdependent; development in one domain influences and is influenced by the development in the other domains. Other forms of development measuring tools such as weight and height charts are also used to assess the growth trajectories of children [33].

There are several validated cognitive measurement and screening tools used for assessing child cognition by measuring different developmental domains. Most of these tools require observation of a series of complex tasks by a trained assessor with specialised equipment. Some examples include the Kaufman Assessment Battery for Children (K-ABC) [36], Malawi Developmental Assessment Tool (MDAT) [37] and the Mullen Scales of Early learning [38]. These assessment tools have strengths and limitations. K-ABC for instance has been widely used in diverse cultural contexts as its subsets make limited demands on verbalization, which is a significant advantage when working with young children [39]. However, the strength of this tool is also linked to its limitation. This assessment emphasises nonverbal intellectual abilities, thus limiting the ability to measure a child's verbal intelligence [40]. It also requires a highly trained psychologist or examiner to interpret the scores of the test. The MDAT tool, developed by Gladstone et al [41] in Malawi, was designed to be culturally appropriate for the rural sub-Saharan African (SSA) setting. It has good reliability and takes approximately 30 minutes to administer. It also has clear pictorial representations of many of the items in the tool, making it easy to use. Although the MDAT demonstrates high sensitivity (97%) [41], it still needs to be validated to identify those with more subtle developmental delay which are more difficult to detect. Despite this limitation, it was developed in Malawi, and may be the most appropriate tool to use in African settings ensuring cultural appropriateness and more representative normative data for such setting.

The Mullen Scales for Early Learning child assessment tool is another widely used cognitive measure, which assesses a child's abilities in visual, linguistic, and motor domains. This tool differentiates between receptive and expressive language processing for infants and preschool children from birth through 68 months [38]. The

theoretical foundation of the Mullen Scales is based on the concept that a child`s intelligence is conceptualized as a network of interrelated but functionally distinct cognitive skills. In addition, the Mullen scales is very detailed and able to identify in which domain developmental delays are occurring. Results from the assessments are reported using T scores to allow interpretation of child scores and target intervention with an emphasis on a child's strengths as building blocks for weaker areas [42]. Each subscale of the tool is standardized to calculate a standard score, percentile and age-equivalent score. The standardization sample for the Mullen Scales included 1849 US children 2 days to 69 months of age [38]. Although this tool was developed in the USA and uses American reference norms to compare child scores, it has been widely used in a variety of populations in Africa to assess cognitive development of infants, toddlers, and young children [43-46]. Several studies on child cognition and neurocognitive development have been conducted by researchers using the Mullen scales for assessing development of HIV affected children in Uganda [44-46], and in intervention studies aimed at child development outcomes and growth in Africa [47]. Other researchers from South Africa have tried to create a translated and culturally and linguistically adapted Mullen tool for South African language [48]. Nonetheless, the use of a potentially culturally inappropriate American tool and normed using North American children remains a limitation. New norms for the target culture must be developed. Further limitations of this tool and development of a shortened form items for screening purposes will be discussed in detail in **Chapter 5** of this thesis.

1.5 HIV and child development

The human immunodeficiency virus (HIV) was first identified in 1984. In 2019 approximately 36.9 million people worldwide are estimated to be living with HIV [49] including 2.1 million children (<15 years) [49], with the majority (81%) of new paediatric HIV infections occurring in children living in Africa [50]. HIV hinders the normal growth of children and prevents those infected and affected by the virus from achieving optimal development outcomes. There is substantial evidence documenting the negative impacts of HIV on child development outcomes, particularly cognitive development [51-57]. Data from multiple studies describing developmental trajectories of HIV positive and HIV-exposed uninfected (HEU) infant's cognitive

development have described the risk of developmental delay and impairment in both groups of infants [54, 55, 58, 59] compared to healthy control infants [57], in resource-limited settings [60-62]. Further research suggests perinatally infected children face greater risk of neurological and neuropsychological deficits compared to HEU infants. These neurological and cognitive dysfunctions have been documented in up to 80% of HIV positive children [54, 63]. These dysfunctions may be due to direct effects of the virus on the central nervous system (CNS) and the brain structures involved in the regulation of emotion, behaviour, and cognition [55, 58, 64-66], exposure to treatment or other HIV related factors. Other studies show that despite successful initiation of antiretroviral treatment (ART), HIV positive children had high levels of persistent neurocognitive impairment [67, 68] that was attributed to the direct neurotoxic effects of HIV infection, resulting in permanent structural CNS damage prior to the initiation of ART or incomplete penetration of the blood-brain barrier by antiretroviral agents [69].

HIV also impacts the neurodevelopment of children indirectly through its negative influences on the child's living environment [57]; children living in HIV affected households are more likely to experience poverty, food insufficiency, community stigma and discrimination, caregiver unemployment, caregiver illness and bereavement [28, 62, 67, 70-72]. In resource limited settings, where poverty and chronic illness such HIV occur, the negative effects on child development are mediated through reduced resources and psychosocial factors associated with reduced parental responsiveness [28] [62].

HIV clusters in families, and many of the burdens, such as community stigma and discrimination, caregiver unemployment, caregiver illness and bereavement, separation and rejection are well documented additional issues that children infected by and exposed to HIV have to navigate [28, 62, 67, 70]. In communities where HIV is widespread, it’s expected that almost everyone is severely affected, even households without HIV-positive members [70]. These HEU children are indirectly affected by HIV and may experience food insecurity in household, poor health and undernutrition, reduced levels of care and stimulation, responsibilities such as caring for an ill family member as well as psychosocial impacts derived by community stigma and caregiver mental health issue such as abuse, trauma, stress and a loss of social connectivity [70].

Furthermore, HIV is often paired with other morbid illnesses in these settings. The cost of medication and lack of appropriate resources for obtaining treatment on top of financial strains, may lead to manifestation of other comorbidities, including poor mental health, in such vulnerable HIV affected communities. Some of the documented risk factors associated with HIV infection for child cognitive or developmental delay including parental risks such as, mental health disorders and poverty [62], will be discussed in depth later in this chapter (**sections 1.6-1.9**).

1.6 Maternal mental health and child development

Chronic conditions such as HIV infection/AIDS can negatively affect the mental health status of an individual. It is common for mental health problems to occur as risk factors for HIV infection, coincidentally with HIV infection, or as a result of HIV infection and its complications for people living with HIV. It is reported that people living with HIV have a higher risk of developing mental health symptoms than those who are HIV negative [73], with depression and depression symptoms being amongst the most common mental disorders reported by people living with HIV (PLWH) [74]. These depression and stress symptoms are likely to emerge or worsen during pivotal disease points such as HIV antibody testing, declines in immune status, and occurrence of opportunistic infections [75] .

The term common mental disorder (CMD) is widely used to describe a cluster of symptoms indicative of disorders such as depression, anxiety, and somatic symptoms of poor mental health [76]. Studies from low-and middle-income countries (LMICs) indicate CMDs are common in women during pregnancy and during the postnatal period [77]. These maternal CMDs can lead to enduring effects on subsequent child development, independently of the social adversity experienced in such settings. Research shows infants of mothers with CMD tend to have poorer motor, cognitive, and socio-emotional development than children of mothers in good mental health [78, 79]. Maternal CMD has also been associated with prolonged labour, low birth weight, child ill health, and child undernutrition, all of which are established risk factors for poor child development [80-84].

The association of maternal stress and anxiety with child developmental outcomes [79, 85] has been established in the general population [86]. Exposure to maternal depression and stress has shown to have a negative influence on child development in infancy and early childhood [7], and is associated with impaired cognitive performance leading to social, behavioural problems and compromised physical health [87-90]. Additionally, it affects a broad range of parenting skills, which are negatively associated with poorer parent-child communication, poorer and less consistent parenting discipline leading to child problem behaviours [85]. A South African study found that maternal depression was related to increased parenting stress and parent–child dysfunction which was again associated with children's behaviour and functioning [91]. Another study examining maternal depression and caregiving during the first year of life in England, found that maternal depression was associated with poorer caregiving of children and that the poorer caregiving was subsequently associated with poorer language development, through an indirect pathway [92].

Further longitudinal cohort studies in LMICs reported that exposure to maternal mental health in the first years of life increased the risk of poor growth and cognitive development and continue to negatively influence child trajectories, persisting across the first eight years of life [93]. The persistent effects of poor maternal mental health on child growth and cognitive development are consistent with a life-course epidemiological framework where negative exposures in vulnerable periods of development can have impact through long periods in a child's life [94].

The impact of maternal mental health on child outcomes starts as early as pregnancy. Studies suggest prenatal exposure to maternal stress and depression through elevated levels of stress hormones during pregnancy has negative consequences on child outcomes [88, 95, 96], and is a determinant of motor and mental development delay in infants [97]. Other studies show a strong association between maternal depression and infant underweight, birth weight, and stunting [98-100] - all directly related to unhealthy development [84]. The relationship between poor maternal mental health such as stress and depression symptoms and child cognitive performance at baseline and after receiving an intervention (12 months later) will be investigated in this thesis (**Chapters 6** and **7**).

1.7 Common mental disorders and HIV

Mental illness and HIV makes substantial contributions to the burden of disease in SSA [101]. There is evidence from South Africa highlighting the high burden of mental health symptoms among individuals who were older in age, less formally educated, and caregivers of young children living in societies plagued by poverty [102], HIV and violence [103].

The psychosocial impact of an HIV diagnosis, an often stigmatized disease, presents a significant stressor that may increase the prevalence of mental disorders for PLWH [101, 104]. This is supported by findings that show HIV positive individuals are more likely to experience CMDs such as depression, anxiety, psychosis and have poorer quality of life [105]. The risk of CMDs is even greater among pregnant HIV positive women who reported higher levels of anxiety, emotional distress, and overall morbidity [106, 107] than those without HIV. These levels of psychiatric morbidity were high in a Zimbabwean sample with 24.3% of HIV positive participants experiencing psychiatric symptoms/signs such as emotional withdrawal, depressed mood, and suicidal thoughts compared to 16.5% who were HIV negative [108]. Other studies suggest that the presence of CMDs such as depression and anxiety speed the progression of HIV disease [109-111].

Despite advances in HIV treatment, mental health burden such as suicide (which includes suicidal ideation, suicide attempts and completed suicides), remains elevated for PLWH in comparison with their HIV negative counterparts [112, 113]. While suicidal ideation is not always a predictor of suicidal behaviour, it is an important risk factor that requires early detection and should act as a trigger for intervention [114]. Risk factors for suicidal ideation in PLWH in SSA include younger age [114, 115], being unmarried and depression [115, 116]. A study of PLWH in Nigeria found that lifetime suicidal ideation was associated with marital status (i.e. being separated, never married, or divorced), and with major depressive episode [116]. Suicidal ideation among PLWH has also been linked to other factors such as lack of social support [115, 117], fear of HIV status disclosure and stigmatization [118]. Poverty further exacerbates the mental health burden among PLWH particularly in resource limited settings [119]. Increased negative life events and the associated stress in addition to

food insecurity all increased the risk of suicidality in studies from Uganda, Peru and Ethiopia [120-122]. Another study investigating predictive models for suicidal ideation and attempted suicide among women living with HIV in the United States, found that AIDS diagnosis, physical or sexual abuse, unemployment and children were all significant predictors of suicide ideation and attempts [123].

The relationship between maternal mental health burdens such as suicidal ideation and other CMDs and the growing child's cognitive development over time, in the context of HIV will be explored further in this thesis (**Chapters 6** and **7**).

1.8 Poverty and child development

Poverty increases young children's exposure to biological and psychosocial risks that affect development through changes in brain structure and function [124], and behavioural changes [28]. It is thought that children in the context of poverty who are exposed to multiple stressors and risk factors are more susceptible to poorer developmental outcomes. Most children seem to show resilience and no long-term negative consequences. However some studies report that exposure to poverty during early childhood is associated with changes in brain development [96], neurocognitive differences (smaller white matter, cortical grey matter, and hippocampal and amygdala volumes) and socio-emotional development measured at school age and early adolescence [95, 97]. Additionally, socioeconomic status of a household was reported to be an indicator of early neurocognitive performance in infants, particularly in neural processing of language and executive functions [96, 125, 126].

Poverty fuelled undernutrition during early childhood may have long-term and irreversible effects on a child's brain development, health and productivity in adulthood [127]. Poor infant nutritional status (stunting and under-weight) is a well-documented risk factor for both cognitive and motor developmental delay [21, 28]. Previous studies have used stunting (height-for-age Z score < −2, based on the WHO growth standard) as an indicator of chronic undernutrition in children [128, 129]. Several studies show early stunting to be associated with poor test performance, less schooling, and low earnings in adulthood [20, 93], and noted that these effects extended into subsequent generations [130, 131]. This was highlighted by a study in

Jamaica which showed parental stunting to be associated with lower cognitive performance in their offspring [132]. Another study found that nutrition played a role in child cognitive development the first 2 years. Of note appropriate stimulation given to children during the first 5 years was found be more beneficial than nutritional support on subsequent development [133] emphasising the role of early child stimulation for adequate development.

1.9 Parenting style and child development

Parent-child interactions during their first years of life are predictive of children's rate of development throughout the three years [134-136]. Positive parenting is generally conceptualized as involved, nurturing, and accepting behaviour [129]. Parenting style of a warm, encouraging and responsive nature alongside adequate cognitive stimulation that encourages infants' immature skills can provide a strong foundation for later development, and facilitate growth in social–emotional and cognitive domains [134, 136-138]. However, parenting skills can be compromised in the presence of factors such as depression and stress [85, 139], negative perception of caregiver's child-rearing experience, or beliefs and attitudes that detract from a parent's sense of importance in their child's life [140]. Parents with high levels of distress tend to be less responsive to their infants and have a negative view of their role as parents [18]. However, whether parenting style mediates child behaviour or vice versa is inconclusive. There is evidence of a circular relationship between child behavioural problems and parenting style. Studies show that parents who report their children as difficult tend to report elevated stress or anxiety and tend to exhibit inconsistent discipline as well as paying more attention to negative behaviours and attribute them to the child [16, 141].

In the presence of HIV, parenting may be challenged and disruptions to parenting may occur as a result of direct or indirect effects of parental HIV infection. Often a diagnosis of parental HIV infection is associated with decreased social support, high levels of stigma, poorer nutrition as well as economic and employment consequences and negative effects on parental mental health [142]. Parental depression is associated with poor adherence to ART, low clinic attendance, and lower levels of exclusive

breastfeeding [143]. These negative effects all compound each other to compromise children's development.

HIV affects parenting ability and strategies in a number of ways that may affect optimal child development. Parenting itself can be a difficult task in resource-limited settings with poverty and harsh conditions being an everyday reality, however for parents living with HIV or caring for a HIV positive child they face additional challenges [85]. HIV positive mothers rearing young children are not only confronted with demands of parenting, but also with an illness that can lead to unpredictable medical, emotional, or social crises. Such demands affect the HIV positive woman's mental health as well as her role functioning [144]. Thus, parenting skills among families affected by HIV need special attention as they have the potential to compromise child outcomes.

Although studies looking at the effect of parenting on child outcomes focus on maternal aspects, fathers can play an integral role in enhancing developmental outcomes for children. Research suggests that paternal caretaking activities and emotional support for a partner are important factors directly related to infant neurodevelopment [44]. Furthermore, parents (mother or father) living with HIV may also be distracted with their own physical and mental health concerns. These factors can potentially affect the quality of care and attention devoted to the child [79, 89, 145, 146]. Other challenges that affect parenting quality in the context of HIV include stigma and discrimination [72].

1.10 Interventions for improving child development outcomes

Effective interventions to mitigate the effect of HIV on the early development of children are available [147, 148] and investing in early interventions for these children can lead to improvements in their survival, health, growth, and cognitive and social development [23]. Children who receive assistance in their early years tend to thrive and achieve greater success in life and as adults have higher earnings than those who do not have these early opportunities [27]. Findings from a study in a low income country (Jamaica) show that a simple **psychosocial stimulation** intervention in early childhood for disadvantaged children can have a substantial effect on labour market

outcomes and can compensate for developmental delays twenty years after the intervention was conducted [27].

Researchers also report that **parenting** interventions can be effective in both changing parenting behaviour [149] and subsequently enhancing a number of child outcomes [145, 146, 150], in both resource rich and resource poor settings [151]. For example, a randomised controlled trial (RCT) in South Africa reported the benefits of providing **support and home visits** to HIV affected mothers by community health workers (CHWs). The home visits and the number of visits by the CHWs were found to be associated with children's cognitive development at 18 months [146]. Another home visiting intervention study showed the cognitive development and child growth among children born to mothers with antenatal depressed mood can be improved by mentor mother home visitors [152]. These home visits encourage caregivers to become more receptive and to engage with their children resulting in better parenting style, and indirectly improving child development. Other intervention studies report the benefits of **caregiver training** programmes for the developmental enhancement of HIV positive and HIV exposed children in low-resource settings [46, 153-155]. Such interventions emphasise the quality of care provided and train parents to become aware of and develop practical strategies for focusing, exciting, expanding, encouraging and regulating the child as learning opportunities arise in the course of their natural everyday interaction [46, 153-155]. The change in the quality of care provided by parents again indirectly impacts child development. These type of caregiver targeted interventions are effective and beneficial approaches for enhancing both caregiver and children outcomes simultaneously.

Social protection interventions such as cash transfer programmes as well as being effective approaches for long term poverty alleviation [59] can improve cognitive outcomes (when combined with attentive parenting) in children affected with HIV [156]. Conditional cash transfers have been widely used in HIV affected families in SSA and have been shown to positively impact the education, health and nutrition of children living in these settings. Such cash transfer programmes are associated with reported reduced hunger and increased average number of meals per day in beneficiary households [157]. Increasing household food security decreases the risk of child undernutrition, which in turn affects cognitive development.

Other alternatives include the **Internal saving and lending schemes** (ISALS), which are community-based programmes that provide access to micro-credit and insurance to vulnerable communities. These self-sufficient programmes unlike conditional or unconditional cash transfers, do not usually require external borrowing or donations [156] and improve economic resilience in disadvantaged populations. Members participating in an ISALS can access the funds and borrow without interest in emergencies and have been incorporated in several intervention programmes previously. Such schemes are popular in Zimbabwe, particularly in rural areas as they impose few transaction costs on members, help build mutual trust, and foster reciprocity that can be called upon in times of difficulties and emergencies [158].

Evidence on the importance of ECD interventions and the associated benefits for disadvantaged children has been described above. In **Chapter 2** of this thesis, I will systematically review available literature on the effectiveness of interventions aimed at improving cognitive outcomes of children, specifically for HIV infected and affected children.

1.11 Zimbabwe

Zimbabwe is a landlocked southern African country with a total land area of 390,757 square kilometres, and an estimated population of 14 million [159]. The capital and largest urban city is Harare. Zimbabwe has 16 official languages, with Shona, Ndebele and English the most widely used languages in the country [159].

Figure 1.1: *Location of Zimbabwe*

*Source: Amsterdamcg, design by Wordpress Themes (*https://www.geographicguide.com/africa-maps/zimbabwe.htm)

Zimbabwe experienced a collapse of the economy and infrastructure between 2001 and 2009, further worsened by hyperinflation, high unemployment, political violence, unprecedented cholera outbreak and recurrent drought [160-162]. The socioeconomic meltdown shattered the livelihoods of the majority of its urban and rural population resulting in extreme poverty and led to a near-total collapse of the public health system [162]. In 2015, after a period of recovery, Zimbabwe's economy began another downward trend that saw a decline in gross domestic product growth due to a drought and fall in commodity prices [163]. In addition, in 2017 the country experienced a period of political instability where long time President Robert Mugabe was replaced by President Emmerson Mnangagwa [164]. The political instability and protracted economic under-performance throughout the previous decade worsened the rate of unemployment, poverty, food insecurity, shortage of health care workers and essential drugs have mutually exacerbated each other [162].

The severe social and economic challenges in the country have resulted in the deterioration of the already fragile health care infrastructures and decline in the quality of health services provided [165]. Some of the challenges that the health care services in Zimbabwe face include a shortage of skilled professionals and health-care staff a worn down infrastructure with ill-equipped hospitals, and a lack of essential medicines and commodities[165] [166]. The system breakdown has been exacerbated by humanitarian crises such as cholera and measles epidemics between 2008 and 2010, by poor maternal and child health services and by consistently falling but nevertheless still-high numbers of people living with HIV.

The majority of the population in Zimbabwe living in rural areas, and it is estimated that 14% of the health facilities are located in urban areas while 86% are in rural areas. However, user fees at different levels of health care limit access to health care for poor people who are not able to pay. The Zimbabwean government policy is to provide free-of-charge health services for pregnant and lactating mothers, children under five and those aged 60 years and over, however this policy has proved to be difficult to implement. Although reports by the Ministry of Health and Child Care (MoHCC) for the period of 2016-2018 indicate that a recent abolition of user fees has been a main driver for people coming in numbers to the health facilities [167]. There are other challenges that prevent access to health services for some of the vulnerable groups in rural settings. These include transport to reach facilities, money for emergency transport in case of referral, access to food and clean water sources, and gender issues including male partners' knowledge [167, 168].

Mental health services are even more scare in Zimbabwe with only six public institutions with psychiatric beds available [169] and eleven registered psychiatrists in the country. The economic conditions have meant that there are limited material and human resources to provide adequate mental health services in the country [165] [167]. Due to the harsh economic conditions, mental health service provision continues to face limited material and human resources, lack of collaboration in service provision, scanty research, stigmatization and discrimination against service users, compromised rehabilitation services and a complication of the HIV/AIDS pandemic which is linked to mental health . In addition, mental health practice in the

country remains largely focused on institutions and with very limited community based services available [165, 168].

1.12 HIV epidemic in Zimbabwe

Zimbabwe is one of the countries with the highest HIV burden in SSA. The main mode of HIV transmission is through heterosexual sex with women disproportionately affected, and with a concomitant epidemic in children through vertical transmission (during pregnancy, childbirth or breastfeeding) [170]. Southern Africa has consistently accounted for the highest number of children living with HIV and the highest number of AIDS related deaths [170]. In 2018, the HIV prevalence was estimated to be 12.7% among 15-49 year olds, with 38,000 people newly infected and 22,000 people estimated to have died from AIDS-related illness [171]. UNAIDS reports that in 2018 there were 4,800 children aged 0 to 14 newly infected with HIV and 84,000 children currently living with HIV. New HIV infections among young women aged 15–24 years were higher than those among young men: 9,000 new infections among young women, compared to 4,200 among young men [171]. UNAIDS further estimated that 19,000 adults aged 15 and over, and 3,300 children aged 0 to 14 died due to AIDS in 2018. In 2018 the number of children (aged 0 to 17) estimated to be orphaned due to AIDS was 580,000 [171].

The high burden of HIV observed in this region could be attributed to several overlapping risk factors; these include poverty, social and political instability, lack of male circumcision, high levels of other sexually transmitted infections, deeply embedded cultural practices and norms, high mobility, and resistance by the some governments to acknowledge HIV risk factors (particularly sexual behaviour) thus delaying implementation of appropriate intervention. However, Zimbabwe has been at forefront of HIV prevention efforts in the region for some decades. The country has committed itself to ending AIDS by 2030 and have a number of programmes implemented in recent years; these include social behaviour change interventions, voluntary medical male circumcision, and condom promotion and free distribution [172]. Zimbabwe seems more likely to achieve HIV epidemic control by 2030 than its southern African neighbours.

In addition, the current global focus in HIV treatment and prevention efforts is on the 90–90–90 targets, which ambitiously envision that by 2020, 90% of PLWH will know their HIV status, 90% of people who know their HIV-positive status will be accessing treatment and 90% of people on treatment will have suppressed viral loads [173]. Zimbabwe is one of the countries in the region that is getting closer to reaching this target. In 2018, 90% of PLWH knew their status [171]. Of all adults aged 15 years and over living with HIV and who knew their status, 89% were reported to be on treatment, while 76% of children aged 0–14 years diagnosed and living with HIV were on treatment [171].

1.13 HIV prevention and MTCT in Zimbabwe

Nearly all young children with HIV are infected through mother-to-child transmission (MTCT) which refers to transmission of HIV from an HIV-positive woman to her child during pregnancy, labour, delivery or breastfeeding [174]. There has been a decline in MTCT of HIV in recent years, with 80% of pregnant women living with HIV globally receiving effective ART in 2017. Overall 91% of HIV positive pregnant women globally live in SSA [175]. Furthermore, global trends in MTCT of HIV show disproportionate number (88%) of all children younger than 15 years living with HIV living in this region [176]. UNAIDS reports that, in Zimbabwe, there were 4,800 children newly infected with HIV and an estimated 850,000 children who are HIV exposed but uninfected in 2018 [171].

In an effort to prevent mother-to-child transmission (PMTCT) of HIV [177], Zimbabwe adopted the World Health Organization 2010 guidelines (Option A) in 2011, where eligibility for ART or therapy was determined by CD4 count and WHO clinical staging; and in the case of breastfeeding infants, they receive infant NVP syrup from birth until 1 week after cessation of breastfeeding [178]. As a result there has been notable reductions in the mother to child transmission rates in recent years [179]. The WHO further consolidated new guidelines in 2013 recommending the provision of lifelong ART to all HIV-positive pregnant and breastfeeding women in high HIV burden settings, regardless of CD4 count or clinical stage (Option B+) [180]. Option B+ provides protection against MTCT of HIV in current and future pregnancies, reduction of transmission of HIV to discordant sexual partners, and increases access to early ART

treatment initiation [181]. In 2014, Zimbabwe implemented Option B+ guidelines and treatment was provided in all 1,560 health facilities nationally [182]. This has had substantial impact on reducing mother to child transmission [180], with UNAIDS estimating mother to child transmission in Zimbabwe to be 6.74% in 2017 [183].

Nonetheless, a number of expecting mothers continue to be missed with prevention, accounting for new paediatric infections [183]. The Zimbabwean Ministry of Health estimates that in 2015, only 54.9% of infants born to HIV-positive mothers receive an HIV test within the first two months of life [172]. Children at risk face several barriers to access HIV testing, treatment consequently care and support. Caregiver reluctance to get HIV tests for their children to avoid issues such as discrimination and stigma, could be one explanation. Once tested, the delay in return of test results can act as an additional barrier.

Overall, the roll out of Option B+ strategies in pregnancy is predicted to decrease the prevalence of HIV infection in children over time, and consequently may lead to many HIV exposed children being born to HIV positive mothers with supressed viral load, resulting in a shift in prognosis and outcomes for children. The ratio of HEU children compared to prenatally infected children will continue to increase.

1.14 Thesis rationale

Global research indicates that the first years of life are pivotal for children's development, with the first three years being the most critical years in shaping their brain functionalities. There is strong evidence for investing in early childhood development, particularly for children living in low-income countries such as Zimbabwe characterised by poverty, HIV, economic and political instability. Furthermore, it is well documented that children who are HIV exposed but uninfected, as well as those who are living with HIV, have increased risk of cognitive delay. Effective HIV prevention such as adopting Option B+ have recently been introduced in an effort to eliminate MTCT in Zimbabwe and globally. HIV treatment is anticipated to affect health outcomes for caregivers of HIV exposed children, but the strains of an HIV diagnosis may still be high and may influence the quality of childcare and stimulation. Additional contextual factors such as maternal mental health status and parenting style may influence the cognitive development of such children. There is a paucity of research that explores the relationship between maternal mental health factors and the cognitive performance of HIV exposed children living in Zimbabwe, where mental health burdens are high among communities living with HIV. The mechanisms by which these factors affect child development is still unclear.

1.15 Thesis aims and objectives

This introductory chapter outlines how cognitive development of children affected by HIV is influenced by a wide range of biological and environmental factors. There are several possible mechanisms for this: direct effects of HIV exposure on the developing brain, indirect effects due to different parenting, and indirect effects due to maternal stress and mental health, all of which were discussed in this introductory chapter. With this in mind, I aim to investigate the relationship between maternal mental health and cognitive development of children in their first three years of life, and in the context of HIV. I use secondary data from the Child Health Intervention for Development Outcomes (CHIDO) trial in Zimbabwe. The trial evaluated a multi-component parenting and child intervention designed for a HIV affected population. The CHIDO intervention package was hypothesised to improve early childhood development indicators, enhance retention in health care for mothers living with HIV (including post-natal care, timely linkage to and retention in HIV care and adherence to ART) as well improving household food security and other measures of economic resilience.

My thesis will focus on understanding the relationships between maternal mental disorders such stress, depression, and suicidality, and early child cognitive development. The specific objectives of my thesis are to:

- review the impact of interventions on cognitive development of HIV positive and HIV-exposed uninfected (HEU) children in sub-Saharan Africa;
- assess the cognitive profiles of the HIV positive and HEU infants at enrolment into the CHIDO trial, compare cognitive scores to a normative US dataset;
- interrogate the full cognitive measure used in the trial for understanding the feasibility of short form development, which may be of great utility for lay health workers in resource limited settings;
- investigate what maternal mental health factors are associated with child cognitive performance in the study sample at baseline;
- investigate the association of maternal depression and common mental disorder symptoms over 12 months period with child cognitive scores;
- investigate the association between maternal suicide ideation and child cognitive development over 12 months period;

- finally, make recommendations for improving child cognitive outcomes in resource-limited settings.

1.16 Thesis hypotheses

The direct neurological effects associated with HIV infection, environmental challenges associated with HIV exposure, and in addition lack of adequate child stimulation due to poor maternal mental health will negatively affect child cognitive development.

CHAPTER 2: The impact of interventions on cognitive development of HIV infected and affected children in sub-Saharan Africa: a systematic review

The previous chapter describes the different factors (biological and contextual) and issues relating to cognitive development of HIV exposed children in resource limited setting. In this chapter I systematically review literature on trials of interventions aimed at enhancing child cognitive outcomes that have been evaluated for use in sub-Saharan Africa.

2.1 Introduction

The early years of childhood are seen as the foundation of intelligence, personality, social behaviour, capacity to learn and future self-nurturing [16]. A child in the early years is particularly sensitive to adverse events [23], making this a very important period in which to address their needs and those of their caregivers. The current literature emphasises the importance of the amount and quality of stimulation provided to children in the early years [27], as well as support and nurturance provided by caregivers [26, 30]. Deficiency in any of these domains can potentially compromise optimum child development [23], affecting subsequent generations, perpetuating a negative cycle of economic and health disparities [16, 29].

HIV affects child development adversely and prevents those infected and affected by the virus from achieving optimal child development outcomes [54, 55, 58, 65]. This has been discussed thoroughly in **Chapter 1** (**section 1.5**). Sub-Saharan Africa (SSA) carries a disproportionate burden of HIV, accounting for more than 70% of the global burden of infection, although it is home to only 12% of the global population [49, 170, 184]. Nonetheless, the scale up and widespread coverage of ART has led to a substantial decline in new HIV infections [170], by reducing transmission generally, and mother to child transmission specifically. Several studies across SSA have provided empirical evidence of the benefits of early ART initiation to HIV positive individuals [185-188]. In general, increasing access to ART for children in low-income countries has significantly impacted the prognosis for HIV positive children leading to more children surviving to adulthood. Yet these children face disadvantages inflicted by HIV, directly or indirectly as they transition into adolescence and adulthood.

Delayed cognitive development, poor expressive and receptive language development and motor development skills are some of the direct impacts of HIV on neuro-development of paediatric patients [54, 62, 67, 189, 190]. Although early diagnosis and treatment can mitigate these delays to some extent [182]. However, these delays are not confined to children living with HIV; those exposed in utero, but uninfected are also affected. Studies show that both HIV positive and HIV-exposed uninfected (HEU) children experience developmental challenges and impairments compared with HIV-unexposed infants [54, 55, 58, 60, 67] in resource-limited settings [60, 61]. HIV-positive

infants however have significantly lower scores on developmental assessments compared to the HEU group [54, 59]. A small cross-sectional study in Zimbabwe investigating the difference in cognitive development of HIV exposed and infected (HEI) infants and the development of HEU infants reported that the HEI group had cognitive delay, including language and motor delay, all of which were significantly worse from the development of the HEU group for all domains [54]. The mean developmental delay measured using the Bayley Scales of Infant and Toddler Development for the HEI group was approximately two months below their mean chronological age for all scales [54].

Nonetheless, early identification of such developmental delays or problems can lead to further developmental and clinical evaluation, diagnosis, and treatment including early developmental interventions. The term Early Intervention typically refers to services given to young children that might require specialised care, generally from birth until the child turns three. The aim of early intervention in children's lives is to promote optimal early child development (ECD) and consequently avoid or reduce future risks to the child's health, growth, and cognitive and social development [23]. The recent Lancet series highlights the importance of ECD and points to the great investment opportunity for intervening at this time [14, 26, 191]. It is also well established that early childhood stimulation (ECS) and interventions to promote such stimulation can have far-reaching positive outcomes [15, 20, 30, 192, 193]. However, many HIV affected children younger than 5 years living in low-income and middle-income countries (LMICs) are still not able to access ECS and reach their potential.

Other available interventions to improve early child development include supporting caregivers' capacity through home visits, cash transfer systems, and legal protection strategies [15, 194, 195]. In addition, studies in low income countries demonstrate that the benefits of caregiver or child targeted interventions are sustained over the long term with improvements in cognitive and developmental outcomes in children from socially disadvantaged populations [15, 20, 30, 150, 192, 193]. For example, a home stimulation programme taught to South African caregivers was found to significantly improve cognitive and motor development of HIV positive children under 3 years old [196]. Studies assessing long-term outcomes from other low-income countries also highlight the importance of such child stimulation interventions for long term

economic benefits child. A study in Jamaica evaluated the long-term impact of an early childhood psychosocial stimulation intervention, which taught parenting skills and encouraged mothers and children to interact in ways that develop cognitive and socioemotional skills, on earnings of stunted children after two decades. This small study found that 20 years after the intervention was implemented, the earnings of the stimulation group were 25% higher than those of the control group and caught up to the earnings of a non-stunted comparison group [27]. The quality of caregiving provided to HIV positive and affected children also plays a role in achieving optimal developmental outcomes [46]. Current literature suggests that parenting interventions can be effective in both changing parenting behaviour [149] and subsequently enhancing a number of child outcomes [145, 146, 150].

Family-based preventive interventions have shown to have potential for promoting family functioning and mental health in HIV-affected children, including addressing behavioural problems that increase risk of HIV infection [197-199]. Policies and interventions which provide support to families, such as paid parental leave [200], time at work for breastfeeding [201], and the provision of free pre-primary education [202], have also proven to have beneficial impact on families and enable them to care for their young children in ways that promote development [191]. Other community programmes such as Internal saving and lending schemes and cash transfer programmes, provide access to micro-credit and improve economic resilience [59] as well as improving child developmental outcomes for HIV affected populations in resource limited settings [156].

The studies discussed above show that a psychosocial stimulation intervention in early childhood for disadvantaged children can have a substantial effect on future outcomes and can compensate for developmental delays. In addition to this a systematic review conducted by Sherr et al. (2014) identified four rigorously evaluated interventions which had been delivered either to the child or to the family/caregiver and significantly improved children's cognitive and motor development [147] [196, 213-215]. However, this systematic review was not confined to LMICs and was completed in 2014. It also covered age groups from 0-18 and was thus not confined to early child development. With this in mind, an updated systematic review was conducted to identify the available effective interventions and their impact on early childhood development,

specifically the cognitive development of HIV positive or HIV-exposed uninfected children (under 5 years old) in sub-Saharan Africa. The search was restricted to papers from 2010 onwards.

2.2 Methods

Literature searches were carried out using the following electronic databases on the 3rd May 2019: PubMed, Cochrane Library, and PsycINFO. The main search terms were: "HIV infected and affected children", "interventions", "cognitive development" in SSA and were entered into search engines with variations to accommodate different databases. A variation of the terms ''child", ''HIV'', "cognitive development'', ''intervention", and ''Africa'' were entered in the search engines (see Appendix for full list of search terms). Reference lists from key articles, books and review articles were also scanned to identify further peer-reviewed studies for possible inclusion. The search was restricted to papers from 2010 onwards and aimed to update the previous review, focus on the younger child (aged 0-5 years old) and confine the search to SSA [147].

2.2.1 Criteria for inclusion and exclusion

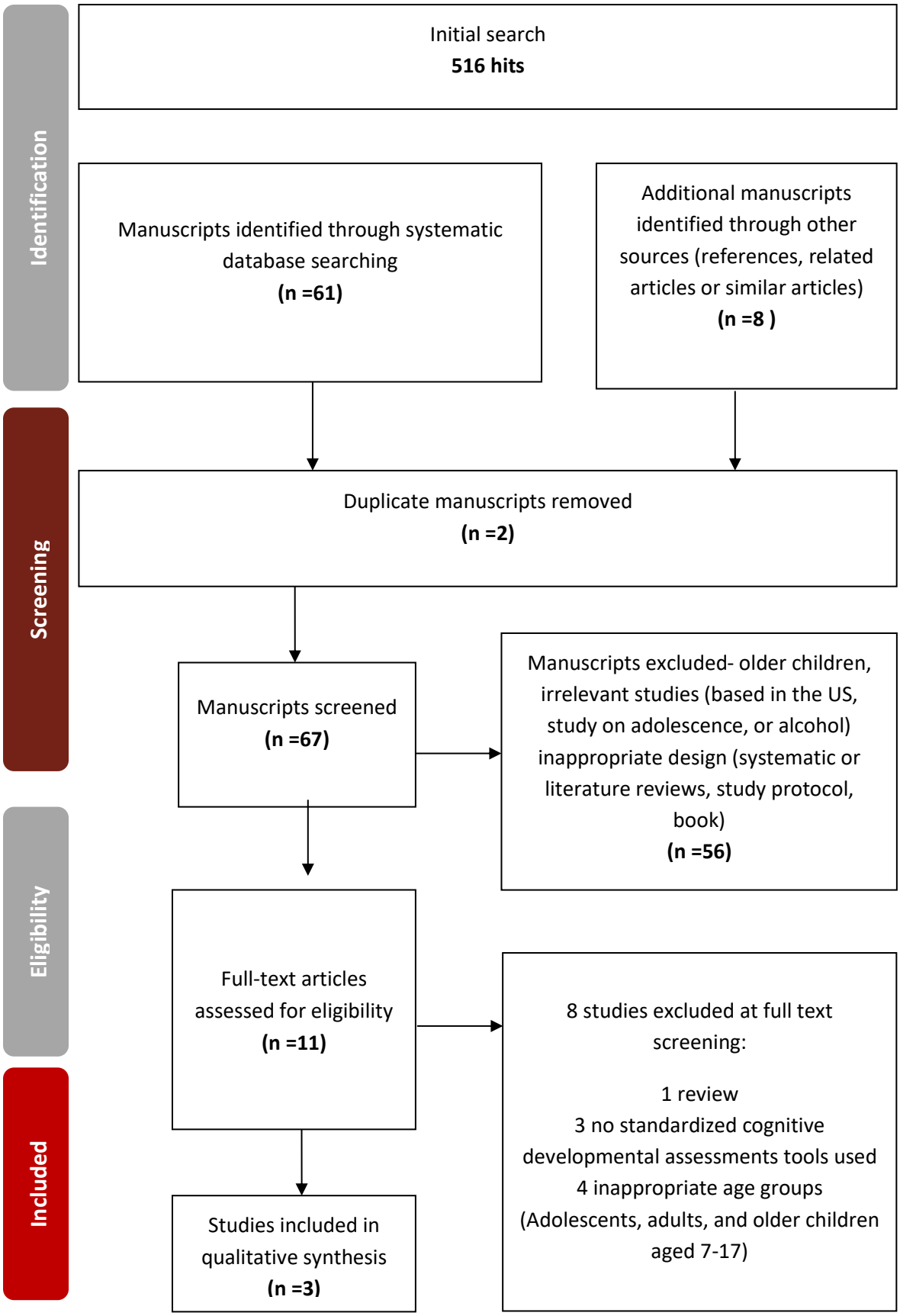
Only peer-reviewed articles presenting empirical evidence from the year 2010-2019 were included in this review. This was to ensure only articles with high quality evidence are included and due to restriction of budget and time limit for translating articles in different language, only English-language articles have been included here. Studies were included if they assessed change in cognitive development using a valid assessment tool following an intervention in HIV positive or HEU children in SSA. The SSA region consists of 48 countries according to the World Bank list [203]. The full list of countries can be found in **Appendix 1**. SSA region was chosen in this review due to the high burden of HIV infection in the area and because the majority of children with HIV live there [49]. The following study designs were included; longitudinal studies, randomized controlled trials (RCT), and pre-post designs. Uncontrolled studies were not included in this review as the aim was to explore the impact of interventions on child developmental outcomes using a comparison group; this would reduce risk of biases and enable me to explore the effectiveness of interventions appropriately.

Participating children had to be 0 to 5 years of age as these are considered to be the early childhood development years. Studies that included the age group specified in the review in addition to children over the age of 5 were excluded, as it would have been difficult to disaggregate by age. Children had to have a confirmed HIV positive status or to be confirmed as HIV exposed through their biological mothers who were HIV positive. A comparison or control group had to be included. Studies needed to use standardized developmental assessments tools for measuring cognitive development of the children. A cognitive measure was defined as a valid measure scoring any aspect of cognitive functioning of the children (i.e. memory, executive functioning, language acquisition, comprehension and decision-making). Interventions were defined as the participating child or caregiver receiving some form of mediation intended to enhance either child's development or caregiver/household current situation.

2.2.2 Search strategy

Initially, key terms entered into a database (PubMed) identified 516 records. This was followed by systematically reviewing the three databases and a total of 61 hits were generated as a result of the search (**Figure 2.1**). A further 8 items were identified through supplementary searches mainly by following up references of relevant articles. Duplicate records were identified and removed. The titles and abstracts of the remaining 67 articles were screened for eligibility. Following the exclusion of non-relevant records, 11 items remained, and full texts were read. After further scanning, 8 non-relevant items, either due to study design or age criteria, were excluded. Three studies met the eligibility criteria for inclusion and were subjected to detailed data abstraction (**Table 2.1**).

***Figure 2.1**: Flowchart- Interventions to enhance child cognitive development systematic review- study selection*



2.2.3 Data extraction

A search of available literature as previously outlined was conducted, and relevant papers were selected. Information on search strategies used, data extraction and reporting findings for papers included in the final analysis were documented (see **Appendix 1**). Full details of papers selected listing the full reference, country of study, study population, intervention used, cognitive assessment measures and outcomes were compiled into a single table and reported (see **Table 2.1).**

2.2.4 Quality assessment

Appraising the quality of evidence collected is an important consideration in research. Thus the quality assessment of the selected studies was carried out using the Standard Quality Assessment Criteria for evaluating primary research papers [204]. This tool assessed the quality of the evidence and methods used to collect the data in the three studies. Each paper was given a total summary score and a liberal cut-off point (0.55) was used for inclusion of studies in the systematic review. This cut-off point was used due to the restrictive and highly specific inclusion criteria chosen already. This assessment was carried out by two independent researchers and any discrepancies between scores were discussed and harmonized.

2.2.5 Risk of bias

The studies included in this review were independently assessed for risks of bias using the Cochrane assessment tool [205]. An informed analysis was made on allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. This was followed by categorizing the selected studies into high, low or unclear risk of bias.

2.3 Results

Studies selected in this review were based in two SSA countries: Uganda and South Africa and consisted of interventions aimed at HIV positive [153] or HEU [206, 207] children. The age range of participating children ranged from 6 weeks to 5 years (**Table 2.1**). Two of the studies were part of the same cluster- randomised controlled trial (registered under same Identifier-NCT01640561 on the Clinical Trials website) [153, 206] and were based in Uganda. Both studies used the same Meditational Intervention for Sensitizing Caregivers (MISC) intervention [208]. The trial population comprised of caregivers, and their HIV positive or exposed children aged 1 to 5 years old (n=341). However, supplementary publications which explored a series of outcomes from this database were identified in this review. For the purposes of the systematic review this was treated as a single intervention trial, but informed by multiple papers.

The South African study used a massage therapy intervention aimed at HEU infants [207] and was a prospective individually randomised controlled trial [207]. All three studies included control groups. Participants in the intervention arm had the same control condition in all studies, where nutritional supplement or food parcels/ formula for infants were provided in addition to the intervention.

***Table 2.1**: Summary of studies and interventions aimed at improving cognitive development of HEU and HIV positive children*

Study	Sample size analysed	Comparison group	Interventions	Cognitive measures	Results
Bass et al. Uganda (2017)	HIV +ve children (aged 2-5 years), N=118 (58 intervention, 60 control)	Receiving nutrition and hygiene information	MISC (a training programme which provides caregivers with strategies for enhancing the development of their children through day-to-day interactions at home, based on Feuerstein's [209, 210] theory of cognitive modifiability)	MSEL [38] HOME [211] COAT [212] BRIEF [213] Early Childhood Vigilance Test [214, 215]	Children receiving MISC intervention had a significant improvement on receptive language score at 12 months [adjusted mean difference=3.13; 95% CI: 0.08 to 6.18] compared to control group; but it did not remain statistically significant at 24 months (adjusted mean difference=2.56; 95% CI: 0.50 to 5.63).
Boivin et al. Uganda (2017)	HEU children (aged 2-3 years), N=221) (122 intervention, 109 control)	Receiving nutrition and hygiene information	MISC	MSEL HOME COAT	The greatest differences between children in the MISC and comparison arms were in the domain of child language acquisition, particularly receptive language. The gains on receptive language scores were noted during mid intervention and post intervention but this

				BRIEF Early Childhood Vigilance Test	difference was not statistically significant at either time point and was not sustained at 24 months.
Perez et al. South Africa (2015)	HEU children (aged 6 weeks-9 months), N=111 (54 intervention, 57 control)	Receiving food parcels and formula for infants as part of a prevention of mother-to-child transmission (PMTCT) programme	Massage therapy	Griffiths Scales of Mental Development [216]	The massage therapy infants showed a higher mean difference between the 6 weeks and 9-month quotients and percentiles for all five scales compared to the control group. There was a significant improvement in the mean difference in scores for the hearing and speech quotient (11.2 vs. 21.9; $p < 0.03$) and the general quotient percentile of the Griffiths Mental Development Scales (7.7 vs. 19.3; $p = 0.03$) in the massage therapy group compared to control group.

2.3.1 Outcomes measures

Bass et al. (2017) and Boivin et al. (2017) reported data collected as part the same RCT in Uganda, thus the same outcome measure tools were used. These included the Mullen Scales of Early Learning (MSEL), the Color-Object Association (COAT), Caldwell Home Observation for the Measurement of the Environment (HOME), the Behavior Rating Inventory of Executive Function (BRIEF) and the Early Childhood Vigilance Test.

Perez et al. (2015) used the Griffiths Scales of Mental Development (Griffiths Scales) for the developmental assessment of infants [216]. The Griffiths Scales provides standardized mental development norms from typical British children and have been previously validated across different cultural groups in South Africa [217, 218].

A detailed description of all the cognitive measurement tools used in the three studies is provided in **Table 2.2**

Table 2.2: Summary of child cognitive measures and their descriptions

Study	Cognitive measures used	Description of measures
Bass et al. (2017) **Boivin et al. 2017)**	MSEL	MSEL is an individually administered comprehensive measure that assesses a child's abilities in visual, linguistic, and motor domains, and distinguishes between receptive and expressive processing for infants and preschool children from birth through 68 months [38]. The MSEL is based on the theory that a child`s intelligence is most accurately conceptualized as a network of interrelated but functionally distinct cognitive skills. It consists of five distinctive cognitive domains; gross motor skills, visual reception, fine motor skills, receptive language, and expressive language [38].
	COAT	COAT measures immediate memory and overall total recall of infants and young children aged 18-36 months, using object placement in colored boxes [212].
	BRIEF	BRIEF evaluates behavior, attention and cognitive problems related to disruption of executive functions as reported in a series of questions to the main caregiver provider; and was assessed by generating a combined Global Executive Composite score [213].
	HOME	HOME measure was used to assess the quality of child–caregiver interactions in the home using a 45 dichotomous "yes/no" items, consisting of seven subscales: availability of learning materials, language stimulation, appropriate physical environment, caretaker responsivity, academic stimulation, parental behavioral modeling and variety in activity and environment. Higher scores of 'yes' answers indicate higher quality interactions [211].

	Early Childhood Vigilance Test	The Early Childhood Vigilance Test was also used to assess and evaluate the vigilance of preschool children [214, 215]. Children's attention span was assessed by measuring the proportion of time spent looking at an animation video.
Perez et al. (2015)	Griffiths Scales of Mental Development	The scale measures the rate of development of infants and young children from birth to 8 years, assessing children's strength and weakness in several developmental areas such as: the Locomotor (assesses gross motor skills, including the ability to balance and to co-ordinate and control movements); Personal-Social (measures proficiency in the activities of daily living, level of independence and interaction with other children) ; Hearing and Language (assessment of hearing, expressive language and receptive language); Eye and Hand Co-ordination (such as fine motor skills, manual dexterity and visual monitoring skills); Performance (assesses the developing ability to reason through tasks including speed of working and precision) ; and Practical Reasoning (measures the ability of a child (2 to 8 years) to solve practical problems, understanding of basic maths concepts and understanding of moral issues). As the infants in the study group were below the age of 2, five of the main areas (excluding practical reasoning) were evaluated and raw scores generated. The raw scores of the five sub-scales were standardized and relayed in terms of quotient, and were used to compare performance of infants at different time points [216]. A global score (general quotient) was generated from the mean score of the five subscale scores and used to measure the overall performance of children [216].

2.3.2 Intervention effect on child outcomes

Both the Boivin and Bass papers evaluated the MISC intervention. The MISC [208] is a training programme which provides caregivers with strategies for enhancing the development of their children through day-to-day interactions at home, based on Feuerstein's [209, 210] theory of cognitive modifiability. Mothers/caregivers are taught how to focus a child's attention, excite a child's interest, expand their cognitive awareness, encourage their sense of competence, and regulate behaviour during play, feeding, bathing and working. The comparison arms in both studies received a manualized nutrition and hygiene information program designed for impoverished households provided by the Uganda Community Based Association for Child Welfare Program.

Bass et al. (2017) reported on the effectiveness of a year-long caregiver training intervention in improving caregiver mental health, quality of caregiving, and child neurodevelopmental outcomes in Ugandan children living with HIV. Participants were 120 women and child dyads recruited (only 118 dyads began intervention) over a 12-month period. Eligible children had confirmed HIV and were between 2 and 5 years of age. Dyads were randomly allocated to two arms: MISC treatment (n=58) or comparison arm who received a nutrition curriculum (n=60). MISC training was provided in 1- hour sessions biweekly. Data were collected at baseline, 6 months (midway through training), at 1 year (completion of training), and at a 24 months. The primary outcome measure was the change in child Neurodevelopment assessed using MSEL at 24 months. At 24 months there were no differences between the two trials arms in MSEL scores or any other outcomes.

Boivin et al. (2017) assessed the effectiveness of delivering the healthy nutrition and cognitive stimulation interventions separately, evaluating their comparative effectiveness in promoting healthy child development and caregiver mental health. The study population consisted of 221 mothers living with HIV and their HEU children aged 2-3 years in a rural district of Uganda. Child eligibility was based on confirmed birth to an HIV-positive mother with the child confirmed as HIV negative with enzyme-linked immunosorbent assay by the study medical officers. 18 clusters were subsequently randomized 1:1 to 2 caregiver training treatment arms (MISC or nutrition

curriculum comparison arm). In Bass et al. (2017) study, an hour-long biweekly individual training session were conducted with caregivers over a period of 1 year. The interventions were delivered by trained Ugandan psychology or social work graduates. Data were collected at baseline, 6 months (midway through training), 1 year (post training), and 2 years after baseline. There were no differences between trial arms on the primary outcomes of MSEL mean composite scores, COAT total recall or the Early Childhood Vigilance Test scores between the two groups at 24 months. However, MISC children had significantly higher BRIEF global executive function scores than comparison group at follow-up (MISC group: 56.8 vs. Comparison group: 52.7; p<0. 01).

Perez et al. (2015) study was a prospective randomized controlled trial aimed at promoting growth and development of HEU children in South Africa. Participating HIV positive mothers and their children were allocated to massage therapy or control group. Mothers in the massage therapy group were taught to massage the face, limbs and back using firm pressure by a team member who was trained by an experienced massage therapy teacher of the Allied Council of Alternative Therapies. The mothers were provided with plain carrier massage oil with no essential oils added and advised to massage their infants for 15 min daily. The need to massage their babies was reinforced at each visit; massage oil was issued when needed. Mothers in the intervention arm were followed up at the clinic every 2 weeks. If they failed to attend the clinic, the community health worker visited their homes. The primary outcome was the scores of Griffiths Scales (general quotient) at and 9 months visit.

Of the 171 mother-infants dyads recruited, 9 infants who tested HIV positive (on PCR) were excluded, leaving 161 dyads. The Griffiths Scale was conducted on 157 (84 controls and 73 massage therapy group) HEU infants at 6 weeks of age. At 9 months, 111 HEU infants (58 controls and 55 massage therapy group) were reassessed using the Griffiths Scale. At 9 months, infants in the massage therapy scored higher in the mean quotient (118.9) for the hearing and speech (Griffiths sub-scale) compared to control group (109.9) (p = 0.002). There was no evidence of difference in the other sub-scales between the two study groups at 9 months follow-up.

2.3.3 Study limitations

Although both Bass et al. (2017) and Boivin et al. (2017) studies were nested within one trial, used the same intervention and outcome measures, however strangely they split trial participants into two groups and report the results of the studies as two separate trials. This is a limitation as the criteria in this review was inclusion of studies of RCT nature only. In addition, both studies used a control group which was receiving a different form of intervention (nutritional supplement) rather than the standard of care, making it difficult to assess the true impact of the MISC intervention. Although there would be ethical implications of withholding both interventions for a study group (i.e. HEU and HIV-positive children) known to be at risk of developmental delays.

Bass et al. (2017) and Boivin et al. (2017) studies tested multiple outcomes, increasing the probability of chance findings, this could explain the significant findings mid-intervention. It is common practice for researchers to specify a small set of measures to serve as the primary outcomes, with another often longer set listed as secondary outcome [219]. Some of the outcome measures used in those studies such as the MSEL and COAT may be culturally inappropriate as they were developed in the USA and use US reference population to compare scores of the children. It is important to use culturally appropriate assessment tools and have locally validated norms.

In Perez et al. (2015) study, the infants were reassessed after a relatively short period of follow-up (at 9 months) and reported improvements in hearing/speech in the intervention group. The literature shows that child development, in particular verbal, will take time to fully be realized. A longer follow-up period would have been useful to assess the true impact of the intervention on children's hearing and speech development. Additionally, mothers participating in this study were recruited from a PMTCT programme during their pregnancy. However, post-natal care provided (such as formula feeding supplements) by the PMTCT programme at their primary health care clinic was not controlled for in both study groups. This could have affected some of the child development outcome. Small sample size was used in this study with only 111 infants assessed on the Griffiths scales at 9 months follow-up. Such small samples can undermine the internal and external validity of the study. The HIV status of the infants was not checked after the baseline assessments at 6-weeks. Infants should

have undergone a confirmatory HIV test after residual maternal HIV antibodies have declined.

2.3.4 Data quality assessment

Data quality of the selected three papers was examined using the Standard Quality Assessment Criteria for evaluating primary research papers. Papers were scored depending on the degree to which the specific criteria were met ("yes" = 2, "partial" = 1, "no" = 0). Items not applicable to a particular study design were marked "n/a" and were excluded from the calculation of the summary score [204]. A summary score was calculated for each paper by summing the total score obtained across relevant items and dividing by the total possible score (**Table 2.3**).

This assessment was done by two independent researchers and results discussed. There were discrepancies in the overall score for Perez et al. 2015, which mostly reflected differences of opinion on the applicability of certain items to specific study designs and on the assignment of "No" versus "partial" to the fulfilment of specific criteria in the checklist. This was discussed, harmonised and results of the quality assessment are shown in **Table 2.3**. The quality scores were checked against the threshold (0.55) decided for inclusion of studies in this review.

Table 2.3: *Quality of data summary*

	Total sum (no of Yes *2) + (no. of partials*1)	Total possible sum (28-(no. of N/A *2)	Summary Score (total score/total possible (sum)
Bass et al. (2017)	23	28	0.82
Boivin et al. (2017)	23	28	0.82
Perez et al. (2015)	22	26	0.85

2.3.4.1 Allocation

All three studies included in the review stated that random allocation was used. The randomisation procedures were adequately described in the methods for all three studies.

2.3.4.2 Blinding

Data collectors and staff conducting the child assessments were blinded to cluster allocation in the Ugandan studies by Bass et al. (2017) and Boivin et al. (2017).

The researchers conducting infant assessments were blinded to study intervention arm in the South African study by Perez et al. (2015). Issues relating to bias and blinding of researchers were also highlighted in the study methods.

2.3.4.3 Incomplete outcome data

There was limited information and data on attrition provided by two of the studies (Perez et al 2015; Bass et al. 2017). In Perez et al (2015) study, the attrition rate was high with 35% (60/171) of infants lost to follow-up. Information on the participants lost to follow-up would have been useful for investigating any differences in characteristics compared to those retained in the study.

In Bass et al. (2017) study, they report 10% (12/118) of children did not complete the follow-up assessment (24 months after baseline). Information on those lost to follow-

up and reasons for drop out of the study were provided as supplementary information, however characteristics of those lost to follow-up were not provided. Boivin et al. (2017) presented data of participants lost to follow-up and provided reasons for study attrition observed across the two study arms.

2.3.4.4 Selective reporting

All studies were judged as low risk mainly due to the availability of sufficient information on the methods for two of them (Boivin et al. 2017; Bass et al. 2017), and CONSORT criteria for reporting trials were followed. The study by Perez et al. (2015) reported on the study outcomes mentioned in the methods.

2.3.4.5 Other potential sources of bias

All three studies were given an unclear status as other potential sources of bias were not discussed. For example, selective reporting of results, which favour the interventions measured in each study was observed.

2.4 Discussion

The aim of this systematic review was to explore interventions available to improve child cognitive development in sub-Saharan Africa.

Interventions to improve cognitive performance in the last nine years were examined in this review. Two interventions were identified in SSA. The massage therapy intervention had a positive impact on expressive language and receptive speech of the HEU children. Whereas in Boivin et al. (2017) and Bass et al. (2017) studies, the results show that MISC had no additional benefits over a less intensive health and nutritional information and support intervention aimed at enhancing child cognitive outcome. Both of these studies investigated child outcomes after 24 months, i.e. 12 months after intervention completion and neither found a significant effect. The effectiveness of interventions can often vary depending on beneficiary or community characteristics. Optimal uptake of ECD interventions offered to HIV positive individuals and their children in rural settings for instance might be impossible due to fear of stigma. These could have led to the interventions provided here being ineffective. Alternatively, this could be due to the fact that this group of children are compounded by other factors

associated with HIV, have different health needs, and may require complex interventions tailored to their needs.

Boivin et al. (2017) and Bass et al. (2017) used a combined caregiver-child intervention compared to Perez et al. (2015) which used child targeted intervention. Another key difference between the two approaches was use of early intervention (6 weeks to 9 month) by Perez et al. (2015) compared to interventions given to older children (2-5 years) in the other two studies. Previous reviews show that there are successful strategies for reducing cognitive delay in HIV positive and HIV exposed negative infants [147]; mainly aimed at children before the age of 3 which consequently improve cognitive and socioemotional development and later academic performance [220]. Although there was a high drop-out rate in the study, the study by Perez et al. (2015) did show that child targeted intervention had an effect on child language. These findings are supported by a past review that shows the positive impact of interventions on child cognitive development [147].

The studies included in this review were based in two SSA countries and although both countries (South Africa and Uganda) have a high burden of HIV, it is difficult to generalise findings to other SSA countries with different economic background, HIV treatment and prevention policies as well as HIV transmission trends. However, despite the well-known high burden of HIV in SSA, only two intervention studies aimed at enhancing child development outcomes were identified in the last decade. There was also a total absence of evaluated interventions in Zimbabwe. Overall, it seems that evaluated effective interventions may be scarce for HEU and HIV positive children in the current setting. If effective interventions were put in place, alongside early identification and treatment of HIV, this would possibly remedy the long-term psychological and socioeconomic challenges associated with developmental delays in HIV exposed children [220].

Furthermore, the paucity and limitations of the intervention trials reviewed here, suggest there is a clear need for intervention research to develop and evaluate culturally appropriate interventions for such HIV affected and infected children from SSA. Different approaches and multicomponent interventions need to be investigated. Comprehensive or multilevel intervention such as family-level intervention,

community-level intervention, or some combinations of these approaches might result in better outcome for these vulnerable populations [147]. Yet these approaches are not commonly used in the field. This could partially be due to lack of resources and funding restriction for such holistic interventions.

2.4.1 Review limitations

There were some limitations, including inclusion of papers published in English language only. There could be articles with interesting findings on different types of interventions and their impact on cognitive development of HIV positive or HEU children from different regions, as well as in different languages such as French. The studies included the age group specified in the review in addition to children over the age of 5 were excluded, due to the difficulty of disaggregating the data by age .

2.4.2 Conclusions

Interventions aimed at improving development outcomes of children affected by HIV directly or indirectly can be beneficial. However, in this review when the effectiveness of interventions to prevent cognitive delay in HIV affected children were explored, the evidence presented were ambiguous and discouraging. The current literature reviewed indicates that well designed intervention trials aimed at enhancing HEU children developmental outcomes in the last nine years are scarce. The two studies identified from Uganda were part of one trial, and limitations in the data analyses and study design were observed in the South African study. There was also disagreement on which tools effectively assess cognitive development of children in African countries, yet we continue to use tools normed using data from children in high income countries. Therefore, despite the five year follow up from the previous review by Sherr et al. [147], it seems that not much has changed. There is still a growing problem affecting these HIV exposed children, yet there is limited evidence and guidance on what intervention works for this group. There is still a specific need for evaluated interventions in SSA for this group of children.

There is growing evidence showing the importance of ECD interventions and the associated gains for children generally, thus identifying effective and scalable interventions for this growing number of HEU children is critical and opportunities to

intervene must not continue to be missed. Further research is desperately needed as children in resource limited settings compounded by adversities are still at risk of not reaching their developmental potential and lagging behind their peers [221].

CHAPTER 3: Setting the scene for the PhD – Background

3.1 Chapter overview

In this chapter, I set the scene for my PhD research. This PhD project was nested within a large trial set in rural Zimbabwe. This chapter will provide a brief background to the trial, and the rationale behind the project. I will summarise the aims and objectives of the trial, and describe the design, methods and intervention components. The published CHIDO trial protocol is presented in **Appendix 2** and contains detailed information on the identification of the sample population, method of sample selection, power calculation, statement of ethical approval and data processing. The study questionnaire is presented in **Appendix 4**.

An overview of the data management tasks undertaken, as well as variables used in this thesis and their definitions, are also described in this chapter.

3.2 Background to the CHIDO trial

Many children in sub-Saharan Africa face severe challenges that affect their development, particularly at the beginning of life. Southern Africa has a generalised HIV epidemic. The current prevalence of HIV is estimated to be 12.7% among 15-49 year olds in Zimbabwe [171].

There is good evidence that early child development is a marker of future child achievement. Furthermore, child stimulation and interventions to promote such stimulation have positive effects [15]. The recent Lancet series has highlighted the issues of early child development and point to a great investment opportunity at this time [14, 79]. Disruptions to parenting may occur as a result of direct or indirect effects of parental HIV infection. Reviews and randomised controlled trials which highlight the benefits of parenting interventions for both parental wellbeing and child outcomes are available [146, 147, 222, 223].

Developmental challenges have been well documented in both HIV positive and HIV exposed children [51, 62, 148, 224]. The mechanisms are unclear. Exposure to the virus, antiretroviral therapy (ART), or living in a family with HIV may all contribute. Effective interventions to mitigate these developmental challenges are available, and when implemented by the caregivers of HIV positive and HIV exposed children, it can improve their performance [60, 147, 152, 206, 223].

Against this background, the CHIDO trial was implemented. The aim of the trial was to evaluate a complex community based group intervention comprising parenting/child development training, coupled with training in economic strengthening and support for HIV case management among HIV positive women with young children. The hypothesis was that this intervention would result in improved child development outcomes, retention in HIV care and adherence to ART (for both mothers and HIV positive infants), as well as improved household food security.

3.3 Aims and objectives

The overall aim of this trial was to determine the impact of a comprehensive community-based intervention which was set up to simultaneously enhance child stimulation, reduce economic insecurity and improve retention in care among HIV exposed and infected children.

The specific objectives of the trial included:

- Measure the impact of a comprehensive multicomponent parenting plus economic strengthening intervention on caregiver and child cognitive development outcomes,
- Conduct a process evaluation to explore acceptability and feasibility of the intervention.

3.4 Methods

3.4.1 CHIDO trial setting and population

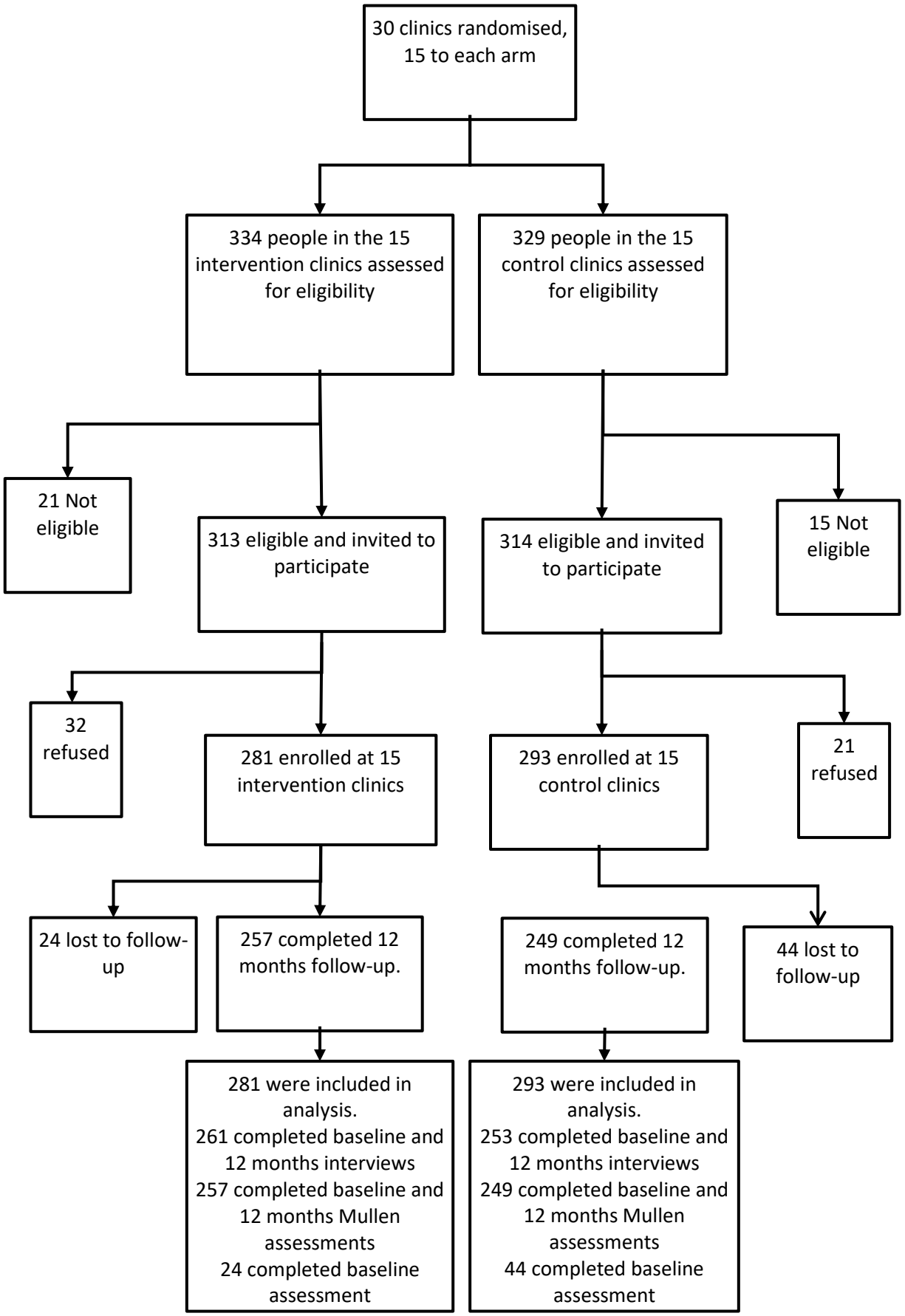
The study was a cluster-randomized controlled trial in 30 clinic sites in two districts (Goromonzi and Mudzi) in Zimbabwe to evaluate the impact of a complex intervention. Mapping of all clinic clusters within the two districts was conducted before recruitment and enrolment in each district. Among the mapped clinics, those with more than 30 annual deliveries were included in the randomization process.

The trial population comprised of primary caregivers (biological mothers and other caregiver), and their HIV positive or exposed children aged 0 to 24 months.

3.4.2 Recruitment and enrolment

A list of eligible infants was extracted from the 'Exposed Infant Registers' at each selected clinic, comprising the name of the biological mother, village, name of the child, date of birth of the child, clinic number of the mother and contact details. Of those eligible women approached and invited to participate in the trial, 97 (14.5% of those eligible) refused enrolment, following the orientation meeting. The 30 clinics and their surrounding catchment areas were randomised into two arms; the usual care arm or the CHIDO intervention arm (**Figure 3.1**).

Figure 3.1: *A flow chart of participant recruitment and enrolment in CHIDO trial*



3.4.3 CHIDO intervention components

3.4.3.1 Usual care arm

Clinics in the usual care arm provided the Ministry of Health and Child Care (MoHCC) standard of care for women living with HIV and their HIV exposed and/or infected children aged 0-24 months delivered according to 2015 National ART guidelines.

3.4.3.2 Intervention arm

In addition to usual care, caregiver-child dyads in the intervention clinics received the CHIDO intervention, a community-based, group intervention. The intervention had three components;

I) Parenting classes to promote early childhood stimulation, which included an evidence-based curriculum to support the promotion of cognitive stimulation, increase the use of positive discipline by parents and improve the nutritional status of children. This was developed and piloted for acceptability and feasibility from existing Zimbabwean (adapted to be age-appropriate) and international materials to strengthen parenting skills. The goals of the curriculum were to a) improve parental promotion of cognitive stimulation; b) improve the nutritional status of children; c) increase the use of positive discipline by parents; and d) enable parents to understand and support the socio-emotional, physical and cognitive development of their children. The ECS curriculum had 18 ninety-minute sessions. A Community Case Worker (CCW) experienced in ECD training, and who received further training and supervision to support caregivers of 0-24 month old facilitated the group. A nurse from the local clinic ran some of the medical sessions in the curriculum. The CCW from that community also attended the sessions and assessed the extent to which lessons learnt were then implemented in the home setting when they conducted their home visits. Where mothers needed guidance on the implementation of lessons learnt the CCW provided assistance.

II) Internal savings and lending scheme to build economic resilience where caregivers in each ECS groups joined an ISALS group. The main aim was to increase household income to enable them to meet costs such as transport to a health facility, clinic user fees, medication and food. These caregivers grouped themselves from within the ECS

group into 6-10 members and agreed to meet fortnightly to save money. Caregivers were trained on how to set up a group, develop a constitution, take meeting minutes and run the ISALS. All groups had different savings options. They could either contribute a set amount to a savings pool at each meeting; or a set amount at the first meeting only; with members able to apply to borrow (and repay) money to cover essential expenditure. If participants were too poor to contribute to an ISALS, they were allowed to earn money through community work to raise their first instalment. Thus, those too poor to contribute were enabled to join and save together with those who could afford to join initially.

III) Case Care Worker to support participants engagement with and retention in HIV care e management. Caregiver-child dyads recruited to the intervention arm of the trial were supported by CCWs to access paediatric (and adult) HIV services within a continuum of care through the case management system. CCWs within the local communities (also referred to as village health workers) with home-based care experience, received additional one-week training in ECS and providing adherence support. Home visits by CCWs supported adherence to ART and retention in care, attendance of caregivers and children at fortnightly meetings, as well as monitoring uptake of parenting skills training within the home environment. These activities complemented the monthly review and adherence support provided at the health facility.

3.4.4 Outcome measures

The primary outcomes of the trial were measured 12 months after baseline (4.5 months post-intervention completion) and included:

3.4.4.1 Cognitive development

The age-standardized Early Learning Composite score was assessed for all infants at baseline and endline. Trained assessors (independent of the implementers) used the Mullen Scales of Early Learning [38] focusing on the four cognitive scales (visual reception, fine motor, receptive language, and expressive language). The Mullen scales is based on the theory that a child's intelligence is most accurately conceptualized as a network of interrelated but functionally distinct cognitive skills [38, 45]. It is an

individually administered comprehensive measure that assesses a child's abilities in visual, linguistic, and motor domains, and distinguishes between receptive and expressive processing for infants and preschool children from birth through 68 months.

3.4.4.2 Retention in HIV care

This outcome was assessed by looking at the proportion of HIV exposed or infected children with full retention in care (>80%) of scheduled visits at 12 months. This was assessed by monitoring HIV testing among infants who were HIV negative at enrolment and medication adherence through clinic and patient records of antiretroviral drug refills/collection as well as self-reported patient questionnaire.

Secondary outcomes of the trial included viral load measurement of HIV positive infants (> 1000 copies per ml), maternal viral load measurement, ART adherence and retention in care for both the HIV positive mothers and the HIV positive infants, parental stress levels and mental health status of caregivers, household food security status and nutritional status of the infants.

3.4.5 Randomisation process

Thirty clinics were randomised 1:1 to CHIDO intervention or usual care. The imbalance between the study arms was minimised by using restricted randomization, taking into account the number of HIV exposed infants per clinic and the district.

3.4.6 Baseline and endline assessments and data collection

Enrolment of participants at baseline and data gathering commenced on January 2016 and was completed in September 2016. Data collected included demographic, socio-economic, maternal mental health and household food security information. Maternal mental health was assessed using the Edinburgh Postnatal Depression Scale (EPDS) and 8-item Shona Symptoms Questionnaire (SSQ-8), and parental stress using the Parental Stress Index Short Form (PSI-SF).

All participating caregiver-child dyads were allocated a unique identifier to ensure patient confidentiality. Data were collected using an interviewer-administered questionnaire and Audio Computer Assisted Survey Instrument for the sensitive parts

of the caregiver questionnaire. The developmental assessment of the child was undertaken using the Mullen scales by a trained assessor.

After baseline data had been gathered, intervention implementation commenced within three months of participant enrolment in all communities and ran between March 2016 and July 2017. The endline survey was conducted between April 2017 and January 2018 among enrolled caregiver-child dyads, with pairs of intervention and control trial sites being assessed at the same survey venue to minimise risk of unblinding of assessors. Survey procedures were as described at baseline.

At endline a dried blood spot sample was collected from all biological mothers to determine HIV viral load and infants to test for HIV antibody status and viral load. Programme attendance records and village health care worker diaries were reviewed, and data were double entered into appropriate databases.

3.5 Research ethics and approval

The trial and associated research presented in this thesis were granted ethical approval by the Medical Research Council of Zimbabwe (MRCZ/A/1943), Research Council of Zimbabwe, University College London (6789/002) and London School of Hygiene and Tropical Medicine (9912). Copies of the ethical approval letters can be found in **Appendix 5.**

The trial was retrospectively registered with the Pan African Clinical Trials Registry (www.pactr.org), registration number PACTR201701001387209, on 16th January 2017 (**Appendix 5**).

All participants were given information about the trial and asked to provide written informed consent to participate. Informed consent was collected according to Good Clinical Practice guidelines. All patient identifying information was removed and dataset anonymised before undertaking any analysis.

3.6 Data management

Mavambo Orphan Care in Zimbabwe undertook the implementation of the programme in the field with technical assistance from World Education. The Centre for Sexual Health HIV/AIDS Research (CeSHHAR) Zimbabwe undertook all aspects of research implementation including working with MoHCC, community sensitisation and entry, community randomisation, enrolment, data collection, follow-up and process evaluation. I worked closely with both teams for the data management aspect of my PhD.

I received the CHIDO baseline data in two batches (1st batch data on 344 dyads and 2nd batch data on 230) over a period of 3 months (July-September 2016). Questionnaire data were collected electronically and directly entered onto tablets pre-programmed using Open Data Kit by trained interviewers. Range and consistency checks were incorporated. However, inconsistencies and errors in several variables (infant's reported age and adjusted age, Mullen raw and T-scores for the 5 domains) were noted. I worked with the field team, data managers and project coordinators in Zimbabwe to rectify these issues. Following rigorous data checks, the final baseline dataset was available for use on 5th October 2017.

The follow-up data were received in April 2018, and I was involved in minimal data management tasks. These included errors detected within the range of each variable categories, where data entry personnel had coded a participant as 999 for a particular variable, indicating missing data. This was dealt with mostly by communicating with the data manager at CeSHHAR and investigating the participants' original scanned questionnaires.

Further analysis was carried out using the dataset that involved creating secondary variables for my PhD research questions. The variables used for analysis in this thesis are described in the following **section (3.7)**.

3.7 Definition of variables

Table 3.1 below describes the variables selected for analysis in this thesis. The definition for each variable and where it was obtained from is also described.

Table 3.1: *Selected variables for all analyses carried out in this thesis*

	Variable definition
Child related variables	
Age	The child's age was obtained from several records. Age was reported (in months) by caregiver on enrollment. However, when the birth date and date of Mullen assessment/interview were used to double check, there were inconsistencies and another variable (adjusted age) was created to use for analysis. Age was mainly reported as a mean (months) as well as categorically (0-<6 months, 6-<12 months, 12-24 months).
Gender	The child's sex was recorded upon enrollment to the trial.
HIV results	This was used for generating child's HIV status variables at baseline. This information was originally only self-reported with no funding to collect data on all infants at enrolment. Following enrolment we raised funds to collect a dried blood

	spot samples from infants to test for HIV antibody status post baseline and from mothers and infants at endline to test for HIV status and viral load.
Birth weight	The baby's weight at birth was reported by the caregiver (in kilograms) and was also cross-checked with weight provided during the Mullen assessments. There were some outliers identified which were rectified after communication with data management personnel.
Growth rate	This was obtained from child's health card provided by caregivers on enrollment and consisted of three possible responses: I) normal, II) moderately underweight or III) severely underweight.
Mullen domains (visual reception, expressive language, expressive language, fine motor, gross motor)	The cognitive profiles of the participating children were assessed using the Mullen Scales of Early Learning. The test scores obtained by the children for each Mullen scale were transformed into an age-standardized T-score, using a US reference population as there was no local Zimbabwean reference population on this index. The standardized T-scores of four components - the fine motor, expressive language, receptive language, and visual reception scales were combined to produce the composite score. Composite scores were used in this analysis to measure general cognitive functioning. Gross motor scale was not included in the ELC score and was used separately as an indicator concentrating on their motor skills [34, 251].

Examiner	The person (mainly 2 trained nurses, and occasionally the trial coordinator) who conducted the Mullen assessments at baseline and 12 months follow-up. This variable was used to identify inconsistencies and issues with child cognitive scoring (i.e. if the child scores by the two assessors were noticeably different). Where possible the same examiner tested child at baseline and endline and was blind to intervention arm status.
Caregiver related variables	
Age	This was obtained from participants on enrollment to the trial where they were asked how old they were on their last birthday.
Caregiver type	Biological mother vs. other type of caregivers (mainly grandmothers)
HIV test	Biological mothers enrolled in the study were asked when they had their last HIV test (before pregnancy, during pregnancy, or following pregnancy).
Marital status	Participants were asked about their marital status. During analysis marital status variable was recoded to: I) married or II) not married (this included those divorced/separated, widowed or never been married).
Education level	Participants were asked what their highest level of education was. During analysis a secondary variable was produced, with responses divided into two levels:

	I) without secondary level of education (i.e. no education or just primary school level) or II) secondary level and above (including higher education diploma or degree)
Employment status	Participants were asked if they were currently employed at the time of study and there were 3 possible responses to this question: yes formally, yes informally and no. During analysis, those responding yes formally or yes informally were combined into one category allowing binary responses (i.e. yes or no).
Edinburgh Postnatal Depression Scale	The Edinburgh Postnatal Depression Scale (EPDS), a postpartum depression-screening questionnaire that has been validated for use in Zimbabwe [225, 226] was administered to participating mothers. The EPDS comprises of 10 questions which generate scores ranging from 0-30. The literature provides a cut-off point ($\geq$12) indicating concerns for referral. These cut-off levels used in past research in similar settings found that this threshold was effective in detecting woman with major, and minor depression with sensitivity of 80% [227]. The EPDS scores also allow for a categorisation into 4 levels: none or minimal (EPDS scores 0-6), mild (EPDS scores 7-13), moderate (EPDS scores 14-19) and severe depression symptoms (EPDS scores 20-30) [139]. The EPDS was not used as diagnostic tool in this research and was used as screening tool for identifying those reporting depression symptoms.

Parental Stress Scores	Parental Stress Index-Short Form (PSI-SF), a self-completed screening tool, was used for identifying different types of stress associated with parenting [228]. This index comprises of 3 subscales: Parental Distress, Parent–Child Dysfunctional Interaction and Difficult Child. Child and Parent domains were combined to form the Total Stress Score. These were scored using the following 5-point scales: (strongly agree, agree, not sure, disagree, and strongly disagree) and generate scores ranging from 40-149. Mean scores were used to report this measure with higher scores indicating higher levels of parenting stress.
Shona Symptom questionnaire-SSQ-8	Common mental disorder symptoms were assessed using the locally developed and validated Shona Symptom Questionnaire (SSQ)-8 [19]. This short form is derived from the longer SSQ-14 version. Scores ranged from 0-8, and scores $\geq$6 were used as a cut-off point for identifying those at risk of CMD. The SSQ-8 tool measures risk of CMD and is not diagnostic.
Suicidal ideation	Suicidal ideation was measured as thoughts of self-harm during screening using a self-reported questionnaire based on the EPDS [225, 226]. The EPDS scale contains a specific target item (item 10-“The thought of harming myself has occurred to me”) which assesses suicidal ideation [229-231] with good sensitivity (77%) and specificity (92%) according to previous studies in South Africa [113, 232]. Those responding “yes, quite often”, “sometimes” and “hardly ever” in the past week were coded as experiencing suicidal ideation, whereas those to respond “never” were coded as not experiencing suicidal

	ideation. The EPDS comprises of 10 questions which generate scores ranging from 0-30, however here the suicidal ideation item (item-10) was excluded from the total score for depression.
Other variables	
Household size	This continuous variable shows the number of people living in the same household (for at least 3 days in the last week). This variable was used to create a categorical variable with three possible responses; 1-3 people, 4-6 people and 7-9 people. This was used for all subsequent analyses in this thesis.
Children	Number of children under 18 years old that live in the same household.
Household hunger scales	A subset of questions from the Household Food Insecurity Access Scale [256] were used to assess household food security. These questions were; I) In the past four weeks, was there ever no food to eat of any kind in your house because of lack of resources to get food? And how often did this happen? II) In the past four weeks, did you or any household member go to sleep at night hungry because there was not enough food? And how often did this happen? III) In the past four weeks, have you had to go an entire day without eating because there was no food in your household? And how often did this happen?

	These questions were used to categorize participants as living in: I) food secure (rarely worried about food access or quality), II) moderately food insecure (sometimes i.e. 3–10 times in the last month, worried about food access or quality), or III) severely food insecure households (≥1 household member going to bed hungry or often worrying about food access or quality). The last two categories (moderate and severe food insecurity were combined during analysis.
Asset Index score	Several indicators were used for generating the asset index score which was used for obtaining participant's socioeconomic status and categorizing them into three levels; low, middle or high. These indicators include; participants religion, education level, number of people living in the same household, source of drinking water, employment status of mother and partner (if they had one), amount of money earned each month and a range of household items (such as electricity, refrigerator, bicycle, cell phone, television etc.).

3.8 Handling of missing data

The proportion of missing data varied by question. There were several variables where non-response rates by participating caregivers were noticeably higher. For example, records relating to child characteristics (growth rate, birth weight) and importantly HIV status were often incomplete or missing. Due to the way the Mullen tool is set-up, the child development assessments were only measured in children aged under 36 months at 12 months follow-up. Initially, this was thought to be missing records (n=109). This led to discussions with the data entry team in CeSHHAR and double-checking original questionnaires and rectifying the issue. In cases where the relevant data were not provided, missing data were accounted for in statistical models built for each analysis in this thesis. In addition, records of child HIV status were updated at 12 months post enrolment following dried blood spot sample collection from the participating infants.

CHAPTER 4: The impact of comprehensive parenting and child stimulation intervention on child cognitive development: CHIDO trial results

4.1 Chapter overview

The background behind the trial set up, as well as the study design and methods used have been discussed in **Chapter 3**. I worked closely with the trial statisticians to analyse and interpret the trial findings relating to child cognitive development.

In this chapter I start by discussing the main trial findings and the impact of the comprehensive intervention on selected outcomes relating to child outcomes. I focus on reporting the child cognitive development outcomes here, as the first step in my PhD research was investigating the participating HIV exposed children's cognitive performance and whether the CHIDO intervention had an effect on their development trajectories.

4.2 Methods

The statistical analysis carried out using the child development data from the trial will be described in this section. A detailed description of all methods used in CHIDO trial can be found in the previous chapter (**Chapter 3.4**).

4.2.1 Statistical analysis

Participants characteristics were compared by trial arm at baseline and the characteristics of those lost to follow-up were also described. Mean differences and 95% confidence intervals (CI) were used to estimate the effect of the intervention for quantitative outcomes using mixed effects linear regression incorporating random effects for clusters and adjusting minimally for baseline prognostic factors. Baseline factors adjusted for a priori were the baseline measurement, strata in Goromonzi (two groups based on the number of children on the clinic register), district (Goromonzi or Mudzi), infant age (0-<6 months, 6-<12 months and 12-24 months) and for quantitative Mullen outcomes, a categorical covariate representing the Mullen examiner at baseline. Data obtained from the trial were analysed in STATA v.15.1 (StataCorp LP, College Station, Texas, USA) using intention to treat principles.

4.3 Results

There were thirty clusters, 15 in each arm, randomised in this trial. 574 caregiver-child dyads were recruited at baseline and 514 (89.5%) were retained at 12 months follow-up.

The characteristics of caregivers and infants at baseline are presented in **Table 4.1.** Most of the caregivers (562/574; 97.9%) enrolled in the study were biological mothers with a mean age of 31.9 years (SD: 6.9). Over half (304/574; 52.9%) had a secondary or higher level of education and 79.4% were married (455/574). There were 36.6% (201/574) caregivers who reported to be in paid employment.

The level of food insecurity was high for this sample with 57.8% (332/574) caregivers reporting to experience moderate to severe hunger in their households. High level of mental health burden was also observed with 40.1% (230/574) of the caregivers screening positive for common mental disorders and 50.5% of the mothers (284/562) screening positive for postnatal depression symptoms. Additionally, 35.3% of the caregivers reported high parental stress levels (PSI_SF parental distress subscale>90th percentile).

Additionally, programme implementation data show the complete intervention package was administered to 91/281 (32.4%) participants, with 161/281 (57.3%) attending ≥14 Early Child Stimulation sessions (data not shown here).

4.3.1 Child characteristics

At baseline, the mean age (months) of the infants was 11.9 (SD 6.5) and 291/574 (50.1%) of infants were female. When infants' anthropometric characteristics were investigated, 87/574 (15.2%) infants were found to be underweight (WHO weight-for-age z-score <-2) and 207/574 (36.1%) were stunted (WHO height-for-age z-score <-2). Infant HIV status at baseline was poorly recorded; 167/574 (29.1%) of caregivers reported they were unaware of their child's status, whereas 367/574 (67.8%) reported their child was HIV negative and 18/574 (3.3%) reported child was HIV positive. Child characteristics were found to be generally comparable between the trial arms (**Table 4.2**). However, there were more infants under six months (26.3% vs. 15.0%) and

infants stunted at baseline (38.4% vs. 34.3%) in the intervention arm compared to the standard of care arm.

At 12 months follow-up, the median age of the children was 1 years (IQR: 0.61, 1.47), 259/514 (50.4%) were females, 76/514 (14.8%) were underweight (WHO weight-for-age z-score <-2) and 181/514 (35.4%) were stunted (WHO height-for-age z-score <-2). All children had an HIV test at 12 months follow-up; 167/574 (28.7%) of caregivers had indicated that they did not know the child's HIV status at baseline but by follow-up only 16/506 (3.1%) had unknown status. Only seven HIV positive infants were on ART, and only two were initiated within six weeks of birth.

Characteristics of children lost to follow-up (60/574: 10.5%) are described in **Table 4.2**. These children were mainly older in age ≥12 months (35/60: 58.3%), 32/60 (53.3%) were females, and 5/60 (8.3%) were reported to be HIV positive by their caregivers. There were 18 children who had a different primary caregiver at follow-up from the person who completed the baseline interview. Overall the characteristics of those lost to follow-up were similar to those who completed follow-up and there was no evidence of systematic difference between the two groups.

Table 4.1: Descriptive characteristics of participants at baseline by trial arm

	Measure and Level	Intervention arm	Standard of care arm	Total
Total	N (% of total)	281 (49.0%)	293 (51.0%)	574
Infant's characteristics				
Age (month)	Mean (SD)	11.7 (6.9)	12.1 (6.0)	11.9 (6.5)
Sex	N (%)			
	Male	141 (50.2%)	142 (48.5%)	283 (49.3%)
	Female	140 (49.8%)	151 (51.5%)	291 (50.7%)
Birth weight (kg)	Mean (95% CI)	2.99 (2.90, 3.08) n=272	2.93 (2.86, 3.00) n=283	2.96 (2.88, 3.04)
Caregiver's Characteristic				
Caregiver type	N (%)			
	Mother	272 (96.8%)	290 (99.0%)	562 (97.9%)
	Other	9 (3.2%)	3 (1.0%)	12 (2.1%)
Age (years)	Mean (SD)	32.1 (7.2)	31.6 (6.6)	31.9 (6.9)
Marital status	N (%)			
	Married	227 (81.1%)	228 (77.8%)	455 (79.4%)
	Divorced/separated	32 (11.4%)	42 (14.3%)	74 (12.9%)
	Widowed	16 (5.7%)	15 (5.1%)	31 (5.4%)
	Never married	5 (1.8%)	8 (2.7%)	13 (2.3%)
Education	N (%)			
	Secondary or above	152 (54.1%)	152 (51.9%)	304 (52.9%)
Employment	N (%)			
	Employed	90 (32.0%)	120 (41.0%)	201 (36.6%)
SES	N (%)			
	Lowest	104 (37.0%)	88 (30.0%)	192 (33.4%)
	Middle	100 (35.6%)	91 (31.1%)	191 (33.3%)
	Highest	77 (27.4%)	114 (38.9%)	191 (33.3%)

Household food security (HFIAS)	N (%)			
	Little to no hunger	116 (41.3%)	126 (43.0%)	242 (42.2%)
	Moderate to severe hunger	165 (58.7%)	167 (57.0%)	332 (57.8%)
Parental stress score (PSI-SF) n=564	N (%)			
	Not stressed (<90th percentile)	180 (65.7%)	185 (63.8%)	365 (64.7%)
	Stressed (>=90th percentile)	94 (34.3%)	105 (36.2%)	199 (35.3%)
Maternal mental health (EPDS) n=562	N (%)			
	Not depressed (score 0-11)	132 (48.5%)	146 (50.3%)	278 (49.4%)
	Depressed (score>=12)	140 (51.4%)	144 (50.0%)	284 (50.5%)
Common mental disorders (SSQ-8) n=573	N (%)			
	No CMD (score 0-5)	168 (60.0%)	175 (60.0%)	343 (59.9%)
	CMD (score 6-8)	112 (40.0%)	118 (40.0%)	230 (40.1%)

***Table 4.2**: Characteristics of children followed up and not followed up at 12 months, by trial arm*

		Intervention arm		Standard of care arm		Overall	
	Measure and Level	**Interviewed at follow-up**	**Lost to follow-up**	**Interviewed at follow-up**	**Lost to follow-up**	**Interviewed at follow-up**	**Lost to follow-up**
Total	N (%)	261 (92.9%)	20 (7.1%)	253 (86.4%)	40 (13.7%)	514 (90.0%)	60 (10.5%)
Child characteristics							
Age (years)	Median (IQR)	1.03 (0.47 to 1.49)	1.10 (0.78 to 1.40)	1.00 (0.68 to 1.43)	1.06 (0.57 to 1.62)	1.00 (0.61 to 1.47)	1.08 (0.63 to 1.56)
Age	0-<6m	70 (26.8%)	4 (20.0%)	37 (14.6%)	7 (17.5%)	107 (20.8%)	11 (18.3%)
	6-<12m	57 (21.8%)	4 (20.0%)	90 (35.6%)	10 (25.0%)	147 (28.6%)	14 (23.3%)
	12-24m	134 (51.3%)	12 (60.0%)	126 (49.8%)	23 (57.5%)	260 (50.6%)	35 (58.3%)
Sex	N (%)						
	Male	134 (51.3%)	7 (35.0%)	121 (47.8%)	21 (52.5%)	255 (49.6%)	28 (46.7%)
	Female	127 (48.7%)	13 (65.0%)	132 (52.2%)	19 (47.5%)	259 (50.4%)	32 (53.3%)
HIV status as reported at baseline	N (%)						
	Positive	9 (3.5%)	3 (15.0%)	4 (1.6%)	2 (5.0%)	13 (2.5%)	5 (8.3%)
	Negative	164 (62.8%)	8 (40.0%)	190(75.1%)	27 (67.5%)	354 (68.9%)	35 (58.3%)
	Prefer not to say	2 (0.8%)	0	0	0	0	0
	Unknown	88 (32.9%)	9 (45.0%)	59 (23.3%)	11 (27.5%)	147 (28.6%)	20 (33.3%)
Birth weight (kg)	Mean (95% CI)	3.00 (2.91 to 3.09)	2.86 (2.72 to 3.01)	2.95 (2.87 to 3.03)	2.80 (2.59 to 3.01)	2.97 (2.91 to 3.04)	2.82 (2.68 to 2.97)
Weight-for-age z-score	Mean (95% CI)	-0.84 (-1.09 to -0.59)	-1.23 (-2.36 to -0.10)	-0.84 (-1.01 to -0.68)	-0.93 (-1.31 to -0.55)	-0.84 (-0.99 to -0.69)	-1.03 (-1.50 to -0.56)

Underweight (z-score <-2)	Yes	40 (15.3%)	4 (20.0%)	36 (14.2%)	7 (17.5%)	76 (14.8%)	11 (18.3%)
	No	221 (84.7%)	16 (80.0%)	217 (85.8%)	33 (82.5%)	438 (85.2%)	49 (81.7%)
Length-for-age z-score	Mean (95% CI)	-1.54 (-1.86 to -1.22)	-1.86 (-2.44 to -1.28)	-1.48 (-1.76 to -1.21)	-1.35 (-1.79 to -0.92)	-1.51 (-1.72 to -1.30)	-1.52 (-1.90 to -1.15)
Stunted (z-score<-2)	Yes	99 (38.2%)	8 (40.0%)	82 (32.5%)	18 (45.0%)	181 (35.4%)	26 (43.3%)
	No	160 (61.8%)	12 (60.0%)	170 (67.5%)	22 (55.0%)	330 (64.6%)	34 (56.7%)
Body mass index (BMI) z-score		0.14 (-0.11 to 0.38)	-0.17 (-1.82 to 1.47)	0.07 (-0.17 to 0.32)	-0.16 (-0.40 to 0.09)	0.10 (-0.08 to 0.28)	-0.16 (-0.74 to 0.41)
Low BMI z-score	Yes	14 (5.4%)	1 (5.0%)	15 (6.0%)	2 (5.0%)	29 (5.7%)	3 (5.0%)
	No	245 (94.6%)	19 (95.0%)	237 (94.1%)	38 (95.0%)	482 (94.3%)	57 (95.0%)
Mid-upper arm circumference z-score		-0.17 (-0.47 to 0.13)	-0.44 (-0.86 to -0.03)	-0.43 (-0.62 to -0.24)	-0.33 (-0.68 to 0.01)	-0.30 (-0.49 to -0.12)	-0.37 (-0.64 to -0.09)
Low MUAC z-score <-2	Yes	13 (6.0%)	1 (6.3%)	14 (6.3%)	1 (2.7%)	27 (6.1%)	2 (3.8%)
	No	203 (94.0%)	15 (93.8%)	210 (93.8%)	36 (97.3%)	413 (93.9%)	51 (96.2%)

4.3.2 Child cognitive scores by trial arm

Child cognitive scores at baseline and 12 months follow-up by trial arm were examined. At baseline, Mullen data were collected on 574 children, but only 506/514 of those followed up had Mullen assessments performed at endline. Six Mullen scores were missing because the child had died. The other two children were found and tested for HIV, but the Mullen test was not performed.

At baseline, mean scores of children were comparable and the overall mean composite score on the Mullen Early Learning Scale was 102.3 (95% CI: 98.6, 106.0), which was similar to the USA reference norms. The mean composite scores of the children were also similar between the two groups (intervention arm 102.6 vs. standard of care arm 102.0), irrespective of their HIV status and trial arm.

The children in the intervention arm had higher scores in fine motor (51.1 vs. 50.2) and visual reception (53.5 vs 52.6) compared to children in the standard of care arm; however, there was no evidence of statistically significant difference between the two groups (**Table 4.3**).

Table 4.3: *Children's mean Mullen T-scores at baseline by trial arm*

Mullen scales (T-scores)	Intervention arm (n=281)	Standard of care arm (n=293)	P value*
	mean (95% CI)		
Expressive language	52.4 (49.7 to 55.1)	53.1 (51.3 to 55.0)	0.44
Receptive language	47.6 (44.5 to 50.8)	47.6 (44.8 to 50.4)	0.95
Fine Motor	51.1 (47.9 to 54.4)	50.2 (47.4 to 53.0)	0.33
Gross Motor	50.1 (47.7 to 52.6)	50.8 (49.2 to 52.4)	0.46
Visual reception	53.5 (49.3 to 57.8)	52.6 (50.2 to 55.1)	0.40
Early learning composite score	102.6 (96.5 to 108.7)	102.0 (97.8 to 106.3)	0.69

**Unadjusted p value*

After 12 months follow-up, the intervention effect on child cognitive outcome was measured. As seen at baseline, the children's mean Mullen scores were similar by trial arm. The mean Mullen composite score was 87.9 at 12 months, a reduction of 14.4 points from baseline. There was no evidence of a difference in Mullen composite score after CHIDO intervention implementation between trial arms (mean of 88.1 in the intervention arm and 87.6 in standard of care arm; adjusted mean difference (aMD)= 0.06; 95% CI: -2.68, -2.80; p=0.97). Children in the intervention arm had slightly higher mean gross motor (50.2 vs 48.2), and visual reception (42.8 vs. 41.5) compared to the children in the standard of care arm. However, there was no evidence of intervention effect on child's overall cognitive score and the Mullen sub scales by trial arm (**Table 4.4**).

Table 4.4: *Children's mean Mullen T-scores at 12 months by trial arm*

Mullen scales (T-scores)	**Intervention arm, n=257**	**Standard of care arm, n=249**	**Adjusted mean difference***	**p value**
	mean (95% CI)			
Expressive language	44.9 (43.1 to 46.7)	45.3 (43.3 to 47.3)	-0.44 (-2.03 to 1.14)	0.58
Receptive language	45.3 (43.1 to 47.5)	45.8 (43.1 to 48.4)	-0.11 (-1.82 to 1.60)	0.90
Fine Motor	41.7 (39.3 to 44.2)	41.0 (38.5 to 43.6)	-0.23 (-2.38 to 1.92)	0.83
Gross Motor	50.2 (47.7 to 52.6), n=196	48.2 (45.4 to 51.0), n=201	1.99 (-0.54 to 4.51)	0.12
Visual reception	42.8 (40.1 to 45.5)	41.5 (38.6 to 44.4)	0.84 (-1.44 to 3.12)	0.47
Early learning composite score	88.1 (84.0 to 92.2)	87.6 (83.1 to 92.1)	0.06 (-2.68 to 2.80)	0.97

** Model adjusted for baseline Mullen scores, clustering by trial site and examiner. The positive mean difference here indicates that those in the intervention arm have higher Mullen scores compare to those in the standard of care arm*

4.4 Discussion

Participating caregiver-child dyads in the CHIDO trial were assessed at baseline and 12 months follow-up and information on their demographic, socioeconomic, mental health status and HIV status collected. In this chapter I examined the children's characteristics at both time points and explored child cognitive development outcomes pre and post CHIDO intervention roll out.

The results show no evidence of a difference in Mullen composite scores and sub-scales after programme implementation between the trial arms. In addition, when compared to normative data (USA reference group), the baseline child development score ranges were comparable, but by 12 months follow-up the scores were lower than normative groups for the entire sample (irrespective of trial arm). The reduction in cognitive development scores observed here among children in both arms of the trial is likely to reflect the multiple challenges to development that these HIV exposed children face. All children in the study were, by definition, HIV-exposed and there is a solid evidence base that both HIV exposure and infection are associated with child developmental challenges. Perhaps the Zimbabwean children and children from the USA follow different growth trajectories and learn things in different order. The Mullen scales might also contain items that are not relevant to Zimbabwean children. For example, asking the children to 'Puts pennies in slot' in a country that does not use coins was not applicable for this group. There were some limitations in implementation and administration of the Mullen assessments in the trial worth considering. The strengths and limitations of this analysis will be discussed further in **Chapter 8 (section 8.3).**

Overall, the comprehensive intervention used in this trial, seemed to have no impact on child cognitive development, although the intervention effect was measured within a median 4.5 months of completion. This could indicate that the benefits of parenting training might need more time to influence child development outcomes. As there was no evidence of difference in child cognitive outcomes by trial arm detected, data were pooled, and child and caregiver data gathered in this trial were used for subsequent analyses to address the research questions in this thesis.

CHAPTER 5: Design and development of a shortened form of child development measurement.

This chapter describes the design and development of a shortened form of the Mullen Scales of Early Learning tool. The Mullen tool is lengthy and complex to administer, requires use of specialised equipment and needs to be administered by a highly skilled and trained assessor. In addition, it is used 'under license' and too expensive to be used in usual care. It is therefore not suitable for use by lay health workers working in rural areas with minimal access to equipment. I therefore investigated the design and feasibility of creating a reduced form comprising a limited number of assessment measures from the Mullen Scales which could be used in low resource settings and assessed its validity. The design and steps used to create this screening tool are described in this chapter.

5.1 Introduction

The Mullen Scales for Early Learning tool is a commonly used developmental measure of cognitive development. The tool has been used across different populations to assess children's cognitive development abilities across a range of domains including visual, linguistic, and motor domains [43-46]. Although the Mullen Scales had not been validated or normed in an African setting, a prominent research group led by Michael Boivin had conducted several studies on child cognition and neurocognitive development using the Mullen scales for HIV affected children in Uganda without difficulties [44-46] and had Mullen trained researchers who we were able to employ to train our research staff. Based on this, the Mullen scales was adopted to determine outcomes in the Child Health Intervention for Development Outcomes (CHIDO) trial which targeted a population of HIV positive and HIV-exposed infants in Zimbabwe [3].

However, following the baseline assessments and the practical use of the Mullen scales in the CHIDO trial, it was considered that the tool would be impossible for lay healthcare workers (LHW) to use to support programme implementation in this setting. This was in part because of its length, because it required specialised training, and scores were difficult to compute. The tool which uses a computerised system for generating cognitive scores was found complex to use at times. Additionally there is a charge each time the score is administered which is prohibitive.

In low-and-middle income countries where skilled clinicians are minimal at grassroots level there is need for a locally validated and appropriate simple, valid and reliable screening tool that can be used by community health workers to identify children at risk of developmental delay. A tool that requires shorter administration time (ideally under 30 minutes), contains culturally appropriate items for the setting, has good reliability, low cost, easy to understand by all who use it, are some of the characteristics of the ideal tool for a more practical use by LHW in field settings. Development of such screening tool would aid early detection of children at risk of developmental delay and enable timely referrals for support and further management. In the CHIDO trial we had extensive data from 574 children aged 0-24 months who have been assessed using the Mullen at two time points. This dataset was used to

explore the possibility of identifying a shorter set of questions/items, aligned with the Mullen Inventory that might be valid and practicable to use by LHW.

5.1.1 Aim of analysis

The overall aim of this study was to derive a robust and valid tool from the Mullen scales to screen for (rather than diagnose) likely child developmental delays in resource-limited settings. The new tool was to be for use by relatively unskilled health workers with minimal equipment and conducted in under 30 minutes. The specific objective of this analysis was to develop and validate a shortened and simplified form of the Mullen Scales of Early Learning tool.

5.2 Methods

The full Mullen scales consist of 160 items within five domains, with children completing items appropriate for their age. Within each domain, the sum of test scores obtained by children is entered into proprietary software which calculates an age-standardised t-score relative to a USA reference population. The standardized T-scores of the fine motor, expressive language, receptive language, and visual reception domains are combined to produce a Composite score; using a USA reference population. A reference population was not available in Zimbabwe or in the Southern Africa region. Scores range from 20-80 (the higher the score the better the performance of the child) for the five domains and range from 49 to 155 for the Composite score which is used as a measure of general cognitive performance. The assessment can take 15 to 60 minutes to administer depending on the child's age [3, 38]. The domain T-scores can be categorised into five levels of performance– very low (20-30), below average (31-39), average (40-60), above average (61-69), and very high (70-80).

5.2.1 Development of the shortened form: Item shortlisting

In order to explore components of a short form, the CHIDO trial baseline dataset was used for this analysis and the following steps were undertaken.

1. The individual item scores were extracted from aggregated variables for each Mullen test item (i.e. for the 574 participating children aged 0-24 months).

2. The items were discussed in person with Mullen tool trained assessors. The assessors were asked a series of questions on what they found difficult about the child assessment, what worked well, items that were particularly challenging to conduct, and if they felt they were able to conduct the assessment accurately and as is reflective of the child's cognitive development. In addition to this, the assessors were asked about items that had low variability i.e. most children were not able not to answer. Based on these discussions, items they identified as difficult to use or not suitable for lay healthcare workers to administer were excluded from consideration at this stage.

3. Items which were not binary in response (i.e. instead of yes or no, have more than 2 categorical answers) were excluded as they were deemed difficult to score and the purpose of this analysis was to create simple and easy to use assessment tool.

4. The Mullen tool is administered differently depending on the child's age (i.e. more difficult tasks or questions are used for older age groups). Therefore, the next step was generation of different age categories for the children; "0-4 months", "5-8 months", "9-12 months", "13-19 months" and "20-24 months". These categories were based on the age categories in the Mullen tool as they were deemed appropriate to use.

5. Within each age group items were excluded if they were not answered by any participants; as well as those items where the children showed no variation in the response as these items did not provide useful data on cognitive performance of the children in that particular age group.

5.2.2 Categorization of the shortened form

The short form was designed with 6 items per age group and 1 point scored per item completed. Within each age group, except for the 20-24 months group, an additional point was added for every month the child was younger than the maximum for that group. For example, a child aged 10 months who completed 5 items would score 5 + (12-10) = 7. This was done to compensate for an increase in scores with age and to ensure appropriate categorization. The child's score was then categorised into low risk, medium risk, and high risk of cognitive delay.

5.2.3 Validity and reliability

Validity and reliability are fundamental elements in the evaluation of any measurement tool [141, 233]. Validity refers to the extent at which the tool truly measures that which it was intended to measure [234]. Reliability on the other hand refers to the extent to which the same results can be obtained using the same instruments more than once [233, 234]. In order to measure the validity and reliability of the proposed shortened form tool, several steps were taken in this analysis. The aim of this analysis was to create a tool that could identify children at risk of developmental delay as measured by the full Early Learning Composite score with 75% sensitivity at each age.

A Cronbach's alpha test [141] was performed within each age group to identify any items whose removal would improve the internal consistency of the scale. The internal consistency had to be determined before further tests were done. Items with high coefficient alpha (item-test correlation 0.50 and above) were identified and noted. However, as high coefficient alpha does not necessarily reflect validity of the tool and highlight the high degree of internal consistency, no further items were dropped at this stage from the tool.

Factor analysis was then conducted on the remaining Mullen items within each age group to establish the underlying structure and identify the items with the highest loading onto the factor(s). After considering additional criteria (high coefficient alpha and good variability), those with low loading factor were eliminated from the tool. Two-factor solutions were also investigated, but this had poor fit and one-factor

solutions were chosen. The final selected binary items were then used to create a 0-6 point scale. Validity was measured by creating the 3 risk categories for cognitive delay (i.e. low risk, medium risk and high risk), and then assessing the sensitivity of the 'high risk' category and the specificity of the 'low risk' category against a cut-off of the composite score (for younger age groups $\geq$ 100 and the two older age groups $\geq$ 81).

5.3 Results

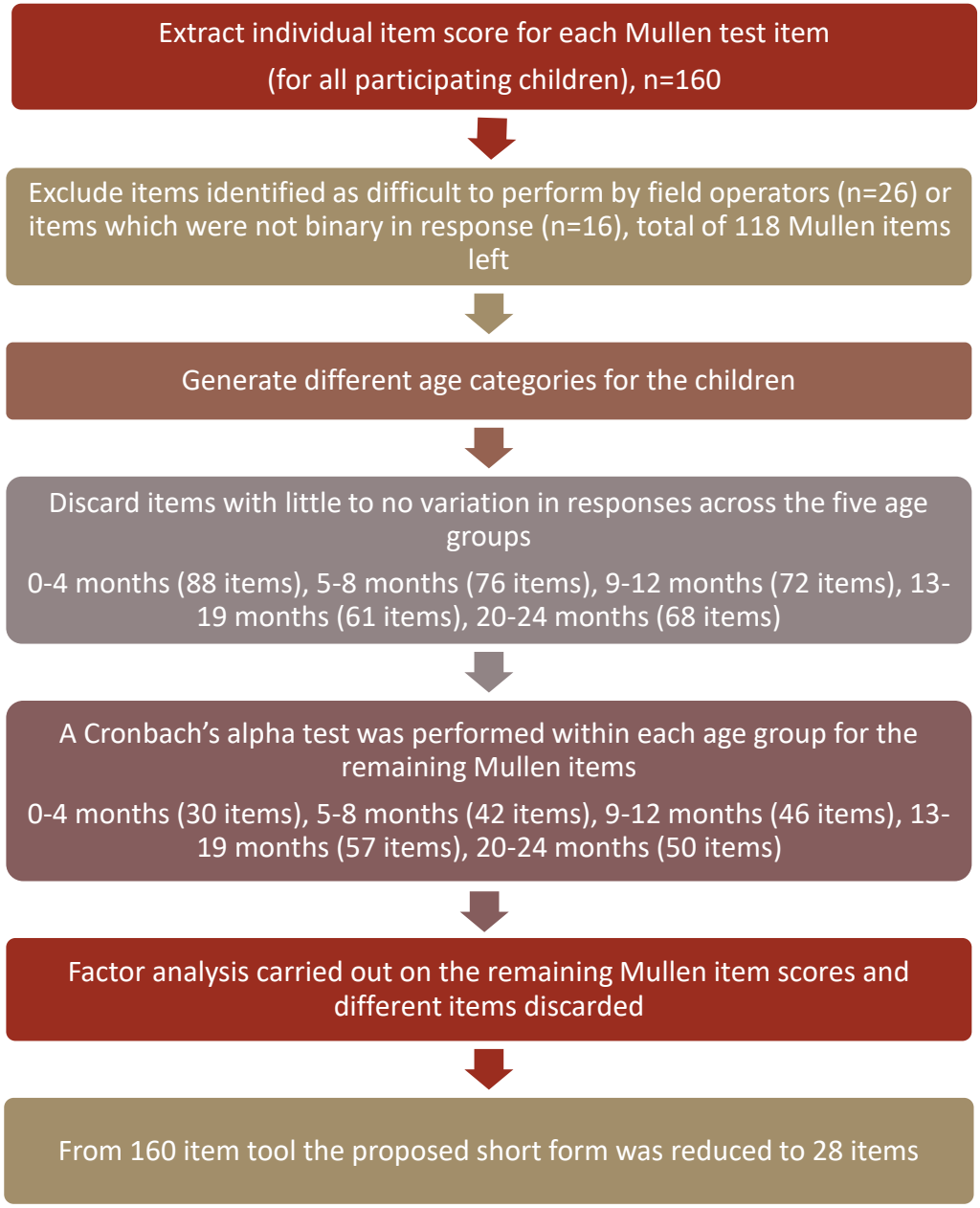
5.3.1 Process of item selection

The Mullen assessment was conducted on 574 children and has 160 test items. Before starting the item selection process, it was very important to discuss the existing tool properties and ease of conducting the assessments with assessors in the field. From the previous analysis (**Chapter 4**) and programme implementation data gathered in the trial it was clear that the full inventory includes items not appropriate for this study group. The tool contains test items such "putting pennies in a slot" for a group of children in a country that does not use coins or asking children to identify items less commonly available in rural villages (door hinges). This would result in majority of the children not being able to respond to such questions and missing the scores. Which is why following consultation with field operators 26 items found inappropriate or difficult for LHW to implement were discarded. A further 16 items were discarded as they were not binary (i.e. yes or no). Five age groups were created; 0-4 months, 5-8 months, 9-12 months, 13-19 months, 20-24 months. There were 118 Mullen items at this stage for each group. Items with little to no variation in responses across the five age groups were excluded further (0-4 months: 88 items, 5-8 months: 76 items, 9-12 months: 72 items, 13-19 months: 61 items, 20-24 months: 68 items).

A Cronbach's alpha test was performed on the remaining Mullen items for each age group (0-4 months: 30 items, 5-8 months: 42 items, 9-12 months: 46 items, 13-19 months: 57 items, 20-24 months: 50 items) and items with high coefficient alpha (0.50 and above) were identified. No further Mullen items were discarded at this stage. The next step consisted of conducting factor analysis on the Mullen item scores. This was followed by identifying several items that had high loading factor and consequently 5-6 items were selected for each age category. Eventually, instead of the full 160 item

Mullen scales, the proposed short form had 28 items, which could be administered according to a child's age category (i.e. not according to the cognitive domains), see **Figure 5.1.**

Figure 5.1: *Flowchart of the short form development*



After the development of the shortened form, different cut-off points were used for creating three categories (Low risk of cognitive delay, medium risk of cognitive delay, and high risk of cognitive delay) for the children, **Table 5.1**. As the factors scores increased with age (except for the oldest age group), one point was added to the total score for each month less than the oldest age in that specific age group to count. This led to changing the 0-6 point scale created from the binary items to scores ranging from 0-11 with appropriate cut-off points.

Table 5.1: *Short form score ranges and cut-off points for the three risk of cognitive delay categories for the different age* groups

Age group	Score range	Low risk	Medium risk	High risk
0-4 months	0-8	0-2	3-4	5-8
5-8 months	0-8	0-2	3-4	5-8
9-12 months	0-8	0-3	4-6	7-8
13-19 months	0-11	0-3	4-5	6-11
20-24 months	0-5	0	1-3	4-5

Table 5.2 summarises the selected items (test code) and corresponding question in different cognitive domains. These selected items in the table had the highest factor loading ranging from 0.04 to 0.08 and were found to have high coefficient alpha ($\geq$ 0.50).

The proposed measurement would contain a brief list of items/tasks from five developmental domains children will be assessed on, scored and categorized accordingly. The majority of the items in such a proposed short form (see **Table 5.2**) would be straightforward to perform by lay workers and require little prompting from assessors. However, some items would require additional materials such as book, toys, and ball for the assessments. These items are standardised in the formalised assessment inventory and there is no data on the use of alternative stimuli items.

Table 5.2: *Selected short form items, output from Cronbach's alpha test and the factor loading level for selected each item,* by age group

Age group	Mullen Item	Corresponding questions	Cronbach's alpha	Factor loading level
0-4 months	GM6	Sits supported, head steady	0.667	0.073
	RL4	Coordinates listening and turning	0.699	0.078
	RL5	Responds to voice and face by vocalizing	0.765	0.085
	RL6	Coordinates listening and looking	0.734	0.081
	VR4	Localizes alternating red ball and schematic face	0.698	0.077
	VR6	Localizes bull's-eye near and far	0.745	0.082
5-8 months	GM11	Sits with arms free	0.647	0.066
	GM12	Pulls self to stand	0.642	0.063
	FM8	Transfers, bangs, drops (ball)	0.590	0.059
	RL9	Recognizes familiar names, words	0.617	0.058
	EL13	Combines jargon/gestures	0.602	0.065
	VR14	Attends to picture	0.700	0.073
9-12 months	GM14	Walks with one hand held	0.597	0.053
	GM15	Stands alone	0.656	0.054
	FM11	Bangs in midline, horizontal movement	0.464	0.041
	RL14	Identifies objects	0.602	0.052
	EL13	Combines jargon/gestures	0.578	0.058
	VR15	Looks for toy covered, then displaced	0.535	0.045

13-19 months	GM12	Pulls self to stand	0.264	0.073
	RL15	Gives toy on verbal request	0.603	0.051
	RL16	Comprehends question I: chair, door	0.672	0.058
	EL14	Combines words/gestures	0.561	0.052
	VR13	Shows interest in book as hinge	0.539	0.045
20-24 months	GM24	Walks 4 to 5 steps, one foot in line	0.544	0.049
	RL20	Follows related commands	0.734	0.067
	RL21	Identifies pictures: car, ball, shoe, doll	0.740	0.068
	EL16	Label picture: ball, dog, baby	0.680	0.062
	VR19	Sorts spoons and blocks by category	0.579	0.053

GM, Gross motor| FM, Fine motor| EL, Expressive language| RL, Receptive language| VR, Visual reception

5.3.2 Validation of selected items for a potential tool

The shortlisted items (**Table 5.2**) were validated against the Composite score derived from the full Mullen scales within this data set. The sensitivity and specificity of the shortlist items to detect the lowest-scoring decile of trial participants, by age group was also assessed. **Table 5.3** summarizes the results of the sensitivity and specificity tests carried out on the shortened form for each age group. The final items chosen for the form all showed high level of sensitivity and specificity (>75%) when assessed against the composite scores for each age group.

Table 5.3: *Sensitivity and specificity of the short form against the Composite score, by age group*

Age group	Sensitivity	Specificity
0-4 months (N=93)	80.0%	96.4%
5-8 months (N=89)	84.6%	100.0%
9-12 months (N=129)	77.3%	100.0%
13-19 months (N=174)	100.0%	88.8%
20-24 months (N=89)	89.5%	96.7%

5.4 Discussion

5.4.1 Tool characteristics

The suggested shortlisted items in the tool here cover a range of questions across the different cognitive domains. All items in the suggested short form are binary in response (i.e. yes or no questions) and most of the items are simple set of questions/tasks which may require minimal training to administer by LHW. The selected items require less specific equipment to use compared to the full tool, which improves ease of use in rural settings and makes it potentially less costly. The number of test items varied based on age groups. The younger age groups (≤12 months) required 6 questions across the five domains whereas only 5 items were found sufficient for the last two age groups (13-19 and 20-24 months). This was predictable

as younger children are not able to interact or do much during infancy making it more difficult to assess their cognitive performance with a brief set of questions. Although the gross motor domain is a separate indicator of child development and not part of cognitive functioning, interestingly more items from the gross motor domain were found to be useful in assessing child performance.

5.4.2 Investigating underlying factors

During the development of the short form, the fact that there could be more than one single underlying concept being measured was taken into consideration. Thus, shortlisting of the test items and discarding of less relevant items was done systematically and carefully. Furthermore, other underlying factors were investigated using two-factor analysis, however all test items loaded onto one factor. This was surprising as child cognitive development consists of several distinct domains with the gross motor domain not included in the overall cognitive score, yet based on the data, one underlying factor was able to define it. This raises the question of whether child cognitive development is a single construct that can be measured holistically.

5.4.3 Validity of potential short forms

Validity was determined against the gold standard of the Mullen composite score in this study and the final items chosen for the form all showed high level of sensitivity and specificity (>75%). However, the Mullen inventory was never validated in the current study setting so may not be a suitable gold standard tool to use for this population. The goal was to identify children at risk of cognitive delay rather than producing a short diagnostic tool which provides a quantitative scores. It would have been good to investigate the difference including or excluding certain items would have made to the sensitivity and specificity of the tool. However, as this was an extensive process, only the final 5-6 items shortlisted were validated against the Composite scores. Other approaches such as use of discriminant analysis to see which items are key factors in predicting delay could be explored in future research.

5.4.4 Benefits and implications of using screening tools

Screening tools are usually administered quickly, using a limited sample of items representing a domain and rely on predetermined cut-off points [33]. They are

designed to identify children who may have impairment and require a comprehensive assessment. However they might be limited in their ability to assess subtle delays that may have a significant impact on subsequent development [33]. It is important to note that just as cognitive abilities and skills, developmental delays become more evident with age; children with no apparent cognitive problems during the first 2-3 years of life might show signs of delay later during school age years. Thus, screening tools are beneficial tools that can be used for continued assessment of vulnerable groups such as the HIV exposed children in this study.

Of importance, most studies assessing child development outcomes use adapted or translated Western tools, with limited validation [39] on children from a different cultural background [235]. Research shows carefully translated and adapted cognitive tools do provide reliable measure in different settings [39, 236, 237] without compromising the psychometric properties of the tests [236]. Most of these tests require further validation to assess their clinical utility as well as establishing appropriate normative standards. Although it requires further validation, the screening tool developed here shows a simplified assessment method that could possibly be tailored and adapted for use in similar settings. The methodology used (mix of qualitative and quantitative approach) serves to strengthen the validity of the short form developed in this study.

Another important consideration is screening tools have to balance the risk of missing a child with delays (sensitivity) versus incorrectly identifying children without true delays (specificity) [238]. It is also important to consider that a certain test does not necessarily measure the same constructs across different cultural settings [237]. Further research in developing screening tools would benefit from considering the cultural influences on test performance which are almost impossible to avoid, but can be accommodated for in a manner that preserves the essential psychometric properties and allows comprehensive assessment of multiple cognitive outcomes [39].

5.4.5 Tool limitations

There were some limitations in this study. The screening tool was generated and validated using data on HIV positive and HIV-exposed children, and it has not been validated on other target groups of children. Therefore, further validation using

different datasets needs to be done to assess the likely performance of the tool for a different set of children. As it is a screening tool, the short form tool is not as sensitive as the Mullen tool in identifying cognitive delay in a specific domain. The new tool did show high level of sensitivity and specificity for identifying children with possible development delays. This was however based on small numbers for some of the age groups and confidence intervals were wide. Although it is common for validation studies to weight the sample and increase the proportion with the outcome, this was a secondary analysis of an existing dataset so that was not possible to do.

5.4.6 Tool acceptability and feasibility

Acceptability and feasibility of a new tool is another important factor. The concept of a shortened form tool was discussed with Mullen trained assessors in the study and was found to have good face validity. However, this was not discussed further with LHW in the study community due to licensing and copy write issues affecting the scale up of such tool. The Mullen scales tool was purchased for use in the CHIDO trial and had fully trained operators using it, thus the data obtained as result was reliable for use for secondary analyses or investigations as done in this study. However, if a shortened form of the tool set is generated for field use, copyright and purchasing requirements of the Mullen scales will be an issue and the utility of such a tool would need to be considered. The copywrite holders did not give permission to use the Mullen to develop a short form or continue developing a short form. Thus from this study, while it seems feasible to do, the legal and copy write requirements are proving a barrier to further validation and assessment. Screening tools may need to be developed from scratch rather than using existing tools as templates, and indeed this may result in more culturally appropriate as well as valid tools for use in this setting. This data shows promise for such an approach.

5.5 Chapter summary

In this chapter, I investigated the possibility of utilizing a sample of items within the Mullen scales to produce a shortened form of the scale from the existing one for field use purposes. The shortened scale designed here allows the use of a simple scoring system to categorize children into three groups based on their total score across the selected 5/6 questions, by age group. This feature is potentially important in field settings enabling community health workers to assess children quickly and identify children who are at risk of cognitive delay and need referral for further assessment. A tool that would take 10-20 minutes to administer to all children (from meeting the participants to completion of child assessment) would have high utility in such settings.

Overall, formal child assessment tools will only give a snapshot of the child's development at a particular time point. Skills that have not yet evolved in early childhood clearly cannot be assessed until such time as they might reasonably be expected to be present, and yet impairment within these characteristics may impact subsequent development significantly [239]. In rural settings, more healthcare providers and children they care for could benefit from brief, cheap, easy to use, valid and reliable cognitive screening tools to identify children in need of referral. The exploration of a short form has been shown to be feasible, valid and has potential for use in field setting. Future development and use will need to address copyright and licencing issues if it was to be utilized by programme implementers.

CHAPTER 6: Cognitive profiles of HIV positive and HIV exposed infants in Zimbabwe, and the role of maternal mental health in child cognitive development

6.1 Introduction

Multiple studies investigating the effects of HIV infection and exposure (without becoming infected) on children's cognitive development have described the risk of developmental delay and impairment in both HIV positive and HIV-exposed uninfected infants (HEU) [54, 55, 58, 59] compared to healthy control infants [57], in resource-limited settings [60-62]. Research also shows children perinatally-infected with the virus face greater risk of neurological and neuropsychological deficits compared to HEU children. This is likely attributable to the direct effects of HIV on the central nervous system and the brain structures involved in the regulation of emotion, behaviour, and cognition [55, 58, 64-66], exposure to treatment or other HIV related factors. HIV can also impact child neurodevelopment through environmental and socioeconomic factors associated with delayed child neurodevelopment, such as poverty fuelled food insufficiency, community stigma and discrimination, caregiver unemployment, or chronic illness and bereavement [28, 57, 62, 67, 70, 71].

The developmental outcomes of children affected by HIV are further influenced by other factors, including the extent of early years stimulation, and maternal mental health [20, 85]. Research suggests that quality of caregiving provided to HIV positive and affected children plays a role in mitigating these negative outcomes [46]. There is substantial evidence in the literature which show that maternal stress and anxiety are negatively associated with child developmental outcomes [79, 85] in the general population and affect a broad range of parenting skills, which are negatively associated with poorer parent-child communication, poorer and less consistent parenting discipline leading to child problem behaviours [85]. Exposure to maternal depression in particular has a negative influence on child development in infancy; a South African study found that maternal depression was related to increased parenting stress and parent–child dysfunction which was again associated with children’s behaviour and functioning [91].

6.1.1 Aim of analysis

The aim of this analysis was to investigate cognitive differences between HIV positive and HIV-exposed uninfected children as well as the relationship between maternal stress and depression scores, and child cognitive performance in Zimbabwe.

6.2 Methods

6.2.1 Assessment measures

The cognitive profiles of the participating children were assessed using the Mullen Scales of Early Learning.

Maternal mental health measures included the Edinburgh Postnatal Depression Scale (EPDS), a postpartum depression-screening questionnaire which was administered to participating mothers. The EPDS was not used as a diagnostic tool for identifying depression but rather as a screening tool. The Parental Stress Index-Short Form (PSI-SF), a self-completed screening tool was also used for identifying different types of stress associated with parenting [228].

A subset of questions from the Household Food Insecurity Access Scale [240] were used to assess household food security. Other sociodemographic information such as: child characteristics (age, gender, birth weight, growth rate-obtained from child's health card), caregiver characteristics (age, marital status) and socioeconomic factors (educational level, employment status, and number of adults living in the household) were also collected.

6.2.2 Statistical analysis

Child and caregiver characteristics as well as socioeconomic factors were described using mean and standard deviations (SD) for continuous variables, and frequency percentages for categorical variables. Only biological mothers (i.e. excluding other type of caregivers) were included in this analysis.

The Mullen scores were reported using mean, SD, and adjusted mean differences (95% CI). Prior to data analysis, score distributions on all dependent measures were examined to test the assumptions of normality and homogeneity of variance. All

analyses were performed using STATA v.14.1 (StataCorp LP, College Station, Texas, USA).

6.2.2.1 Maternal stress and mood and cognitive development of children

Linear regression models were fitted to relate Mullen scores to exposure variables maternal stress (using PSI-SF), and mental health (using EPDS) respectively. EPDS and PSI-SF total stress scores were tested against the Mullen scales both univariably and adjusting for confounders. HIV status was included in the models *a priori*. Results are reported using mean EPDS scores, mean total stress scores, SD, unadjusted and adjusted mean differences (**section 6.3.5** and **6.3.6**).

6.2.2.2 HIV status and cognitive development of children

For this analysis children with unknown HIV status were excluded. Child HIV status was established by caregiver report and/or clinic records at trial enrolment or baseline assessment. HEU children were defined as having confirmed HIV negative status but born to an HIV positive biological mother. Student's t-test and Pearson's chi square were used to test for differences in selected demographic infant and caregiver characteristics by HIV status (**Table 6.1**).

Univariate models were used to assess the relationship between Mullen scores and the child's HIV status, and multivariate regression was then used adjusting for potential confounders - i.e. variables that were associated with both the outcome and the exposure ($p<0.2$). Infant's age and gender were included in the models *a priori*.

6.3 Results

The first step in this analysis was to investigate the cognitive profiles of the participating children at baseline by HIV status. This was followed by examining maternal health factors associated with child development. Therefore, **Table 6.1** shows selected child are maternal characteristics stratified by HIV status. A detailed description of the 574 participating dyads characteristics (by trial arm) has been provided in **Chapter 4 (Tables 4.1 and 4.2)** and is summarized in **Table 6.3** for the sample.

6.3.1 Participants characteristics

Of the 671 eligible caregiver-child dyads invited to participate in the trial, 574 (85.5%) caregivers agreed to do so. The sample included 562 (98.0%) biological mothers and 12 (2.0%) other caregivers-mainly grandmothers.

Data from the biological mothers only (n=562) were included for this analysis. This was due to the use of a mental health measure (EPDS) designed for assessing depression symptoms in postpartum women in the trial. For the HIV status and child cognitive development models, children with unknown HIV status were further excluded (n=165), leaving a total of 397 dyads. The characteristics of the 397 dyads are described in the following **section** (**6.3.2**).

6.3.2 Child and caregiver characteristics by HIV status

From a total of 397, there were 16 HIV positive and 381 HEU children. HIV status was not associated with child's age at enrolment in the trial, gender, or birth weight (**Table 6.1**). However, the mothers of HEU children were slightly older than HIV positive children's mothers (mean: 32.1 vs. 29.1; p=0.05). In addition, mothers caring for HIV positive children reported higher mean stress scores compared to the HEU group (95.8 vs. 85.0; p=0.01). There was no difference noted in the maternal depression scores by child HIV status.

Table 6.1*: Selected child and caregiver characteristics by HIV status*

Characteristics	HIV Positive children (n=16)	HEU children (n =381)	Total (n=397)	p-values
Child				
Age (Months), mean (SD)	14.6 (5.5)	14.1 (5.5)	14.1 (5.5)	0.71
Gender, n (%)				0.71
Female	9 (56.3)	196 (51.4)	205 (51.6)	
Male	7 (43.8)	185 (48.6)	192 (48.4)	
Birth weight (kilograms), mean (SD)	2.8 (0.7)	3.0 (0.5)	3.0 (0.5)	0.19
Caregiver				
Age (Years) , mean (SD)	29.1 (6.0)	32.1 (6.1)	32.0 (6.1)	0.05
Maternal depression scores (EPDS), mean (range), SD	12.2 (0-30), 7.9	11.6 (0-30), 6.4	11.6 (0-30), 6.5	0.72
Maternal depression scores - categories of EPDS, n (%)				0.71
None or minimal depression score (0-6)	4 (25.0)	92 (24.2)	96 (24.2)	
Mild depression score (7-13)	5 (31.3)	134 (35.2)	139 (35.0)	

Moderate depression score (14-19)	4 (25.0)	117 (30.7)	121 (30.5)	
Severe depression score (20-30)	3 (18.8)	38 (9.9)	41 (10.3)	
Maternal total stress scores (PSI-SF), mean (range), SD	95.8 (40-142), 22.0	85.0 (40-142), 15.9	85.4 (40-142), 16.3	0.01

HEU, HIV-Exposed Uninfected **|** *PSI-SF, Parental Stress Index-Short Form* **|** *SD, Standard Deviation.*

6.3.3 Child cognitive profiles at baseline

Results of the cognitive function analyses by HIV status are shown in **Table 6.2**. Child's HIV status was associated with gross motor scores, with the HEU children having higher mean gross motor T-scores compared to HIV positive children (50.3 vs. 40.6; aMD: 8.02; 95% CI: 1.93 to 14.11; p=0.01).

There was no evidence of difference by HIV status on the other developmental domains or on the overall score (HIV positive children 101.3 vs. HEU children 100.0; aMD: -1.18; 95% CI: -9.14 to 6.79; p=0.77). The result show both groups of children have similar mean scores on most of the Mullen sub-scales. The difference observed in gross motor scores across the two groups here was not used as an indication of their cognitive performance, but simply differences in motor functioning.

***Table 6.2**: Mullen T-scores of the HIV positive and HIV-exposed uninfected children*

Mullen scale	HIV Positive children (n=16)	HEU children (n=381)	Adjusted Mean difference (95% CI)	p value*
	Mean (SD)	Mean (SD)		
Expressive language	51.3 (13.8)	51.2 (10.4)	-1.92 (-6.69 to 2.83)	0.43
Receptive language	48.4 (13.2)	46.2 (11.7)	-0.51 (-6.19 to 5.17)	0.86
Fine Motor	51.2 (13.4)	49.8 (11.7)	-2.27 (-8.09 to 3.54)	0.44
Gross Motor	40.6 (14.7)	50.3 (11.2)	8.02 (1.93 to 14.11)	0.01
Visual reception	50.9 (16.0)	52.0 (13.1)	1.62 (-4.76 to 8.01)	0.62
Early learning composite score	101.3 (22.8)	100.0 (18.4)	-1.18 (-9.14 to 6.79)	0.77

**Linear regression models relating Mullen scales and HIV status were fitted*
Models were adjusted for infant's age, gender, growth rate and mother's age

6.3.4 Maternal mental health at baseline

Selected infant and caregiver baseline characteristics are summarized in **Table 6.3**. Overall, the mean age of the children was 11.9 (SD=6.5) months, 287/562 (51%) were girls, and based on the child' health card almost half were moderately underweight at time of enrolment 273/562 (49.1%).

The mean age of mothers was 31.5 years (SD=6.3). Over half (301/562) of mothers had completed secondary school level education and 206/562 (36.7%) were in paid employment. Most households (n=502, 89.3%) had 1-3 resident adults, and two in five (n=227, 40.4%) households reported moderate to severe food insecurity.

The mean maternal depression score on the EPDS scale was 11.5 (SD=6.5). When using the EPDS cut-off scores for mild, moderate and severe depression, over half (n=361, 64.2%) of mothers experienced mild or moderate depression, with 58 (10.3%) mothers categorised as having severe depression. The mean maternal stress score on the PSI SF scale was 84.8 (SD=16.3), high scores indicating higher levels of parenting stress (range: 49-149).

***Table 6.3**: Baseline characteristics of study sample*

Characteristics	Total Sample (n=562)
Infant	
Age (Months), mean (SD)	11.9 (6.5)
Gender, n (%)	
Female	287 (51.1)
Male	275 (48.9)
Birth weight (kilograms)~, mean (SD)	3.0 (0.5)
Growth rate~, n (%)	
Normal	262 (47.1)
Moderately underweight	273 (49.1)
Severely underweight	21 (3.8)
Caregiver	
Age (Years), mean (SD)	31.5 (6.3)
Education level (Completed secondary school and above), n (%)	301 (53.6)
Marital status ~ ^, n (%)	
Married	447(79.7)
Divorced/separated	74 (13.2)
Widowed	27 (4.8)
Never been married	13 (2.3)
Employment status (Employed), n (%)	206 (36.7)

Number of adults living in the same household [+], n (%)	
1-3 adults	502 (89.3)
4-6 adults	50 (8.9)
7-9 adults	3 (0.5)
Household food security, n (%)	
Little to no hunger	335 (59.6)
Moderate to severe hunger	227 (40.4)
Maternal depression scores (Edinburgh Postnatal Depression Scale -EPDS), mean (range), SD	11.5 (0-30), 6.5
Maternal depression scores -*categories of EPDS,* n (%)	
None or minimal depression score (0-6)	143 (25.4)
Mild depression score (7-13)	190 (33.8)
Moderate depression score (14-19)	171 (30.4)
Severe depression score (20-30)	58 (10.3)
Maternal total stress scores (PSI-SF), mean (range), SD	84.8 (49-149), 16.3

PSI-SF, Parental Stress Index-Short Form | SD, Standard Deviation

~ *Missing data: Growth rate variable had 6 missing records* **|***Birth weight variable had 2 missing records***|** marital status variable had 1 missing record

^ *Marital status variable was recoded to married/not married*

+ *There was 1 inaccurate record for the variable "Number of adults living in the same household" which was excluded from the table*

6.3.5 Association of maternal depression symptoms with child cognitive outcomes

Results from multivariate models suggest that maternal stress and depression scores were associated with the child's cognitive scores. Higher maternal EPDS depression scores were associated with lower child cognitive scores in the early learning composite score (adjusted mean difference (aMD)= -0.28; 95% CI: -0.50 to -0.06; p=0.01) and all domains; expressive language (aMD=-0.14; 95% CI: -0.27 to -0.01; p=0.04), fine motor skills (aMD=-0.17; 95% CI: -0.33 to -0.01; p=0.03), gross motor (aMD=-0.22; 95% CI: -0.40 to -0.04; p=0.02), visual reception (aMD=-0.22; 95% CI: -0.40 to -0.05; p=0.01), and weakly associated with receptive language (aMD=-0.15; 95% CI: -0.30 to 0.01; p=0.07) (**Table 6.4**).

Child's age, and caregiver's employment status, were found to negatively influence the relationship between maternal depression scores and Mullen scores, thus were adjusted for in models.

Table 6.4: *Summary of association of maternal mental health (using EPDS) with child cognitive outcomes*

Mullen scale	Unadjusted mean difference (95% CI)	Adjusted mean difference (95% CI)	p value*
Expressive language	-0.16 (-0.30 to -0.03)	-0.14 (-0.27 to -0.01)	0.04
Receptive language	-0.13 (-0.27 to 0.01)	-0.15 (-0.30 to 0.01)	0.07
Fine Motor	-0.14 (-0.28 to -0.00)	-0.17 (-0.33 to -0.01)	0.03
Gross Motor	-0.06 (0.20 to 0.07)	-0.22 (-0.40 to -0.04)	0.02
Visual reception	-0.14 (-0.29 to 0.01)	-0.22 (-0.40 to -0.05)	0.01
Early learning composite score	-0.25 (-0.46 to -0.04)	-0.28 (-0.50 to -0.06)	0.01

** Linear regression models relating Mullen scales and maternal depression were fitted. The models were adjusted for tested confounders (child age, HIV status and caregiver's employment status).*

6.3.6 Association of maternal stress with child cognitive outcomes

Similarly, maternal stress scores were associated with infant cognitive scores (**Table 6.5**). Higher stress scores were associated with poorer child scores in the early learning composite score (aMD=-0.11; 95% CI: -0.20 to -0.02; p=0.02) and in expressive language (aMD=-0.07; 95% CI: -0.12 to -0.01; p=0.01), gross motor skills (aMD=-0.12; 95% CI: -0.18 to -0.05; p<0.01), visual reception (aMD=-0.09; 95% CI: -0.16 to -0.02; p=0.02), and weakly associated with receptive language (aMD=-0.06; 95% CI: -0.13 to 0.00; p=0.06).

A list of possible confounders which could exaggerate, hide or distort the relationship between child's HIV status and Mullen scales were examined. Child's age, growth rate, and examiner to administer Mullen assessments were found to be confounders in the relationship between maternal stress scores (PSI-SF total stress) and Mullen scores, and adjusted for in the models.

Table 6.5: *Summary of association of maternal stress (using the PSI-SF total stress score) with child cognitive outcomes*

Mullen scale	Unadjusted mean difference (95% CI)	Adjusted mean difference (95% CI)	p value*
Expressive language	-0.12 (-0.17 to -0.07)	-0.07 (-0.12 to -0.01)	0.01
Receptive language	-0.09 (-0.14 to -0.03)	-0.06 (-0.13 to 0.00)	0.06
Fine Motor	-0.06 (-0.12 to -0.01)	-0.02 (-0.08 to 0.05)	0.58
Gross Motor	-0.08 (-0.13 to -0.02)	-0.12 (-0.18 to -0.05)	<0.01
Visual reception	-0.11 (-0.18 to -0.05)	-0.09 (-0.16 to -0.02)	0.02
Early learning composite score	-0.19 (-0.27 to -0.10)	-0.11 (-0.20 to -0.02)	0.02

** Linear regression models relating Mullen scales and maternal stress were fitted.*
The models were adjusted for tested confounders (child age, HIV status, growth rate, and examiner conducting the Mullen assessments).

6.4 Discussion

6.4.1 HIV status and cognitive development of children

In this study, HIV status had no impact on child cognitive development but was associated with children's gross motor functioning. Although there is evidence in the literature for a difference in the cognitive performances between HIV positive and HEU children [57, 241], with the HIV positive children experiencing a range of developmental delays [60, 67, 217], there was no difference detected in the overall cognitive scores between the two groups in this study. This could be due to the small proportion of children with a diagnosis who were HIV positive in the sample, limiting our ability to detect an association, or the fact that both groups of infants lived in an HIV endemic population affected by the multifaceted ramifications of HIV. In addition, early diagnosis and sufficient viral load suppression within the first 3 years of life is known to be associated with higher neurocognitive performance in HIV positive children [182], this could explain the findings here as some of the HIV positive children were on treatment.

The findings of this study were consistent with other studies that report HIV positive infants experience an increased risk of developmental delays in the gross motor domain compared to HEU children [54, 59, 63]. Motor functions are easier to accurately measure compared to other developmental domains and cognitive constructs, this could explain the observed difference in the motor functions of the children here. Other studies in SSA report that the motor development of HIV positive children is more affected than their cognitive development [190]. The structural damage caused to the brain as a result of the virus could offer biological explanation to the findings relating to motor delay in this study. In addition, only 7/19 HIV positive children were on ART, initiating treatment at different ages ranging from birth to 18 months; the delay in treatment initiation for some of these children could perhaps contribute to the gross motor delay observed here.

6.4.2 Maternal stress and mood and cognitive development of children

The results of this analysis show the high level of mental health burden among HIV positive mothers in rural Zimbabwe. Although the EPDS scale used was not diagnostic,

the general literature cut-off points [225] indicate that 10% of mothers had scores in the severe range, while over half of the sample had scores falling in the mild to moderate range. Stress levels were also notably high and maternal stress was found to be higher in the group caring for HIV positive infants. In addition, higher maternal stress and depression symptoms were found to negatively influence infant cognitive performance and development for this HIV affected sample. The negative association with child cognitive outcome observed here could be driven by the high proportion of mothers who are reporting mild to moderate depressive symptoms. The association of maternal depression severity with child cognitive development will be examined further in **Chapter 7**.

As discussed in previous chapters, there is evidence in the literature that shows exposure to poor maternal mental health can have negative influence on child development and is associated with delayed cognitive development [79, 85, 90]. The result of this study adds to the body of literature that suggests higher maternal stress and depression symptoms are associated with poorer infant cognitive performance in an HIV endemic rural setting in SSA. Of note, paternal mental health is also known to affect child development and mood [242, 243], although the mental health status of fathers was not assessed, it could contribute to the findings here. Contrary to findings from a Ugandan study where caregivers' depression scores were related only to the measure of child behaviour and not to the performance-based measures of cognition [44], the results here indicate that high maternal stress and depression symptoms are associated with poorer child expressive language and visual reception ability in particular. It is reported that infants of depressed mothers tend to show affectively less positive facial expressions and vocalization, more withdrawal, less attentiveness to the mother, decreased activity level, greater fussiness, and overall less engagement with people and objects [244]. Another study examining maternal depression and caregiving during the first year of life in England, suggested that maternal depression was associated with poorer caregiving of children and that the poorer caregiving was subsequently associated with poorer language development, through an indirect pathway [92].

In the presence of chronic illness such as HIV, home environment and external stressors could contribute to explaining findings of how maternal depression scores

and child cognitive performance are linked. As discussed above maternal depression and stress influence the level of stimulation and quality of interaction caregivers provide their infants. Coping with challenges associated with HIV such as household food insecurity, poor health and undernutrition, can have negative psychosocial impact and put a strain on the mental health of the caregivers, resulting to the reduced child stimulation. The impact of reducing the quality of early child stimulation will have on child cognitive development will be discussed further in **Chapter 8 (section 8.2**).

Previous studies also report that depression or stress among HIV positive mothers [85] is high when caring for HIV positive children [79] as well as being associated with poorer child outcomes [87, 89, 90]. The results of this study did show that mothers caring for HIV positive children tend to have higher stress levels. It is possible that the association could be explained by both directions – the mood and stress could be affecting child development, or child development delays is affecting maternal mood and stress. However, the cross-sectional nature of the data used here limits our ability to further explore the direction of association between maternal mental health and child cognition. Other limitations of this analysis as well as its strengths will be discussed in **Chapter 8 (section 8.3).**

Despite the limitations, the results of this study demonstrate the potential importance of maternal mood and stress levels in child language and visual perception development within the current study setting. Introducing a comprehensive intervention, which incorporates elements of parental stress and depression reduction, as well as adequate child stimulation, may address this. Studies exploring the drivers of maternal stress and depression symptoms could also prove to be insightful for future research.

6.5 Chapter summary

Understanding the role of HIV and maternal mental health in child development is critical. In this chapter, the relationship of maternal mental health and cognitive scores of HIV exposed children was explored on recruitment to the CHIDO trial. The cognitive profiles of the children in the trial were investigated first and compared to a normed USA reference sample. The results indicate that although there was a difference in gross motor development, there was no evidence of difference in the overall cognitive functioning of the children by HIV status. When the role of maternal mental health and child cognitive development were explored, higher maternal depression and stress scores were found to be associated with lower child cognitive scores overall and several developmental domains. However, there was a circular pattern observed between maternal mood disorders and child dysfunctional behaviour, where maternal mental disorders and child's behavioural problems exacerbate one another.

CHAPTER 7: The impact of maternal mental health on child cognitive development: A longitudinal analysis over the first 3 years of life

7.1 Chapter overview

In the previous chapter the mental health state of mothers at baseline was assessed. The relationship between maternal stress and depression scores and child cognitive performance was also explored. Due to the cross-sectional nature of the analysis in **Chapter 6**, it was not possible to determine whether there is causal effect relationship between maternal mental health issues and child cognitive development. Maternal depression symptoms and stress were reassessed after 12 months as part of the trial, making it possible to explore and understand the relationship between maternal mental health and child cognitive development longitudinally. The relationship between maternal suicidal ideation and its association with child development were also examined in this chapter.

I started by investigating if there were any overlaps between the mental health disorders reported by mothers in this study. The possibility of using a combination of mental health measures (i.e. EPDS, SSQ-8 and EPDS-item 10), on cross-sectional level to assess the mental health status of the participating mothers was explored. These scales (EPDS and SSQ-8) measure different forms of mental disorders and there should be no overlap. To explore whether the same mothers that are reporting CMD are also reporting other mental disorders including depressive symptoms or more extreme disorders like suicidal ideation, a descriptive analysis of the participants scoring below and above the cut-off points on the three scales was carried out (**Table 7.1**). Of the 574 participating mothers, 57.7% had responded to the mental health question on both EPDS and SSQ-8 and 32.3% (107/331) of the mothers scored above the cut-off points on the three assessments. However, it was not appropriate to take the three mental health measuring scales and use them as one tool as they all measure different things ranging from the risk of common mental disorders, postnatal depression to more extreme disorders like suicidal tendencies. Therefore, the different forms of mental disorders experienced by the mothers over a period of time were examined

individually as well as their association with child cognitive development, using the same analysis technique in this chapter.

This chapter is separated into three sections. In the first section the relationship between maternal common mental disorders and child cognitive outcomes is examined at baseline and 12 months follow-up (**section 7.2**). This is followed by investigating effect of maternal depression symptoms and suicidal ideation over time on child cognitive development, respectively in **sections 7.3** and **7.4**.

Table 7.1: *Descriptive tables of participants scoring below and above the threshold on three mental health measures*

Maternal mental health measures	Below cut-off, N (%)	Above cut-off, N (%)	Total
Common mental disorders (SSQ-8)	344 (59.9)	230 (40.1)	574
Depression symptoms (EPDS)	278 (49.5)	284 (50.5)	562
Suicidal ideation (EPDS item-10)*	391 (69.6)	171 (30.4)	562
Depression symptoms + suicidal ideation	250 (63.6)	143 (39.4)	393
Depression + CMD	239 (56.2)	186 (43.8)	425
Depression + suicidal ideation + CMD	224 (67.7)	107 (32.3)	331

Cut-off for depression symptoms on EPDS ≥12, and risk of CMD on SSQ-8 ≥6
**Those responding "Yes, quite often", "Sometimes" or "Hardly ever" to the question -"The thought of harming myself has occurred to me" (EPDS item 10) were categorised as experiencing suicidal ideation*

7.2 Effect of maternal common mental health disorders on child cognitive development at 12 months

7.2.1 Introduction

Maternal mental health is an important factor in healthy child development [245, 246]. Exposure to maternal CMD has been associated with increased risk of poor growth and cognitive development in infants that persists to later ages [245]. Evidence from low- and middle-income countries (LMICs) shows that the children of mothers with CMD tend to have worse growth, cognitive and language development, even when taking social adversity into account [247-249]. The relationship between maternal anxiety-mood disorders and poor childhood development is often exacerbated by low socio-economic status [126, 246]. A systematic review examining the link between poverty and CMD in adults in LMICs reported that CMD is strongly associated with lower levels of education and socio-economic status, rapid social change, violence and insecurity, particularly among women in low resource settings [250]. However, the majority of studies in the review were cross-sectional, thus making it difficult to draw clear conclusions regarding the direction of the poverty-CMD relationship [250]. The evidence presented in this review was supported by other studies from Africa which demonstrate an association of CMD with caregiver income and level of education [103] as well as child development [246], however the direction of this association also needs further exploring.

Furthermore, studies in LMICs show that maternal CMD is associated with child language development in HIV-affected populations [7, 251]. There is also good evidence that HIV is associated with elevated mental health burden [105, 107, 116]. HIV in pregnancy is commonly reported and global initiatives focus on treatment to reduce transmission of the virus to the infant [252-254]. However scant attention is paid to the mental health burden of the mother and how this may affect child development. There is a need for more evidence from LMICs investigating the impact of maternal CMD for mothers with HIV over a period of time on child cognitive outcomes, especially during the early stages of development.

7.2.1.1 Aim of analysis

The association of maternal CMD (including depression symptoms) and child cognitive scores will be investigated in this longitudinal study.

7.2.2 Methods

7.2.2.1 Study sample

Mother-child dyads from the trial were assessed for mental health at baseline upon enrolment and were reassessed after 12 months. The analysis of the association between CMD and child cognition includes all primary caregivers (i.e. biological mothers and other caregivers) that completed the mental health assessments at both time points whose children also completed developmental assessments at both time points.

7.2.2.2 Assessment measures

Socio-demographic information were collected on participant characteristics (age, marital status), and socioeconomic factors (educational level, employment status, asset index score, and number of adults living in the household). A subset of questions from the Household Food Insecurity Access Scale [18] was used to assess household food security in the study. These were used to categorize households as: food secure, moderately insecure or severely insecure.

Common mental disorder (CMD) symptoms were assessed using the locally developed and validated Shona Symptom Questionnaire (SSQ)-8 [19]. Scores range from 0-8, and scores >6 were used as a cut-off point for identifying those at risk of CMD. The EPDS, a postpartum depression-screening questionnaire (with scores ranging from 0-30), was administered to participating mothers [20, 21]. A cut-off point (>12) was used for identifying participants with high depression symptoms. Parental Stress Index-Short Form tool was used for identifying different types of stress associated with parenting [22]. The Mullen Scales of Early Learning [23, 24] was used for assessing child cognitive development.

7.2.2.3 Statistical analysis

Student's t-test, and Pearson's chi square were used to compare characteristics of participants by CMD symptoms. Characteristics of the sample were described using means, standard deviations (SD), frequencies and percentages.

Mixed-effects linear regression was used to compare child cognitive outcomes by caregiver over 12 months. The CMD categorical dependent variable consisted of four levels: women who did not experience CMD symptoms at both baseline and 12 month follow-up (reference group), women experiencing CMD at baseline but not at 12 months follow-up (i.e. those improving), women who did not experience CMD at baseline but experienced CMD at 12 months (i.e. those deteriorating), and women who experienced CMD at both baseline and 12 months follow-up (chronic group).

Adjusted mean differences were reported comparing the mean children's cognitive scores at follow-up by caregiver's CMD categories. Models were adjusted for tested confounding variables; household food insecurity and the code for the person conducting Mullen assessments. Baseline Mullen scores of participating children were adjusted for *a priori*. Clustering within study sites was accounted for by incorporating a random effect for cluster and adjusting for it in all models. All analyses were conducted using STATA v.15.1 (StataCorp LP, College Station, Texas, USA).

7.2.3 Results

7.2.3.1 Participants characteristics at baseline

At baseline, all 574 caregivers enrolled in the trial completed the assessments, with 230 (40.1%) caregivers reporting CMD symptoms above the cut-off on the SSQ-8 scale (**Table 7.2**).

The mean age of the mothers was 31.9 years (SD=6.9), 52.9% had completed secondary level of education and above, over three quarters were married (79.3%), and 36.6% reported being formally or informally employed. The mean household size was 5.2 (SD=1.8), and 37.6% reported moderate to severe hunger in the household. Over half the women (53.0%) reported that they were diagnosed with HIV before their pregnancy and were aware of their status prior to conception.

There was no evidence of differences by trial arm in baseline prevalence of CMD among the caregivers (48.7% CMD symptoms in the intervention arm vs. 51.3% control arm; p=0.92). However, CMD symptoms were associated with caregivers' education level, marital status, food insecurity, child cognitive scores, and parental stress and depression symptoms (**Table 7.2**). Caregivers with CMD symptoms were less likely to have completed higher education (46.9% vs. 56.9%; p=0.02), more likely to be unmarried (27.8% vs. 16.0%; p<0.01), and more likely to live in households with moderate to severe hunger (50.0% vs. 29.4%; p<0.01) compared to the group without CMD symptoms. Caregivers with CMDs also experienced elevated parental stress (PSI-SF mean- 93.1 vs. 79.4; p<0.01) and depression symptoms (EPDS mean- 16.2 vs. 8.3; p<0.01). In addition, CMM symptoms in caregivers were weakly associated with caregiver employment status and household asset index score (p=0.08).

Table 7.2: *Caregiver demographic, socioeconomic, reproductive, mental health characteristics and child cognitive development by CMD symptoms at baseline*

Caregiver characteristics	**No CMD symptoms (n=344)**	**CMD symptoms (n=230)**	**Total (n=574)**	**p value**
Trial arm, n (%)				0.92
Intervention	169 (49.1)	112 (48.7)	281 (49.0)	
Control	175 (50.9)	118 (51.3)	293 (51.0)	
Age (Years), mean (SD)	31.6 (6.5)	32.3 (7.6)	31.9 (6.9)	0.22
Education level (Completed secondary school and above), n (%)	196 (56.9)	108 (46.9)	304 (52.9)	0.02
Marital status, n (%)				<0.01
Yes	289 (84.0)	166 (72.2)	455 (79.3)	
No	55 (16.0)	64 (27.8)	119 (20.7)	
Relationship status^, n (%)				0.01
Married	289 (84.0)	166 (72.2)	455 (79.3)	
Divorced/separated	32 (9.3)	42 (18.3)	74 (12.9)	
Widowed	15 (4.4)	16 (7.0)	31 (5.4)	
Never been married	8 (2.3)	5 (2.2)	13 (2.3)	

Employment status (Yes-employed), n (%)	116 (33.7)	94 (40.9)	210 (36.6)	0.08
Household size (number of people living under the same roof) , mean (SD)	5.2 (1.7)	5.3 (1.9)	5.2 (1.8)	0.31
Hunger scales, n (%)				<0.01
Little to no hunger	243 (70.6)	115 (50.0)	358 (62.4)	
Moderate to severe hunger	101 (29.4)	115 (50.0)	216 (37.6)	
Asset Index score (terciles), n (%)				0.08
Low	108 (31.4)	84 (36.5)	192 (33.5)	
Middle	109 (31.7)	82 (35.7)	191 (33.3)	
High	127 (36.9)	64 (27.8)	191 (33.3)	
Tested for HIV, n (%)				0.36
Before pregnancy	186 (54.6)	116 (50.7)	302 (53.0)	
During or following pregnancy	155 (45.5)	113 (49.3)	268 (47.0)	
Parental Stress Index at baseline, mean (SD)				
Parental distress	29.2 (6.5)	36.2 (7.1)	32.0 (7.6)	<0.01
Difficult child	26.6 (5.8)	30.8 (6.8)	28.2 (6.6)	<0.01
Parent-child dysfunction	23.6 (5.5)	26.0 (6.6)	24.6 (6.0)	<0.01

Total Stress score	79.4 (13.8)	93.1 (16.2)	84.9 (16.2)	<0.01
EPDS at baseline, mean (SD)	8.3 (5.4)	16.2 (5.0)	11.5 (6.5)	<0.01
Child cognitive development at baseline (Mullen scales), mean (SD)				
Expressive Language	53.8 (11.0)	51.2 (10.4)	52.8 (10.8)	<0.01
Fine Motor	52.0 (11.2)	48.6 (11.7)	50.7 (11.5)	<0.01
Gross Motor	51.0 (10.6)	49.6 (11.3)	50.5 (10.9)	0.13
Receptive Language	48.8 (11.3)	45.7 (11.8)	47.6 (11.6)	<0.01
Visual reception	55.0 (12.4)	50.2 (12.8)	53.1 (12.7)	<0.01
Early Learning Composite Score	104.9 (17.2)	98.3 (18.6)	102.3 (18.0)	<0.01

EPDS: The Edinburgh postnatal depression scale **|** *SSQ-8: Shona Symptom Questionnaire* **|** *CMD: common mental health disorder*

^ *Relationship status variable was recoded to married/not married during analysis*

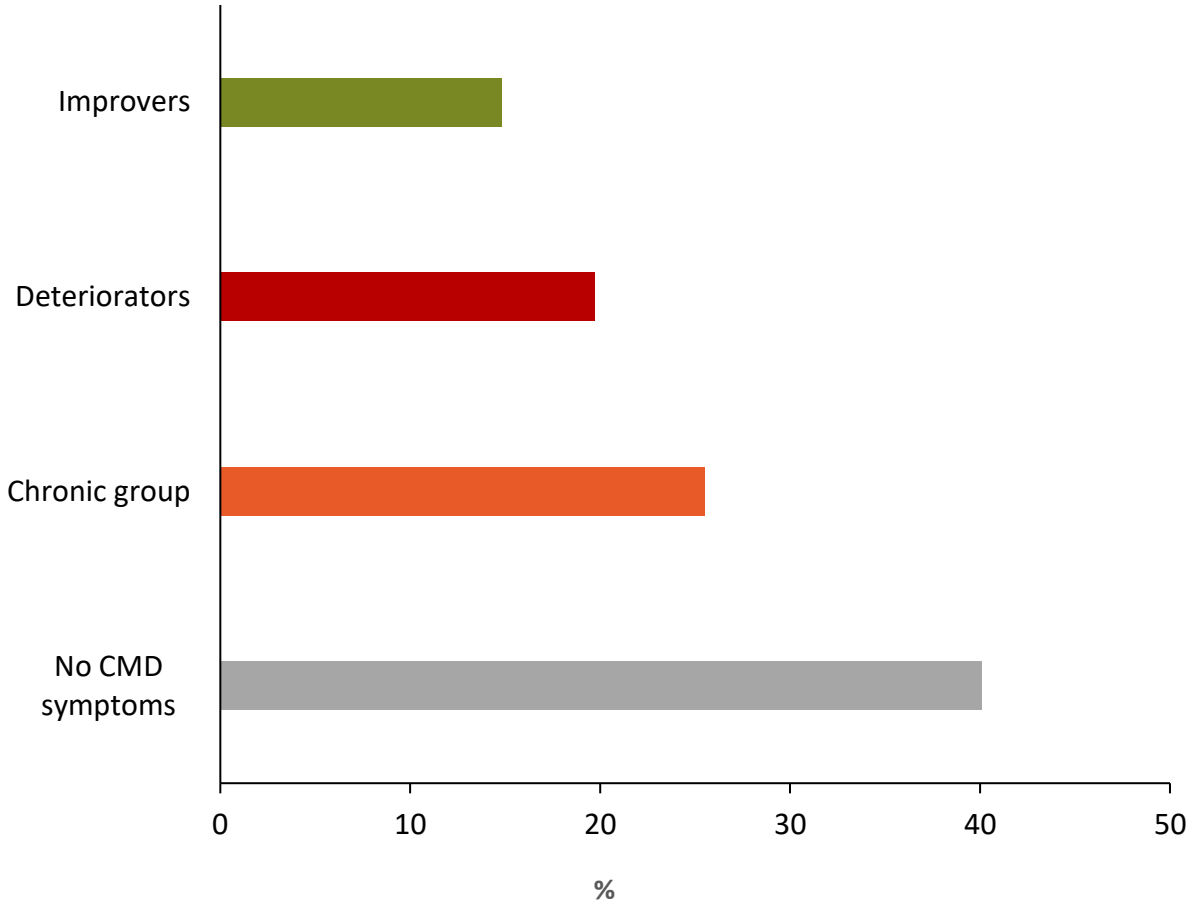
*SSQ-8 cut-off points (No CMD symptoms=scores 0-5***|** *CMD symptoms= 6-8 scores)*

7.2.3.2 Caregiver CMD symptoms change over 12 months

Of the 574 caregivers that completed the baseline assessments, 90.1% (n= 514) completed a follow-up survey after 12 months.

Of the 514 caregivers, the largest proportion (n=206; 40.1%) did not report CMD symptoms at baseline or follow-up. However, 131 (25.5%) reported symptoms of CMD at both time points. There were 101 (19.7%) caregivers who reported emerging CMD symptoms at 12 months only, and 76 (14.8%) who reported CMD at baseline but not at 12 months follow-up.

Figure 7.1*: Categories of change in CMD symptoms reported using the SSQ-8 from baseline to 12 months*



7.2.3.3 Caregiver CMD symptoms and child outcome

The table below (**7.3**) shows child Mullen scores by caregiver CMD categories. Overall, the mean scores of the children were comparable by CMD categories with the children of the reference group (i.e. no CMD symptoms) scoring higher on most of the developmental domains. However, the children of mothers with chronic CMD had consistently lower mean T-scores across all child development domains, compared to the other three groups.

Table 7.3: *Mullen T-scores of children at 12 months follow-up by caregiver CMD categories*

Mullen Scales (T-scores)	No CMD symptoms (n=206)	Improvers (n=76)	Chronic (n=131)	Deteriorators (n=101)
			Mean (SD)	
Expressive language	45.8 (9.1)	43.6 (8.8)	44.4 (10.5)	45.8 (8.9)
Receptive language	47.2 (10.1)	45.9 (9.2)	43.8 (11.1)	43.9 (9.4)
Fine Motor	42.4 (11.3)	40.9 (11.5)	39.6 (9.8)	42.1 (10.9)
Gross Motor ^	50.4 (11.0)	47.1 (11.5)	47.7 (13.2)	50.0 (9.2)
Visual reception	43.4 (10.8)	42.2 (12.3)	40.5 (10.7)	41.7 (10.7)
Early learning composite score	90.0 (15.4)	87.1 (15.0)	85.2 (16.0)	87.5 (14.6)

^Only measured in children aged <36 months at follow-up (n=397)

Results of the multivariable regression models shows no evidence of difference in the overall cognitive score of the children by caregiver CMD categories (**Table 7.4**). Children of caregivers with chronic CMD symptoms had lower receptive language (adjusted mean difference (aMD) -2.81; 95% CI: -5.1 to -0.6; p=0.05) compared to the children of those caregivers who did not report CMD symptoms at either baseline or endline.

Table 7.4: *Association of caregiver CMD over time with child Mullen scores at 12 months*

Mullen scales	No CMD symptoms	Improvers	Deteriorators	Chronic	p value*
		Adjusted mean difference (95% CI)			
Expressive language	Ref	-0.71 (-3.32 to 1.90)	1.60 (-0.72 to 3.92)	-0.48 (-2.99 to 1.28)	0.33
Receptive language	Ref	0.24 (-2.45 to 2.92)	-1.66 (-4.05 to 0.74)	-2.81 (-5.07 to -0.56)	0.05
Fine Motor	Ref	1.40 (-1.58 to 4.38)	1.82 (-0.83 to 4.48)	-0.87 (-3.40 to 1.67)	0.24
Gross Motor ^	Ref	-1.40 (-4.86 to 2.08)	0.30 (-2.98 to 3.58)	-0.77 (-3.83 to 2.30)	0.81
Visual reception	Ref	1.85 (-1.05 to 4.75)	-0.06 (-2.55 to 2.67)	-0.96 (-3.49 to 1.57)	0.35
Early learning composite score	Ref	1.13 (-2.87 to 5.12)	0.09 (-3.46 to 3.63)	-2.86 (-6.34 to 0.62)	0.23

***Model adjusted for baseline Mullen scores, household food insecurity, clustering by trial site and examiner*

^*Only measured in children aged <36 months at follow-up (n=397)*

Mothers with no CMD symptoms at baseline and follow-up were used as a reference group (n=206) for the model above

7.2.4 Discussion

The prevalence of CMD symptoms at baseline was high (40%). CMD symptoms were associated with caregivers' education level, unmarried status, and food insecurity. CMD symptoms were also negatively associated with child receptive vocabulary. The findings of this study were consistent with previous research that show caregivers with mental disorder were less likely to have individual sources of income or employment and had less formal education than other caregivers [102, 103, 255], leading to household food insecurity. However, it is unclear whether these harsh living conditions drive poor mental health, or whether those with poor mental health gravitate towards social deprivation such as unemployment, school dropout and food insecurity. For all these mothers HIV was an additional factor which may contribute to the complex cycle of poor mental health and social deprivation. It is well established that HIV illness is associated with a profound mental health burden [101, 102]. Those with mental health problems are more likely to become infected in the first place, and the demands of living with a life threatening health condition, often stigma bound, may negatively affect mental health [142, 256]. Poor maternal mental health such as chronic or recurrent maternal depression may affect child development and especially when it occurs in the context of adversity such as poverty and dealing with HIV illness as experienced by this study population [257]; this was evident in the results of this study. The likely mechanism is that poverty and food insecurity influence maternal anxiety and depression, and that these factors can be thought of as indirect contributors to children's development, with their effect mediated by maternal mental health status [246].

There is further evidence in the literature of the effect of chronic maternal depression on child development [258]. As observed with maternal depression, mothers experiencing chronic CMDs might be engaging less in early child stimulation practices and verbally interacting less with their children compared to those who have no CMD symptoms [259]. This could explain the low language scores reported by the children of the chronic CMD group. However, contrary to the findings here, a cross-sectional study examining maternal CMD in rural Ethiopia reported that maternal symptoms of CMD were associated with both child global development and most developmental sub-scales except for language domain [246]. Another study reported mothers with

chronic depressive symptoms were more likely to engage in parenting behaviours associated with child health and development than mothers with depressive symptoms at only 1 time or not at all [260].

Of importance it can be difficult to disentangle anxiety and depression symptoms in patients experiencing CMDs. Hadley et al. (2008) reported that when symptoms of mental disorders were separated into high symptoms of depression and anxiety, depression was responsible for the association observed between overall child developmental scores and maternal symptoms of CMD [246]. There is usually an overlap between the two categories (i.e. depression and anxiety symptoms), with symptoms reported by patients in each category being highly related. Nonetheless this is important to understand in order to help tailor mental health care for HIV positive mothers and ensure their children reach their potential.

7.3 Effect of maternal depression symptoms and child cognitive outcome

7.3.1 Introduction

There is strong evidence in the literature that exposure to maternal depression has negative influence on early childhood development, and is associated with impairment in cognitive performance leading to social, behavioural problems and compromised physical health [87-90]. The implications of poor maternal mental health on child development were discussed in depth in **Chapter 1** (**sections 1.6- 1.7**) of this thesis. In addition, this was evident in the results of **Chapter 6**, where the association of maternal depression symptoms at baseline and poorer child development outcomes were investigated and described in detail. After a 12 months follow-up period, mothers' mental health was re-assessed (using EPDS) and models relating exposure of depression symptoms overtime to child cognitive outcomes were built. For the post-natal depressive symptoms and child cognition models, only biological mothers were included in the analysis. Results of these analyses are described in **section 7.3.3** of this chapter.

7.3.1.1 Aim of analysis

The aim of this analysis was to investigate the impact of prolonged exposure (over 12 months) to maternal depression symptoms on child cognitive outcome.

7.3.2 Methods

The methods used for this analysis have been described in **Chapter 6 (section 6.2).** Further analysis carried out using follow-up data are described below.

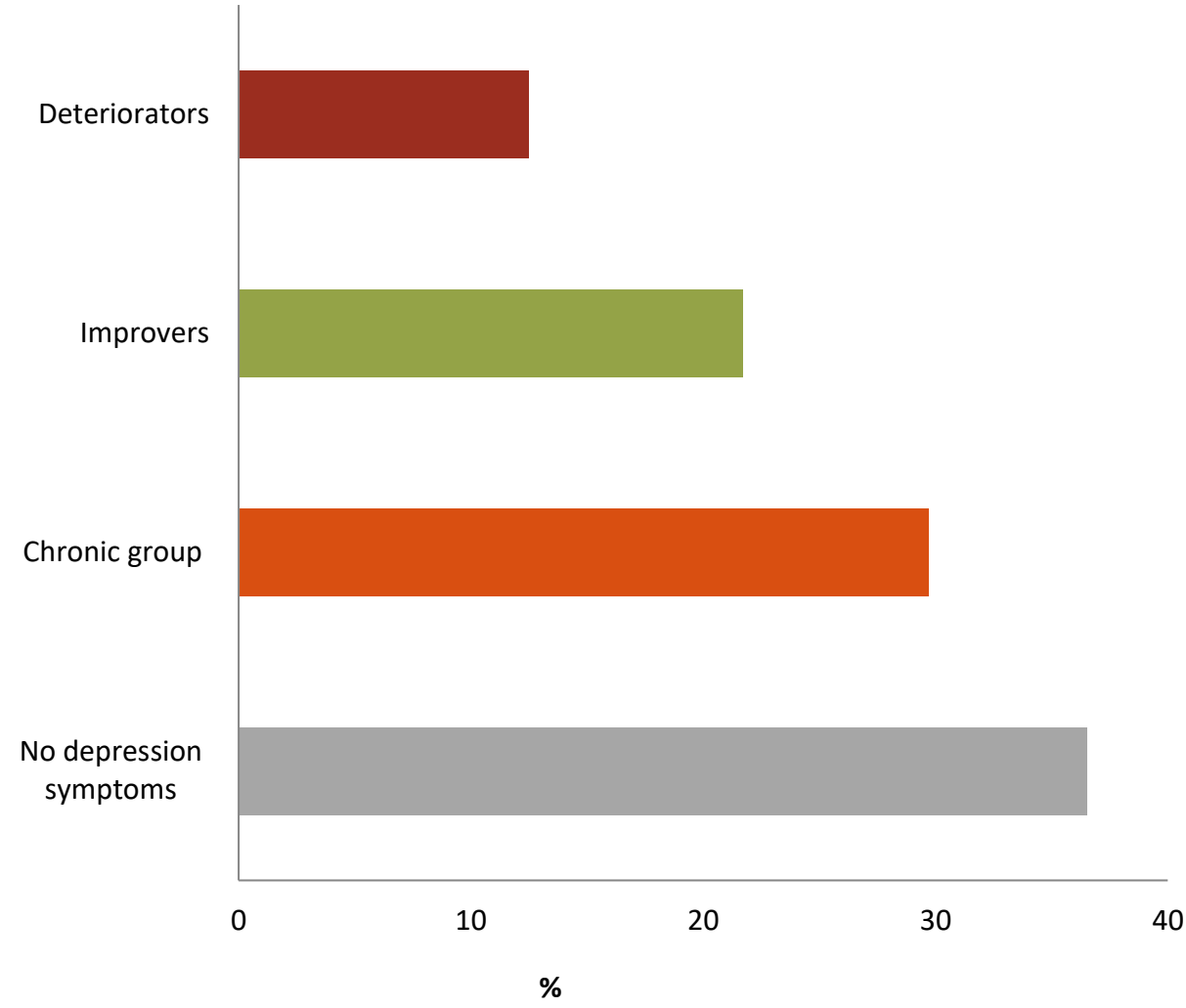
7.3.3 Results

7.3.3.1 Maternal depression symptom change over 12 months

Using the follow-up EPDS data participating mothers were categorized into four levels: women who did not experience depression symptoms at both baseline and 12 month follow-up (reference group), women experiencing depression symptoms at baseline but reported no longer experiencing depression symptoms at 12 months follow-up, women who did not experience depression symptoms at baseline but experienced depression symptoms at 12 months, and women who experienced depression symptoms at both baseline and 12 months follow-up (chronic group).

Of the 514 caregivers to complete follow-up assessments, 177 (36.5%) did not report experiencing depression symptoms at both baseline and follow-up. However, almost a third (n=144, 29.7%) of the mothers reported chronic depression symptoms (i.e. at both time points). There were 59 (12.5%) caregivers who reported depression symptoms at 12 months only, and 105 (21.7%) who reported depression at baseline but not at 12 months follow-up, (**Figure 7.2**).

***Figure 7.2**: Categories of change in maternal depression categories using the EPDS from baseline to 12 months follow-up*



7.3.2.2 Association of maternal depressive symptoms over time with child Mullen scores

Mixed-effects linear regression was used to compare child cognitive outcomes at 12 months by maternal depression categories and adjusted mean differences reported. Models were adjusted for tested confounding variables (i.e. code for the person conducting Mullen assessments) and baseline Mullen scores were adjusted for *a priori*. Clustering within study sites was accounted for by incorporating a random effect for cluster in all models.

Table 7.5 below shows child Mullen scores by maternal EPDS categories. Although the cognitive scores of the children were similar, the children of mothers with chronic depression scored the lowest on all of the sub-scales, compared to the other three groups.

Table 7.5*: Mullen T-scores of children at 12 months follow-up by maternal EPDS categories*

Mullen scale	No depressive symptoms (n=177)	Improvers (n=105)	Deteriorators (n=59)	Chronic (n=144)
Expressive language	45.7 (9.3)	45.7 (8.8)	45.0 (9.2)	43.5 (9.5)
Receptive language	46.5 (9.9)	47.4 (8.8)	44.3 (10.2)	42.9 (10.5)
Fine Motor	42.7 (11.2)	40.8 (10.9)	41.8 (10.8)	39.5 (9.9)
Gross Motor ^	50.3 (11.1)	50.3 (10.7)	48.7 (11.1)	47.0 (12.2)
Visual reception	42.4 (10.5)	42.2 (11.3)	42.3 (12.7)	40.7 (10.6)
Early learning composite score	89.4 (15.0)	88.8 (14.4)	87.5 (16.7)	84.3 (15.1)

^ *Only measured in children aged <36 months at follow-up (n=397)*

Results of the multivariable models showed no evidence of difference in child cognitive scores by maternal EPDS categories, except for child receptive language score (**Table 7.6A**). The children of mothers with chronic depressive symptoms scored 2.1 units lower on the receptive language domain compared to the children of the reference group (aMD: -2.1; 95% CI: -4.3 to 0.0; p=0.03).

A further descriptive analysis was undertaken to understand the composition of the chronic group as well as examining their children's cognitive scores (Table 7.6B). Of the 144 mothers in the chronic group, the majority (58.3%) reported moderate depression symptoms (i.e. scores 14-19 on the EPDS), followed by 25% reporting severe depression symptoms (scores 20-30) and 15% reporting mild depression symptoms. The cognitive scores of the children were examined for the mothers experiencing chronic depression symptoms. The children of mothers with severe depression had consistently low mean scores across the Mullen sub-scales compared to the other two groups, although results were not statistically significant.

Table 7.6A: *Association of maternal depressive symptoms over time with child Mullen scores at 12 months*

Mullen scale	No depressive symptoms (n=177)	Improvers (n=105)	Deteriorators (n=59)	Chronic (n=144)	p value*
			Adjusted mean difference (95% CI)		
Expressive language	Ref	0.55 (-1.66 to 2.76)	0.40 (-2.29 to 3.09)	-0.92 (-2.97 to 1.13)	0.60
Receptive language	Ref	1.53 (-0.78 to 3.85)	-0.64 (-3.46 to 2.18)	-2.13 (-4.28 to 0.02)	0.03
Fine Motor	Ref	-1.19 (-3.71 to 1.33)	0.87 (-2.19 to 3.92)	-1.41 (-3.76 to 0.93)	0.40
Gross Motor ^	Ref	-0.001 (-3.01 to 3.01)	-1.13 (-4.74 to 2.48)	-1.94 (-4.71 to 0.83)	0.51
Visual reception	Ref	0.81 (-1.62 to 3.25)	1.92 (-1.04 to 4.88)	0.41 (-1.86 to 2.68)	0.63
Early learning composite score	Ref	1.05 (-2.26 to 4.35)	1.32 (-2.69 to 5.33)	-1.77 (-4.83 to 1.29)	0.32

Model adjusted for baseline Mullen scores, examiner and clustering of trial sites

***^** Only measured in children aged <36 months at follow-up (n=397)*

Mothers with no depressive symptoms at baseline and follow-up were used as a reference group (n=177) for the model above

Table 7.6B: Child Mullen scores by severity of depression for chronic group (n=144)

	Maternal depression scores -categories of EPDS		
	Mild depression	Moderate depression	Severe depression
Total, n (%)	23 (15.9)	84 (58.3)	37 (25.7)
Mullen Scale, mean (SD)			
Expressive language	43.9 (9.2)	44.9 (9.6)	40.2 (9.1)
Receptive language	45.3 (12.2)	43.2 (10.7)	40.9 (9.1)
Fine Motor	42.2 (9.5)	40.5 (10.3)	35.9 (8.6)
Gross Motor	49.3 (12.1)	47.8 (12.4)	43.6 (11.5)
Visual reception	42.4 (11.1)	40.9 (11.0)	39.4 (9.5)
Early learning composite score	87.8 (16.5)	85.7 (15.4)	79.5 (13.1)

7.3.4 Discussion

The impact of short and prolonged exposure to maternal depression symptoms on child cognitive outcome were explored in this study. The high prevalence of common mental disorders such as depression symptoms and stress in this group of mothers was evident from the cross-section analysis carried out in **Chapter 6.** At 12 months follow-up, the results were consistent with baseline findings and high levels of stress and depression symptoms were still being reported by the participating mothers. Almost a third of the mothers were reporting chronic depressive symptoms at 12 months follow-up. In addition to this, maternal depression symptoms were found to negatively impact child receptive language ability. Longitudinal data were used to further generate four categories of depression and investigate the changes in maternal depression symptoms from enrolment to 12 months. Of the four categories, chronic depression was closely associated with lower child cognitive scores. Children of mothers with chronic depression also consistently scored low compared to the other groups across the developmental sub-subscales assessed. A further examination of the chronic mother's group and their depression severity using EPDS categories (mild, moderate, and severe) was carried out. The association between EPDS depression categories and child cognitive scores was examined. However, there was no significant association found between severity of maternal depression symptoms and child cognitive scores.

The results here are consistent with a study in Zimbabwe that reported high levels of psychiatric morbidity in HIV positive participants experiencing psychiatric symptoms/signs such as emotional withdrawal, and depressed mood [108], compared to a HIV negative group. It is common for PLWH to report such co-morbidities; it could be that maternal stress and depression symptoms are exacerbated when living with a chronic condition such as HIV, where child caregiving duties and coping with psychological and medical demands of dealing with life-threatening condition are difficult [85]. Furthermore, persistence of maternal depression over time seems to be particularly important in terms of language development for children [261]. The results here are consistent with the findings of the previous chapter and **section 7.2** that indicates poor child receptive vocabulary is associated with high maternal depression symptoms. A study in Brazil found that children of mothers who experienced chronic

depression (post-partum and 12 months later) had on average poorer language skills than those children who were exposed to depression only at one time point or not at all [261]. Other studies report the impact of maternal depression on child development is influenced by the amount of time the child is exposed to the disorder, the severity of maternal depression symptoms and the time of exposure [259, 262]. Mothers with chronic depression might be compromising the level of care and quality of stimulation given to their child, particularly in verbal interactions [259]. However other studies report no evidence of association between infant developmental outcomes and the presence of high levels of maternal depression symptoms at more than one time-point (i.e. chronic) even after adjusting for confounding variables such as infant undernutrition, birth weight, prolonged labour and illness episodes [125]. This could perhaps be due to the fact that some children adapt well and develop resilience in the face of adversities or traumatic experiences coupled with low level of care and stimulation provided by their caregivers. This will be discussed further in **Chapter 8** of this thesis. Nonetheless, based on the findings here, it is recommended that common mental disorders generally and depression specifically, should be monitored and addressed in HIV positive mothers, in resource limited settings particularly. There would be benefits of mental health support and provision for both the mothers and their children's cognitive development.

7.4 Effect of maternal suicidal ideation on child cognitive development

7.4.1 Introduction

Suicidal ideation may precede suicide planning and attempted suicide and is a distressing psychological phenomenon, indicative of low mood and poor quality of life [263]. There are several studies of suicide ideation that show maternal suicidal ideation is associated with poorer mother-infant relationship, and as a consequent negatively impacts infant development [244, 264]. Research also shows that in the long term, the quality of the early mother-infant relationship could predict aspects of child development, such as diverse forms of psychopathology, behavioural problems, and disruptions in cognitive abilities [265, 266]. Thus, early identification and treatment of PLWH with suicidal ideation can help to improve their mental health, adherence to treatment and overall quality of life [267] and consequently result in long term gains for their children's development. Previous studies across Africa have examined predictors of suicidal ideation in pregnancy/postpartum using cross sectional data [113, 268]. However, current literature lacks clarity on the relationship between maternal suicidal ideation or behaviour and the child's cognitive development, specifically in the context of HIV.

7.4.1.1 Aim of analysis

The aim of this study was to assess the association between suicidal ideation among mothers living with HIV in Zimbabwe, and child cognitive development using longitudinal data.

7.4.2 Methods

7.4.2.1 Study sample

Participants included caregiver-child dyads recruited in the CHIDO trial [3] and were assessed at baseline upon enrolment. At 12 months follow-up, dyads were re-assessed. This analysis was confined to biological mothers and their children who completed both assessments.

7.4.2.2 Assessment measures

General demographic information such as: participant characteristics (age, marital status), socioeconomic factors (educational level, employment status, asset index score, and number of adults living in the household) as well as child's HIV status were collected. All children had an HIV test at follow-up.

Suicidal ideation was measured as thoughts of self-harm during screening using one item from EPDS [225, 226]. The suicidal ideation item (item-10) was excluded from the total score for depression. In addition, EPDS and PSI-SF were used to assess participants depression and stress levels at baseline [228]. Common mental disorders were assessed using the SSQ-8 [269]. Child cognitive development was assessed using the Mullen Scales of Early Learning [38, 45] here. Participants household food security was assessed using the subset of questions from the Household Food Insecurity Access Scale [240].

7.4.2.3 Statistical analysis

In order to compare participants by suicidal ideation, descriptive analyses were used to summarise the study sample's characteristics at baseline using means, standard deviations, frequencies and percentages.

A logistic regression model was built to identify risk factors associated with suicidal ideation at baseline and was reported using odds ratio. Mixed-effects linear regression was used to compare child cognitive outcomes by maternal suicidal ideation over 12 months. Suicidal ideation over time was categorised into 4 groups. Women who did not report suicidal ideation at both baseline and 12 months follow-up were grouped as non-suicidal. Women reporting suicidal ideation at baseline but not at 12 months follow-up were grouped as improving; women who did not experience suicidal

ideation at baseline but did at 12 months were grouped as deteriorating, and women who experienced suicidal ideation at both baseline and 12 months follow-up were marked as the chronic suicidal ideation group.

Mean children's cognitive scores at follow-up were compared by mother's suicidal ideation categories and presented as adjusted mean differences. Only variables found to be associated with suicidal ideation in bivariate analyses at $p < 0.2$ were included in the multivariate model. Clustering by study sites was accounted for by incorporating a random effect for clinic in all models. *A priori* adjustments included baseline child Mullen scores, mother's age and the code for the person conducting Mullen assessments. All analyses were conducted using STATA v.15.1 (StataCorp LP, College Station, Texas, USA).

7.4.3 Results

7.4.3.1 Participants characteristics at baseline

Prevalence of suicidal ideation at baseline by demographic, socioeconomic, reproductive and mental health characteristics is presented in **Table 7.7**.

At baseline, from the 574 participants enrolled, all 562 biological mothers completed the mental health assessments (the remaining 12 were other primary caregivers). The mean age of the mothers was 31.5 years (SD=6.3), over half (53.6%) had secondary school and above level of education, over three quarters were married (79.7%), and 36.7% reported being formally or informally employed. The mean household size was 5.2 (SD=1.7), and 37.7% of the households reported experiencing moderate to severe hunger. Over half of the women (55.5%) were diagnosed with HIV before their pregnancy and were aware of their status prior to conception. HIV status was ascertained for 493 children at follow-up and of these 15 (3.0%) were HIV positive.

7.4.3.2 Maternal characteristics by suicidal ideation

There was no evidence of differences by trial arm in baseline prevalence of suicidal ideation among HIV positive mothers (53.2% suicidal ideation in the intervention arm vs. 46.8% control arm; p=0.13). Suicidal ideation was associated with mother's age, marital status, household size, food insecurity, and parental stress and depression symptoms (**Table 7.7**). Mothers with suicidal ideation (n=171) were likely to be slightly younger (mean age: 30.7 vs. 31.9; p=0.05), unmarried (34.2% vs. 14.3%; p<0.01), lived in households that experience moderate to severe hunger (53.8% vs. 30.7%; p<0.01), have elevated parental stress (PSI-SF mean- 91.9 vs. 81.8; p<0.01) and depression symptoms (EPDS mean- 14.6 vs. 9.3; p<0.01) compared to the non-suicidal group (n=391).

***Table 7.7**: Maternal demographic, socioeconomic, reproductive, mental health characteristics by suicidal ideation at baseline*

	Non-suicidal (n=391)	**Suicidal (n=171)**	**Total (n=562)**	**p value**
Trial arm, n (%)				0.13
Intervention	181 (46.3)	91 (53.2)	272 (48.4)	
Control	210 (53.7)	80 (46.8)	290 (51.6)	
Age (Years), mean (SD)	31.9 (6.3)	30.7 (6.2)	31.5 (6.3)	0.05
Education level (Completed secondary school and above), n (%)	218 (55.8)	83 (48.5)	301 (53.6)	0.11
Relationship status^, n (%)				<0.01
Married	335 (85.7)	112 (65.9)	447 (79.7)	
Divorced/separated	33 (8.4)	41 (24.1)	74 (13.2)	
Widowed	14 (3.6)	13 (7.7)	27 (4.8)	
Never been married	9 (2.3)	4 (2.4)	13 (2.3)	
Employment status (Yes-employed), n (%)	146 (37.3)	60 (35.1)	206 (36.7)	0.61

Household size (number of people living under the same roof), mean (SD)	5.1 (1.6)	5.4 (1.9)	5.2 (1.7)	0.02
Hunger scales, n (%)				0.01
Little to no hunger	271 (69.3)	79 (46.2)	350 (62.3)	
Moderate to severe hunger	120 (30.7)	92 (53.8)	212 (37.7)	
Asset Index score (terciles), n (%)				0.17
Low	126 (32.2)	63 (36.8)	189 (33.6)	
Middle	126 (32.2)	61 (35.7)	187 (33.3)	
High	139 (35.6)	47 (27.5)	186 (33.1)	
Tested for HIV, n (%)				0.33
Before pregnancy	214 (54.7)	86 (50.3)	300 (53.4)	
During or following pregnancy	177 (45.3)	85 (49.7)	262 (46.6)	
HIV status of child, n (%)				-
HIV positive	8 (2.4)	7 (4.5)	15 (3.0)	
HIV exposed and negative	329 (97.6)	149 (95.5)	478 (97.0)	

HIV exposed, status unknown	54	15	69	
Parental Stress Index, mean (SD)				
Parental distress	30.1 (6.9)	36.1 (7.4)	31.9 (7.6)	<0.01
Difficult child	27.6 (6.3)	29.7 (7.1)	28.2 (6.6)	<0.01
Parent-child dysfunction	24.0 (5.8)	26.1 (6.4)	24.6 (6.0)	<0.01
Total Stress score	81.8 (15.0)	91.9 (17.0)	84.8 (16.3)	<0.01
Maternal depression scores (EPDS), mean (SD)	9.3 (5.7)	14.6 (5.0)	10.9 (6.0)	<0.01
Maternal depression scores- EPDS, n (%)				<0.01
None or minimal depression score (0-6)	139 (35.6)	12 (7.0)	151 (26.9)	
Mild depression score (7-13)	149 (38.1)	55 (32.2)	204 (36.3)	
Moderate depression score (14-19)	91 (23.3)	72 (42.1)	163 (29.0)	
Severe depression score (20-30)	12 (3.1)	32 (18.7)	44 (7.8)	
SSQ-8, mean (SD)	3.6 (2.3)	6.3 (1.7)	4.4 (2.5)	<0.01
SSQ-8 (using ≥6 as cut off), n (%)				<0.01
No CMD (scores 0-5)	286 (73.2)	51 (29.8)	337 (60.0)	
CMD symptoms (scores 6-8)	105 (26.9)	120 (70.2)	225 (40.0)	

EPDS: The Edinburgh postnatal depression scale **|** *SSQ: Shona Symptom Questionnaire* **|** *CMD: common mental health disorders*

^ *Relationship status variable was recoded to married/not married during analysis*

A logistic regression model was built to identify risk factors associated with suicidal ideation at baseline. Results show that mothers with suicidal ideation were also more likely to experience food insecurity (OR: 3.2; 95% CI: 1.9 to 5.6; p<0.01), report severe depression symptoms (OR: 16.8; 95% CI: 4.5 to 62.3; p<0.01) and CMD symptoms above the cut-off (OR: 5.5; 95% CI: 2.9 to 10.5; p<0.01) compared to the non-suicidal group (**Table 7.8**). Being unmarried was also found to be a risk factor for suicidal ideation in this group of women (OR: 0.2; 95% CI: 0.1 to 0.4; p<0.01). Mothers' age and number of people living in the household were not risk factors for suicidal ideation for this study population.

***Table 7.8**: Logistic regression model of risk factors associated with maternal suicidal ideation at baseline (n=562)*

	N	Odds Ratio (95% CI)	p value
Age group (years)			
16-19	16	Ref	
20-30	216	4.2 (0.8 to 21.2)	0.08
31- 40	282	2.1 (0.4 to 10.7)	0.35
41-49	48	1.1 (0.2 to 6.4)	0.92
50-70	-	-	-
Married			
No	115	Ref	
yes	447	0.2 (0.1 to 0.4)	<0.01
Number of people living in the household			
2-3	83	Ref	
4-6	375	1.4 (0.6 to 3.2)	0.40
7-9	95	1.4 (0.5 to 3.7)	0.55

10-13	9	3.8 (0.5 to 28.1)	0.20
Hunger scale			
Little to no hunger	350	Ref	
Severe to moderate hunger	212	3.2 (1.9 to 5.6)	<0.01
Maternal depression (EPDS category)			
None	151	Ref	
Mild	204	2.5 (1.1 to 5.8)	0.04
Moderate	163	2.7 (1.1 to 6.7)	0.03
Severe	44	16.8 (4.5 to 62.3)	<0.01
SSQ-8			
No CMD	337	Ref	
CMD symptoms	225	5.5 (2.9 to 10.5)	<0.01

OR: Odds ratio **|** *EPDS: The Edinburgh postnatal depression scale* **|** *SSQ: Shona Symptom Questionnaire* **|** *CMD: common mental disorder*

7.4.3.3 Child cognitive scores by suicidal ideation

Following the identification of risk factors associated with suicidal ideation in this study group, the relationship between maternal suicidal ideation and child cognitive development at baseline and 12 months was explored. The mean Mullen scores of the children at baseline was examined by their mother's suicidal ideation (**Table 7.9**). The children had similar mean Mullen scores across the five scales, regardless of maternal suicide ideation (non-suicidal 102.7 vs. suicidal 102.0, p=0.65).

Table 7.9*: Child cognitive development by suicidal ideation at baseline*

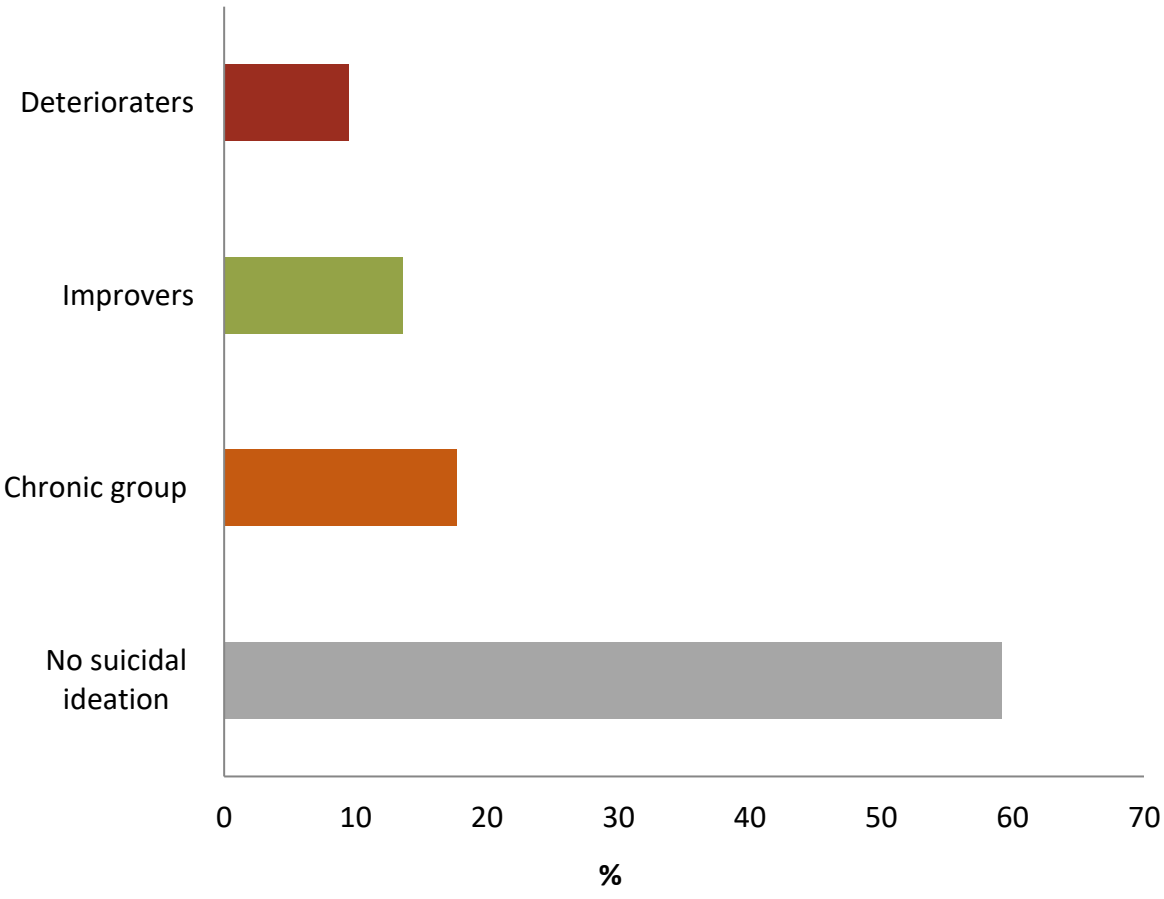
Mullen scales	Non-suicidal (n=391)	Suicidal (n=171)	Total (n=562)	p value
	Mean (SD)			
Expressive Language	53.2 (10.6)	52.3 (11.0)	52.9 (10.7)	0.33
Fine Motor	50.9 (11.0)	50.5 (12.3)	50.8 (11.4)	0.76
Gross Motor	50.9 (10.7)	49.7 (11.3)	50.5 (10.9)	0.23
Receptive Language	47.7 (11.3)	47.7 (12.0)	47.7 (11.5)	0.99
Visual Reception	53.3 (12.2)	52.7 (13.8)	53.1 (12.7)	0.62
Early Learning Composite Score	102.7 (17.1)	102.0 (19.7)	102.5 (17.9)	0.65

7.4.3.4 Suicidal ideation at baseline and follow-up

The participating mother's mental health and children's cognitive scores were re-assessed at 12 months follow-up. Of the 514 participants that completed the follow-up survey, only 485 (86.3%) pairs of interviews were both completed by the child's biological mother. In the case of the remaining caregivers (n=29), they indicated that caregiving responsibility has been taken over by the grandmother or other relative due to mother's death (n=12) or unavailability.

Of the 485 mothers, 86 (17.7%) reported suicidal ideation at both time points, whereas 66 (13.6%) had suicidal ideation at baseline but not after 12 months. There were 46 (9.5%) mothers who reported emerging suicidal ideation at 12 months only. The largest group (n=287; 59.2%) did not report suicidal ideation at either time point (**Figure 7.3**).

Figure 7.3: *Categories of change in maternal suicidal ideation from baseline to 12 months follow-up*



7.3.4.5 Association of maternal suicidal ideation with child Mullen scores over time

Table 7.10 shows Mullen scores by maternal suicidal ideation categories. The children of the improvers and reference group (i.e. no suicidal ideation) had similar mean Mullen scores on most domains. However, the children of mothers with emerging suicidal ideation (i.e. deteriorators) had consistently lower mean T-scores across all child development domains, compared to the other three groups.

***Table 7.10**: Mullen T-scores of children at 12 months follow-up by maternal suicidal ideation categories*

Mullen Scales (T-scores)	No suicidal ideation (n=287)	Improvers (n=66)	Deteriorators (n=46)	Chronic (n=86)
		Mean (SD)		
Expressive language	45.4 (9.2)	46.1 (9.6)	42.2 (8.3)	44.3 (10.0)
Receptive language	46.1 (9.6)	46.8 (9.4)	41.3 (12.2)	44.1 (10.6)
Fine Motor	41.9 (11.2)	42.3 (10.9)	37.3 (9.5)	40.5 (9.8)
Gross Motor ^	49.9 (11.3)	50.7 (11.3)	44.0 (11.8)	48.3 (11.4)
Visual reception	42.5 (10.9)	42.7 (11.3)	37.2 (10.7)	41.7 (11.2)
Early learning composite score	88.7 (15.2)	89.4 (14.3)	80.5 (14.9)	86.2 (15.8)

^Only measured in children aged <36 months at follow-up (n=397)

In multivariable analysis, children of the deteriorators group had lower receptive language (aMD: -4.2; 95% CI:-7.2 to -1.2; p=0.02), visual reception (aMD: -4.4; 95% CI: -7.6 to -1.2; p=0.04), and overall composite score (aMD: -6.1; 95% CI: -10.3 to -1.8; p=0.03) compared to the children of the reference group (**Table 7.11**). There was also an evidence of difference in the children's gross motor functioning by maternal suicidal ideation categories (aMD: -5.2; 95% CI: -8.9 to -1.5; p=0.01).

Table 7.11*: Association of maternal suicidal ideation over time with child Mullen scores at 12 months*

Mullen Scales (T-scores)	**No suicidal ideation (n=287)**	**Improvers (n=66)**	**Deteriorators (n=46)**	**Chronic (n=86)**	**P value***
		Adjusted mean difference (95% CI)			
Expressive language	Ref	1.23 (-1.20 to 3.67)	-2.27 (-5.13 to 0.59)	-0.26 (-2.47 to 1.95)	0.25
Receptive language	Ref	1.12 (-1.45 to 3.69)	-4.18 (-7.19 to -1.16)	-1.49 (-3.81 to 0.82)	0.02
Fine Motor	Ref	0.70 (-2.10 to 3.49)	-3.45 (-6.76 to -0.15)	-0.87 (-3.40 to 1.65)	0.16
Gross Motor ^	Ref	2.16 (-1.08 to 5.40)	-5.18 (-8.91 to -1.46)	0.03 (-3.08 to 3.14)	0.01
Visual reception	Ref	0.71 (-1.99 to 3.41)	-4.37 (-7.56 to -1.18)	-0.37 (-2.80 to 2.07)	0.04
Early learning composite score	Ref	1.35 (-2.28 to 4.98)	-6.05 (-10.34 to -1.77)	-0.98 (-4.26 to 2.31)	0.03

***Model adjusted for baseline Mullen scores, mother's age, clustering of trial sites and examiner*
^Only measured in children aged <36 months at follow-up (n=397)

7.4.4 Discussion

The aim of this study was to explore maternal suicidal ideation in the presence of HIV and the association between such ideation over time with child cognitive development. Suicidal ideation in this group was found to be high. At baseline, almost a third of the mothers reported suicidal ideation, and this was reduced to 27.2% at endline. Mothers with suicidal ideation were also more likely to be divorced or separated and report elevated stress and depressive symptoms. The results also show evidence of association between maternal suicidal ideation over time and child cognitive performance for this sample. Maternal suicidal ideation was found to negatively affect children's visual and receptive language ability. Additionally, children of mothers with emerging suicidal ideation tended to have lower cognitive scores across the developmental domains.

When maternal suicidal ideation was examined in this group, consistent with findings from other studies, the presence of suicidal ideation was associated with marital status, food insecurity, maternal depression and stress [113, 115-117]. Household food insecurity was more common in mothers with suicidal ideation. The lack of support system or household food security may all contribute to the mother's mental well-being and likelihood of unhealthy suicidal thoughts or behaviour manifestation. Alternatively, suicidal ideation may mitigate against relationship formation and affect the ability to gather resources ensuring food security for these women. Other studies in rural areas report being single or widowed, and being older in age is associated with increased food insecurity in PLWH [270]. Considering this was a rural population, there could also be high levels of food insecurity simply due to higher levels of poverty compared to urban areas , or limited availability of plots of land per family [271]. Although the direction of the effect between suicidal ideation and the factors discussed above cannot be definitively established, these associations point to both warning signs and intervention opportunities.

The findings here suggest a clustering of negative life events such as HIV, and other life stressors results in elevated and chronic suicidal ideation. Suicidal ideation may be a result of the burden of these stressors and contemplating suicide a pathway to escape from them [272]. Similar to previous studies, maternal mental health was associated

with child development in the language and visual domains [7, 79]. These mental health burdens and stress may be distracting mothers from parenting and child stimulation reducing visual and verbal interactions. This in turn could be affecting the crucial child development steps.

As discussed above, the burden of mental health was noticeably high in this rural population, with close on a quarter of the sample recording suicidal ideation at baseline. Although this goes down over time, the rates at follow-up are still high and indicate an unmet mental health need. Deteriorating maternal mental health in particular seems to affect child cognition. Improving mental wellbeing or cessation of suicidal thoughts in mothers may potentially feed into improved child outcomes over time. The findings of this study also provide valuable information on the characteristics of HIV positive mothers at risk of suicidal ideation in Zimbabwe. Results from this study can aid the development of suicide prevention and synergic intervention measures for HIV positive mothers and their children in similar context.

7.5 Chapter summary

As discussed in **Chapter 6**, the burden of mental health issues was high in this study population. With this in mind, I designed sub-studies to assess the impact of prolonged maternal mental health symptoms on child development. This chapter presents an overview of the design and analysis of these sub-studies. The selection of participants for analysis, variables and the statistical methods used for each sub-study were also described.

There is substantial evidence that maternal mental health can affect children in many domains, including their cognitive and socio-emotional development [84, 94, 245]. The results described in this chapter were consistent with these findings. Child receptive language development was consistently associated with poorer maternal mental health in this HIV affected sample. More specifically, maternal common mental disorders including depression symptoms over prolonged period were negatively associated with one domain of cognitive development, child receptive vocabulary. The results also show that maternal suicidal ideation can negatively affect child development domains and is associated with attainment in the child. Children's visual and receptive language ability were the developmental domains most affected by maternal suicidal ideation. In addition to this, children of mothers reporting emerging mental disorder (either depression symptoms, CMD or suicidal ideation) exhibited lower cognitive performance across all the developmental domains. Although some of these findings were not statistically significant it highlights the role deteriorating mother's mental health plays in child development. The longitudinal studies described in this chapter add useful insight to the literature on the role of maternal mental health burden in child development, with specific focus in Zimbabwe.

CHAPTER 8: Discussion

8.1 Summary of key findings and relevance

The research in this thesis focused on understanding the relationships between maternal mental disorders such as stress, depression, and suicidality, and early child cognitive development. The hypothesis was that cognitive impairments associated with HIV infection, environmental challenges associated with HIV exposure like poverty, and lack of adequate child stimulation due to maternal mental health problems will all play a negative role in child development and these HIV exposed children may display signs of cognitive developmental delay.

Initially, a systematic review (**Chapter 2**) was conducted to identify effective interventions aimed at enhancing child developmental outcomes in sub-Saharan Africa. Studies assessing the impact of interventions on cognitive outcomes of HIV affected children aged 0-5 years old were reviewed; this yielded little to no evidence of evaluated interventions for this group of children. There is existing literature that points to the benefits of child or caregiver targeted interventions in early childhood for disadvantaged children and the substantial impact it can have on their future achievements [27, 150, 202, 273]. However, from the review conducted in this thesis, it was evident that there is no clear consensus across the literature on which interventions are most effective for improving cognitive outcomes of HIV affected children. There is still growing evidence showing the risk of developmental delay for HIV exposed children in resource limited settings. Additionally, the causes of poor child development in HIV affected children are clearly multifactorial. Thus, there is an urgent need for intervention studies to develop comprehensive approaches which address some of these factors for this disadvantaged group of children.

As this PhD research was nested within a large RCT, child cognitive development outcomes pre- and post-multicomponent intervention (parenting programme, ISALS and case-management) roll out were investigated in **Chapter 4**. The characteristics of participating children and their caregiver as well as maternal mental factors relating to child cognition were also investigated. The data shows that of the 574 caregiver-child dyads recruited in the CHIDO trial, 89.5% were retained at 12 months follow-up, which

was a high follow-up rate for rural population. Of note, HIV status was not well known at the time of enrolment to the study, with only 69.1% (397/574) of caregivers reporting awareness of their child's HIV status at baseline. Of the caregivers who reported knowing their child's status, 67.8% reported the child was HIV negative, and (16/397) 4.0% reported the child was HIV positive. However, HIV status was found to not be associated with child's characteristics such as age at enrolment, gender, or birth weight for this group of children. The results of this analysis show that there was no evidence of intervention effect (measured 4.5 months post-intervention completion) on child's overall cognitive score and the Mullen sub scales by trial arm (mean of 88.1 in the intervention arm vs. 87.6 in standard of care arm; aMD= 0.06; 95% CI: -2.68, -2.80; p=0.97).

It is possible there was insufficient time after the intervention for it to have taken effect. Although, programme implementation data (data not shown here) suggest that attendance to the early childhood stimulation sessions (one component of the intervention) was sub-optimal. This could be attributed to structural barriers such as distance or timing of the intervention. The distance caregivers had to travel to take part in intervention sessions in some sites could have undermined attendance. The high levels of food insecurity and prevalence of poor maternal mental health in this sample are all factors which are likely to impede participation and optimal uptake of intervention components for this group. Alternatively, it could be that child cognitive development outcomes may take longer to improve following parental child stimulation training.

The child cognitive assessment tool (Mullen scales) used in this research was found to be a complex instrument for field use, despite comprehensive training and limiting the number of trained assessors. The next chapter (**Chapter 5**) focused on interrogating the full cognitive measure used in the CHIDO trial, as well as designing and developing a shortened form for field use purposes. A range of qualitative and quantitative approaches was considered during the development of this tool. The design of the shortened scale from the full inventory was found to be feasible and led to the identification of a smaller set of questions (28 items instead of 160 test items) with a simple scoring system to categorize children into three categories of cognitive delay

risk. The use of such short form would be beneficial in field settings and allow community health workers to assess children quickly and identify children who are at risk of cognitive delay and need referral for further assessment. However, copyright and purchasing requirements of the Mullen scales would be an issue for utilizing such shortened tool in the field.

Of note, there are several cognitive assessment tools available which incorporate similar tasks developed widely, however, most are standardised for high-income country populations. It is important to consider that although some tools have been used globally, instruments adapted in one setting may not measure the same construct as originally designed, or as adapted in other settings, and may not perform equivalently across countries. It was evident from the findings in **Chapter 5** that there is still a need for culturally appropriate, brief, easy to use, valid and reliable cognitive screening tools to identify children at risk of cognitive delay in resource limited rural settings.

In **Chapter 6**, the cognitive differences between the children in the sample were investigated by HIV status, there was no evidence of an association between the child's HIV status and their cognitive development. There was no difference in the overall cognitive score (HIV positive children 101.3 vs. HEU children 100.0; aMD: -1.18; 95% CI: -9.14 to 6.79; p=0.77) and sub-domains with the exception of gross motor (HEU children 50.3 vs. HIV positive children 40.6; aMD: 8.02; 95% CI: 1.93 to 14.11; p=0.01). As highlighted in the introductory chapter of this thesis, the cognitive development of children affected by HIV can be influenced by a wide range of biological and environmental factors. The direct effects of HIV exposure on the developing brain is known to be detrimental, however, the results here show no difference in cognitive functioning of the children by HIV status. This could be due to the fact that there was a small number of HIV positive children in the study, thus limiting analytical power for detecting a difference between the study groups.

Furthermore, several maternal mental health factors were measured at enrolment and after 12 months and their impact on child cognitive development was assessed. At baseline, maternal depression and stress were negatively associated with child cognitive development (**Chapter 6**). The next set of analyses (**Chapter 7**) explored the

association between child cognition and maternal factors (risk of common mental disorders, depression symptoms and suicidal ideation) after 12 months of follow up. Maternal mental health was again found to be negatively associated with child development, particularly their visual and receptive language ability. The high levels of maternal mental health burdens reported in this study show that despite improvements in HIV treatment and services affecting health outcomes for caregivers of HIV exposed children, the strains of living with an HIV diagnosis or caring for an HIV positive child is still high. In addition to this, there is evidence in the literature that points to pregnancy related mental health challenges [92, 113, 244, 264]. Therefore, mothers living with HIV are not only confronted with demands of parenting but also with a stigmatised illness that can lead to several emotional or social issues negatively affecting their roles as mothers. It is understandable that catering to their child caregiving duties and coping with psychological and medical demands of dealing with life-threatening condition can be difficult.

The circumstances in which the mothers in this study lived in may have had an impact on their mental health and well-being. The impact of ongoing political and economic changes in the lives of participants in the trial should be taken into consideration when interpreting the mental health findings here. The trial was implemented during a time of political unrest, where Zimbabwe was in the process of changing presidents and undergoing social and economic challenges associated with the shift in ruling parties. Thus, in the climate of political instability and economic collapse, it is not surprising the high rate of unemployment, poverty, and food insecurity observed in this study setting. The high level of mental health burden noted in this study could also be attributed to the factors mentioned above. Considering the participating mothers were recently pregnant, living with or caring for someone living with a chronic illness, as well as living through unstable times that could affect their livelihood and food security, it is not surprising to see the high burden of reported mental health issues. However, even when mental health services are sought, the treatment gap for mental health in rural settings in Zimbabwe and Africa generally is extremely high.

8.2 Finding interpretations and further explanations

Further mechanisms and theories relating specifically to the child development outcomes are described below to further understand the relationship between maternal mental health and child cognitive development observed in this research.

8.2.1 Positive parenting, child stimulation and development

The importance of early stimulation and responsive parenting style in child development have been discussed throughout this thesis. As described in the **Chapters 1** and **2**, it is evident that child stimulation and interventions to promote such stimulation have positive and long-term effect on child development. We also know that during the early sensitive periods of child development, healthy emotional and cognitive development can be shaped by responsive, and dependable interaction with caregivers, while chronic or extreme adversity can interrupt normal brain development. Research shows that when children have a caring, consistent and responsive caregiver who interacts in a stimulating way with the child can achieve optimal development. However, HIV-related factors can lead to changes in the family environment, challenges in parenting, and can have negative impacts on parent–infant interaction resulting in reduced child stimulation. HIV positive and HIV exposed children are already at a disadvantage with the virus directly affecting their brain structure and development (when left untreated). Compounded by an unstimulating home environment or poor parenting will likely exacerbate their developmental challenges.

A healthy brain architecture can be built by appropriate input from a child's senses as well as stable, responsive relationships with caring adults. If an adult's responses to a child are unreliable, inappropriate, or simply absent, the developing architecture of the brain may be disrupted, and subsequent physical, mental, and emotional health may be impaired [274]. In such cases not only does the brain not receive the positive stimulation it needs, but the body's stress response is activated, flooding the developing brain with potentially harmful stress hormones [275]. Furthermore, when strong, frequent, or prolonged adverse experiences such as extreme poverty or

repeated abuse are experienced without adult support, stress can becomes toxic, as excessive cortisol disrupts developing brain circuits [24, 274].

8.2.2 Toxic stress response and child development

Stress is the body's natural reaction to situations that occur within and outside the body. The physiological response to stress is hardwired into the human body and is essential for survival [275]. However, chronic or prolonged exposure to stress can have detrimental impact on the developing brain [276]. Toxic stress responses which includes a prolonged or permanent abnormal physiologic response to a stressor can lead to risk of organ dysfunction [277]. Although, the brain will continue to function under extreme stress, the rate of growth may slow down, creating a vulnerability to anxiety, depression and less resilience to stress in individuals [278]. The younger the brain, the more damaging the effects of toxic stress can be [278].

In this study, the prolonged activation of the stress response systems due to adversities in the participating children's environment may have disrupted their development and brain architecture linked to neural degeneration in specific regions [279]; increasing their risk of stress-related disease and cognitive impairment [274]. Responsive relationships with caring adults as early in life as possible may prevent and even reverse the damaging effects of such toxic stress response [274].

8.2.3 Poverty and child development

The results of this study indicate that children of mothers reporting chronic mental health symptoms exhibit signs of developmental delay in verbal and visual sub domains. As discussed above, poverty in addition to poor mental health may mitigate against mothers displaying positive parenting style and interacting with the child in a way that could enhance their children's development. Poverty can act as a barrier to effective parenting and hinder caregivers capacity to provide adequate care to their children [280]. Research shows depression and stress associated with poverty can impair parenting and lead to an increase in self-doubt about parenting capacity [280]. Although this might not be the case in this study sample, there is further evidence in the literature that indicate parents on a lower-income are less likely to have less capacity to be nurturing and supervise their children adequately, and these behaviours

are exacerbated in the absence of a supportive partner, depression or lack of social support [280]. Experiences of chronic poverty early in life may lead to changes to the children's brain structures such as the amygdala and the hippocampus, the parts which are crucial for learning, memory and processing emotions [277, 281]. Therefore, early interventions that promote attentive or positive parenting practices, in addition to addressing deficits in the caretaking environment of young children can potentially ameliorate the impact of early adversity and deprivation as experienced by the children in this study.

8.2.4 Resilience in HIV affected families

Resilience theory is a set of ideas related to the impact of challenging events on individuals and families and how well they have adapted to that traumatic experience [282]. Resilience and the ability to recover or adjust to difficult situations is a positive indicator of human beings' capacity. There is evidence in the literature that shows resilience in HIV-affected children and families affected by adversities [283, 284]. Studies report that parenting and family support, in particular, are associated with resilience in HIV affected children [283]. Factors such as family attitudes toward parenting and the availability of supportive caregivers to provide nurturance and guidance are critical to the mental health and psychosocial adjustment of HIV-affected children [283]. These findings are reiterated by studies in South Africa examining the predictors of mental health resilience in children affected by HIV that report child, family and community factors act together to promote resilience in this high-risk group of children [285]. Other research that focuses on family dynamics indicates strong associations between poor parenting style and children's own poor functioning and ineffective problem solving as they grow older [285]. In this study sample, the high level of mental health burden reported by participating mothers could have affected their parenting style and prevented them from providing a nurturing and warm environment for their children to thrive. However, there is evidence in the literature that suggests despite this, some children develop and show resilience regardless of high levels of HIV-related distress [286]. This could be the case for the children in this study as HIV was found not to be associated with their cognitive development, despite the difference observed in gross motor functioning.

8.3 Strengths and limitations of this research

There were a number of strengths and limitations associated with this research. These are discussed in detail below.

8.3.1 Strengths

Pilot study was conducted prior to the CHIDO trial, which informed the trial design and implementation. Data were obtained from 574 dyads at baseline of whom 514 were followed for 12 months. The large sample size here was representative of the study population. This increased the statistical power during analysis and enabled assoications between outcomes of interest to be detected. There was a small proportion of missing data noted during analysis, any resultant bias would likely be very minimal due to the low levels of missing data. The follow-up rate was also very high for a rural population over 12 months. This limited the attrition bias which would have otherwise made the findings more reflective of those retained in the study. Additionally, child development outcomes were examined using a few assessors, blinded to trial arm to minimise risk of reporter biases. Importantly, where possible the same assessors assessed the same children at baseline and endline. Other strengths of the research here include the utilization of previously used and validated assessment tools in Africa like the EPDS and SSQ-8. The SSQ-8 was developed and adapted from the longer SSQ-14 and have been previously used to assess risk of CMD in Zimbabwean women. This increases the validity of the mental health findings in this study and allowed for better comparability with studies and programmes using the same tools.

The mental health studies in **Chapter 7** examine longitudinal changes in maternal CMD, depression symptoms and suicidal ideation over a 12 months period for women living with HIV. The use of longitudinal data in this thesis offers opportunities to observe changes in the mental health status of participating mothers over time. Previous studies which have examined the relationship between suicidality and mother-infant interactions have used cross-sectional data [264] and some have examined maternal suicidal ideation predictors in similar settings [122, 268]. However, the study in **Chapter 7.4** is the only one to my knowledge that investigates the impact

of maternal suicidal ideation on child's cognitive development over time in Africa. The approach used in **Chapter 7** of creating four groups of women to capture the longitudinal aspects of their mental health is one of the unique features of the work in this thesis.

Overall findings of this research emphasise the importance of maternal mental health for child developmental outcomes. The results here also provide valuable information on the characteristics of HIV positive mothers at risk of CMD, depression symptoms and suicidal ideation in rural Zimbabwe. The evidence provided from this work can contribute to shaping health policies in the country and highlight the mental health screening and treatment gap for HIV positive mothers in Zimbabwe.

8.3.2 Limitations

Nevertheless, there were some limitations worth considering. The data for analysis were collected as part of a trial. Pragmatic RCTs which assess effectiveness of interventions are useful in informing decision-making by researchers and policy-makers in real world settings. However, they require strict inclusion and exclusion criteria, this could limit the generalizability of the findings of this study to broader populations in Africa and other settings [287]. Although there are some universal issues which are relevent in different contexts such as the high prevalence of mental health disorders reported by PLWH [101, 105, 288-290], as well as the importance of good parenting and child stimulation for enhancing child development. Another point for consideration for data obtained from RCT inlucde the changes over time may not reflect a true field situation. As the trial results (**Chapter 4**) also showed no differences in cognitive development of the children by trial arm (which allowed me to pool the data), there may have been some intervention exposure considerations that were missed.

I was also underpowered to detect a difference between HIV positive and HEU infants (**Chapter 6** analysis) due to the small number of the HIV positive group, increasing the risk of chance effects. In addition, the Mullen scales uses a USA reference group which is not ideal given the setting of the study in Zimbabwe. Cultural biases in such scales should be taken into consideration. The Mullen scales has been used to good effect in

other studies of cognitive performance in Africa [43, 45, 194]. However, in the current study setting it was unable to detect any cognitive differences between our study groups. This could be because the tool contained items that did not apply to Zimbabwean children such as asking children to 'Puts pennies in slot' in a country that does not use coins thus comparisons of scores obtained from such adapted instruments may be misleading. However, it was only evident the tool was not culturally appropriate for our study setting after the implementation of the trial. Therefore, it is of importance to examine the validity and robustness of child assessment tools and consider its limitations and cultural relevance before adopting for a study. When assessing child development locally validated scales and reference groups should be considered for use. In addition to this, despite a high follow-up rate in this study, there could be specific mental health issues associated with loss to follow-up that might have affected the final analysis of the mental health chapter (see **Appendix 6**). It was also not possible to differentiate depression symptoms and anxiety when assessing caregivers' mental health using the SSQ-8 scale. When using the SSQ-14 in HIV positive individuals, the items in the questionnaire [269] could identify somatic symptoms which can be associated with HIV infection rather than CMD– although this tool has also been validated for HIV positive populations [291].

Eventhough HIV status was controlled for the mental health and child outcomes analysis, the direction of effect in the association between child development and maternal CMD cannot be categorically ascertained. It may well be that observing a child with development challenges was affecting the mood of a mother – herself diagnosed with HIV either before conception or during pregnancy.

8.4 Implications for future research

The findings show culturally appropriate and locally validated cognitive tools are needed in identifying HEU children at risk of cognitive delay in low resource settings. From the findings in this thesis, it is evident that such tools should be developed from scratch rather than using exiting tools as template. In addition to this, future studies should consider developing an assessment tool using items/questions that reflect the real-life experiences of the study sample. Alternatively, studies conducted in similar

resource limited settings like Zimbabwe might find it more beneficial to use assessment tools available on open access such as the MDAT [41] or Developmental Score (D-score) [292] to avoid issues that arise from using culturally inappropriate tools.

It was evident from the findings in this thesis understanding the context of the study and the social or economic factors that could be affecting participants and their mental health is of importance. Future researchers should take into consideration the context in which studies are carried out and use qualitative approaches to help understand contextual factors that could affect study population. For example, a series of qualitative interviews of mothers' experiences of the CHIDO intervention implementation were carried out as part of the process evaluation. Although this was not a particular area of research focus in this PhD, data gathered could have contributed to our understanding of compressive intervention deliveries and be beneficial for refining future interventions. Thus, future studies delivering multicomponent interventions in similar settings should consider use of qualitative data collected to complement findings. This would enable researcher to deconstruct complex interventions and understand the mechanisms or drivers of observed change in the study population.

The benefit of using longitudinal data have been highlighted throughout this thesis. Based on the findings here, longer follow-up period might be more beneficial when evaluating the impact of a comprehensive parenting intervention on child development in randomised controlled trials. Future studies examining the association of maternal factors with child cognition would also benefit from longer follow-up period to assess child development over time. This will allow examination of changes in maternal mental health and the impact this might have on child cognition, helping researchers understand the relationship between the variables of interest and determine any causal effect relationship observed.

8.5 Conclusions and recommendations

As a result of public health interventions, rates of mother-to-child HIV transmission have been falling and more children are being born HIV-exposed yet uninfected. With

the roll out of Option B+ strategies in pregnancy, the level of HIV infection in infants is dramatically decreasing. On the other hand, the number of HEU children is increasing. HIV treatments available may improve health outcomes for caregivers, however the strains of an HIV diagnosis could still be influencing the quality of care and stimulation provided to children. It was evident from this research that living with HIV positive caregiver with mental health issues has negative impact on the chidlren's development. Thus, this future generation of HEU children should be placed in the center of future interventions and policy making.

The importance of maternal mental health has been highlighted in this thesis. Mothers in this study reported high levels of stress and low mood and these factors could influence cognitive development of young infants. In settings of high HIV prevalence and poverty, these concurrent common mental health burden needs urgent recognition and prioritization, given what is known about the impact of maternal depression on child language development. When considering public health policy and interventions in other LMICs with similar resource constraints the social or contextual factors contributing to caregiver mental health should be of high relevance [103]. Several studies in Zimbabwe indicate high HIV prevalence and elevated mental health burdens generally, and suicidal challenges specifically [7, 293-296]. Researchers working in the field of HIV and child development need to consider adopting multicomponent interventions to address such mental health challenges especially in areas where there is known high level of mental health burdens. These would be of benefit directly to the HIV positive mothers, and in turn may affect child development outcomes.

Furthermore, findings from this thesis indicate that the course of caregiver mental health over time has an effect on child development, particularly in the language and visual developmental domains. Deteriorating maternal mental health was found to negatively affect child cognition. We know early child development is critical for later achievement. Given that a proportion of these children were HIV positive and all were HIV exposed there is already concern for their cognitive development. The literature shows clear evidence of developmental delay for children in the presence of HIV infection and HIV exposure [56-58]. This seems to be compounded by poor or chronic

mental health issues. Therefore, ways to routinely identify and modify severe caregiver mental health challenges such as anxiety, depression, and suicidality are needed. The consistent association between chronic CMD and child development observed here serves to strengthen the case for governmental organisations such as Ministry of Health and other national health programmes to include maternal mental health on the agenda of child intervention programmes and centre of postnatal care in similar rural settings.

In conclusion, there could be an enduring negative impact for children exposed to multiple problems such as HIV and maternal mental health issues, and protection and targeted interventions for this group are much needed. Improvements in therapeutic outcomes have changed the needs of these HIV exposed and HIV positive children; while the emphasis was initially on their survival it is now moving on to their quality of life, day-to-day functioning, and transition to adulthood. The psychosocial needs of this growing population of children must be at the centre of future interventions. Thus, in order to improve child development over time, scalable child stimulation programmes specific for HIV exposed infants coupled with a specific mental health component for their caregivers are recommended. In addition to this, culturally appropriate and locally validated cognitive tools are needed for tracking the development of such disadvantaged children at risk of cognitive delay in sub-Saharan African. Findings from this study can inform programmers and researchers on the development of synergic intervention measures for HIV positive mothers and their children in similar context.

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APPENDIX 1: Systematic review

- ***Countries that form the SSA region***

Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde (Cabo Verde), Central African Republic, Chad, Comoros, Democratic Republic of the Congo, Republic of the Congo, Ivory Coast (Côte d'Ivoire), Equatorial Guinea, Eritrea, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Togo, Uganda, Zambia Zimbabwe

- ***Search strategies***

PubMed search

1. HIV and cognitive* and Africa - 411
2. (caregivers/psychology) OR caregiver* - 70020
3. ((infant*) OR Newborn) OR Neonate - 1384030
4. Child* OR preschool- 2589068
5. ((caregivers) OR (((infant*) OR Newborn) OR Neonate)) OR (Child* OR preschool)- 3250474
6. child development*- 404246
7. cogniti* - 463162
8. neurodev* - 32439
9. (language* OR motor skills OR memory OR intelligence OR IQ)- 644033
10. HIV*- 347628
11. (((CD4* OR viral* OR Antiretroviral Therapy, Highly Active)- 813794
12. RCT OR Randomised control trial OR longitudinal OR pre-post- 334344
13. Sub-Saharan Africa* OR SSA* OR *Africa*- 351672
14. Intervention* OR treatment outcome- 2037409
15. ((HIV) AND cognitive) AND Africa - 407
16. ((((("2010"[Date - Publication] : "3000"[Date - Publication])) AND ((((((((((caregivers/psychology*) OR (((infant*) OR Newborn) OR Neonate)) OR (Child* OR preschool))) AND (((child development*) OR cognition*) OR

neurodevelopment) OR (language* OR motor skills OR memory OR intelligence OR IQ))) AND HIV*) AND (RCT OR Randomised control trial OR longitudinal OR pre-post)) AND (Sub-Saharan Africa* OR SSA* OR *Africa*)) AND (Intervention* OR treatment outcome)))))- 45

17. Cochrane Library search

18. Child* or infant* or newborn* or neonates*:ti,ab,kw- 185753
19. HIV*:ti,ab,kw-23473
20. Caregivers*- 8453
21. #1 and #2 and #3– 137
22. Neuro* or cognitive*:ti,ab,kw (Word variations have been searched)- 188178
23. Child Development* and stimulation*:ti,ab,kw (Word variations have been searched)- 886
24. developmental assessment*:ti,ab,kw (Word variations have been searched)- 2544
25. #5 and #6 and #7- 79
26. *intervention*:ti,ab,kw (Word variations have been searched)- 335990
27. *Africa* or SSA or sub-saharan Africa*:ti,ab,kw (Word variations have been searched)- 21318
28. #4 and #8 and #9 and #10-2

PsycINFO search

1. exp Caregivers/ - 26521
2. (infant* or newborn* or neonates*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]- 120418
3. (Child* or preschool).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]- 773304
4. (Caregivers or (infant* or newborn* or neonates*) or (Child* or preschool)).af. – 1505563
5. exp Infant Development/ or exp Education/ or exp Mothers/ or exp Mother Child Relations/ or exp Developmental Psychology/ or exp Emotional Development/ or child development*.mp. or exp Parenting/ or exp Cognitive Development/ or exp Early Childhood Development/ or exp Childhood

Development/ or exp Home Environment/ or exp Psychosocial Development/ or exp Family/ - 843229

6. limit to (full text and abstracts)- 76369
7. (cognition* or neurodev* or language* or motor skills or memory or intelligence).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]- 674099
8. 5 or 7- 1387317
9. (HIV* or CD4* or viral* or Antiretroviral Therapy, Highly Active).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]- 60329
10. Limit 9 to (full text and abstracts)- 9329
11. (RCT or Randomised control trial or longitudinal or pre-post).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]- 125280
12. (Sub-Saharan Africa* or SSA*).mp.or *Africa*/ [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]- 4716
13. (Intervention* or treatment outcome).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]- 417277
14. 4 and 8 and 9 and 11 and 12 and 13- 15
15. limit 14 to yr="2010 -Current"- 14

APPENDIX 2: CHIDO Trial protocol paper

TITLE: EVALUATING THE EFFECTIVENESS OF A MULTI-COMPONENT INTERVENTION ON EARLY CHILDHOOD DEVELOPMENT IN PAEDIATRIC HIV CARE AND TREATMENT PROGRAMMES: A RANDOMISED CONTROLLED TRIAL

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Abstract

Background: HIV infection in a family may affect optimum child development. Our hypothesis is that child development outcomes among HIV-exposed infants will be improved through a complex early childhood stimulation (ECS) programme, and income and loans saving programme for HIV positive parents.

Methods: The study was a cluster-randomized controlled trial in 30 clinic sites in two districts in Zimbabwe. Clinics were randomised in a 1:1 allocation ratio to the Child Health Intervention for Development Outcomes (CHIDO) intervention or Ministry of Health standard care. The CHIDO intervention comprises three elements: a group ECS parenting programme, an internal savings and lending scheme (ISALS) and case-management home visits by village health workers. The intervention was aimed at caregiver-child dyads (child aged 0-24 months) where the infant was HIV exposed or infected. The primary outcomes were cognitive development (assessed by the Mullen Scales of Early Learning) and retention of the child in HIV care, at 12 months after enrolment. A comprehensive process evaluation was conducted.

Discussion: The results of this cluster-randomised trial will provide important information regarding the effects of multi-component interventions in mitigating developmental delays in HIV-exposed infants living in resource-limited environments.

Trial registration: This trial is registered with the Pan African Clinical Trials Registry (www.pactr.org), registration number PACTR201701001387209; the trial was registered on 16th January 2017 (retrospectively registered).

Word Count: 216

Keywords: Early childhood stimulation; internal savings and lending scheme; case management; HIV exposed infants; Zimbabwe

Background

Early childhood experiences shape the long-term physical, emotional, and psychological health in children [1]. Improving these experiences using early childhood stimulation (ECS) could have long-term positive impacts on academic achievements, and socialisation skills [2]. In addition to appropriate ECS, having a consistent, responsive caregiver and a stable environment during these early years contributes to promoting optimal health and development [3, 4].

Child development opportunities are enhanced with good quality caregiving, stimulating environments, adequate nutrition, health care, protection, and socialisation. International literature has shown that parenting interventions can be effective in changing parenting behaviour [5] and subsequently enhancing various child outcomes [6, 7]. Conversely, HIV, especially in the context of poor socioeconomic environments, can threaten child survival and well-being [8]. HIV can affect child development indirectly through factors such as access to quality childcare, food insufficiency, economic hardships, unemployment, and bereavement [9, 10]. Studies on children infected [11] and affected [12] by HIV have shown poorer child development outcomes than uninfected and unaffected children [13], with considerably more evidence on adolescents than young children [14], and greater effect shown in resource-poor settings [15]. Studies in low-and middle-income countries have demonstrated sustainable benefits of interventions aimed at enhancing child development with improvements in cognitive and developmental outcomes [16, 17, 18, 19].

HIV affects parenting ability and strategies in a number of ways. Parents living with HIV may be distracted with their own physical and mental health concerns which can potentially affect the quality of care and attention devoted to the child [20, 21, 22]. Although the importance of ECS to child development is well established [3, 4] and parenting interventions have been shown to be effective in both resource rich and resource poor settings [23], little has been done to look at the impact of ECS in environments where HIV is generalised and also among very young children.

Many children in Sub-Saharan Africa face severe challenges affecting early development. Southern Africa has a generalised HIV epidemic. The current prevalence of HIV is estimated to be 14.6% among 15-64 year olds in Zimbabwe [24]. Despite notable reductions in the mother-to-child transmission rates, to 6.7%, at the population level [25], UNAIDS estimated that mother-to-child transmission is 6.39% [26]. The number of children orphaned due to AIDS is estimated as 524,581 [26]. High poverty (72% consumption poverty) with 25% of children living in extreme poverty [27] may also be a driver of poor child outcome.

Developmental challenges have been well documented in both HIV positive and HIV exposed infants [28, 29, 30, 31]. The mechanisms are unclear. Exposure to the virus,

antiretroviral (ART), or living in a family with HIV may all contribute, with the concomitant environmental risks associated with having parent(s) who are HIV-positive being one of the most influential factors among all those included. Effective interventions to mitigate these are available, and when implemented by the caregivers of HIV positive and HIV exposed children, it can improve their performance [12, 32, 33]. The intervention, we hypothesise, will result in improved long-term child development outcomes, reduced need for second and third line ART, reduced opportunistic infections and AIDS diagnoses and increased child survival (Figure 1).

Methods

Aims and objectives

The overall aim of this trial was to determine the impact of a comprehensive community-based intervention set up to simultaneously enhance child stimulation, reduce economic insecurity and improve retention in care among HIV exposed and infected children aged 0-24 month.

The specific aims of the trial include:

1. To pilot an intervention aimed at improving early childhood development (ECD), strengthening household economic resilience, enhancing adherence and retention in paediatric HIV care and treatment programs amongst caregivers and their HIV exposed children aged 0-24 months in Zimbabwe and modify the intervention in line with findings,
2. To evaluate the final intervention using a cluster-randomized controlled trial design,
3. To disseminate findings to influence policy and programming in Zimbabwe.

Collaborations

This trial was a collaborative project run by researchers from University College London, Centre for Sexual Health and HIV /AIDS Research (CeSHHAR) Zimbabwe, Liverpool School of Tropical Medicine, London School of Hygiene and Tropical Medicine, World Education, Stellenbosch University and Oxford University. CeSHHAR Zimbabwe was responsible for implementing and conducting all the research-oriented activities. World Education was responsible for providing technical support and ensuring delivery of the intervention by their implementing partner, Mavambo Orphan Care, as well collection of routine monitoring and evaluation data.

Trial setting

The trial was set in thirty health facilities in two districts in rural Zimbabwe, Goromonzi (n=20) and Mudzi (n=10). Eligible health facilities were those providing and initiating maternal and paediatric ART with at least 30 eligible caregiver-child dyads on their

HIV-exposed babies register. Health facilities were selected for the trial based on mapping of all facilities within the district and were at least 15 kilometres apart to minimise the risk of contamination.

Trial population

The trial population comprised of primary caregivers (biological and non-biological), and their HIV positive or exposed infants aged 0-24 months. Dyads must have been living in the catchment areas of designated trial health care facilities, planning to live full time in the community for the 18 months trial duration, willing to attend meetings in the community once every two weeks, and prepared to provide their residential address and other locator information for follow-ups. Only singleton births were eligible for inclusion. Dyads that included children with chronic illness, not including HIV exposed infants, or children with mental/physical disabilities as recorded by the health worker were excluded.

Pilot study

A 3-month pilot was conducted prior to the trial (August to October 2015). We recruited 50 caregiver-child dyads seeking health services in five clinics excluded in the trial and geographically separated from the trial clinics. The aim was to assess the acceptability and feasibility of the intervention, to determine feasibility and procedures for trial recruitment, examine preliminary data and to assess the relevance and appropriateness of the parenting programme content adapted to HIV affected families. The pilot resulted in minor changes to the finalised design of the trial and informed the final protocol. These changes included reducing ECS content per module, and increasing modules from 12 to 18, to be conducted fortnightly as opposed to proposed weekly or monthly. Cluster sizes were changed from an initial 16 caregiver-child dyads to either 12 or 24 caregiver-child dyads per cluster to cater for manageable Internal Savings and Lending Scheme (ISALS) composition. These changes informed the final study protocol.

Trial design

Thirty health facilities and their surrounding catchment areas were randomised to the Child Health Intervention for Development Outcomes (CHIDO) intervention or standard of care (Figure 2). Randomization of the 30 selected clusters was conducted with minimisation on the number of HIV exposed infants (0-24 months) in the Exposed Infant Registers, to ensure that the number of eligible caregiver-child pairs was similar by arm.

Recruitment and enrolment procedures

A list of eligible infants was extracted from the 'Exposed Infant Registers', comprising the name of the biological mother, village, name of the child, date of birth of the child,

ART number of the mother and contact details. For the 30 trial clinics there were a total of 1509 eligible infants extracted from the health facility PMTCT registers. Case care workers (CCW) in catchment areas of villages with the highest number of clinics were asked to invite all eligible caregiver-child dyads who met the trial inclusion criteria (n=671) to attend an orientation meeting to learn about the trial. If the biological mother listed in the register was no longer the primary caregiver, the non-biological caregiver was invited to participate as long as the child was listed as HIV exposed. Eligible caregivers who provided verbal consent to participate were booked for enrolment procedures – n=574 and 97 (14.5%) declined enrolment. Enrolment in the CHIDO intervention and usual care arms occurred concurrently, with one clinic from each arm recruited at a time for implementation purposes. Enrolment took 6 months to complete. Follow up for each pair of clinics was 12 months after the CHIDO intervention arm has started receiving the intervention in their community.

All eligible caregiver-child dyads were given trial information and asked to provide written informed consent to participate. Informed consent was collected according to Good Clinical Practice guidelines.

Table 1 summarises the scheduled trial timeline, from participants' enrolment, intervention roll out, follow up assessments to data analysis phase.

Intervention components and data collection preparation

Usual care arm

Clinics in the usual care arm received the recommended standard of care provided by Zimbabwean Ministry of Health and Child Care (MoHCC) for HIV exposed and/or infected children aged 0-24 month delivered according to 2013 National ART guidelines.

Intervention arm

In addition to usual care, children in the intervention clinics received the CHIDO intervention, a community-based, group intervention, delivered to caregiver-child dyads in groups of twelve every fortnight over 12 months. The intervention had three components i) early childhood stimulation; ii) internal savings and lending scheme to build economic resilience and iii) support from a case care worker to support engagement with and retention in HIV care (Figure 3). At completion of the trial the details of the intervention will be made available online.

Early childhood stimulation programme; An evidence-based curriculum to support the promotion of cognitive stimulation, increase use of positive discipline by parents and improve the nutritional status of children was developed and piloted for acceptability and feasibility from existing Zimbabwean (adapted to be age appropriate) and international materials with the aim of strengthening parenting skills. The goals of the

curriculum were to a) improve parental promotion of cognitive stimulation; b) improve the nutritional status of children; c) increase the use of positive discipline by parents; and d) enable parents to understand and support the socio-emotional, physical and cognitive development of their children. The ECS curriculum had 18 ninety-minute sessions. A community worker experienced in ECD training, and who received further training and supervision to support caregivers of 0-24 month old facilitated the group. A nurse from the local clinic run some of the medical sessions in the curriculum. The CCW from that community also attended the sessions and assessed the extent to which lessons learnt were then implemented in the home setting when they conduct their home visits. Where mothers needed guidance on implementation of lessons learnt the CCW provided assistance.

Internal savings and lending scheme; Caregivers in each ECS groups joined an ISALS group. The main aim was to increase household income to enable them to meet costs such as transport to health facility, clinic user fees, medication and food. These caregivers grouped themselves from within the ECS group into 6-10 members, and agreed to meet fortnightly to save money. Caregivers were trained on how to set up a group, develop a constitution, take meeting minutes and run the ISALS. All groups had different savings options. They could either contribute a set amount to a savings pool at each meeting; or a set amount at the first meeting only; with members able to apply to borrow (and repay) money to cover essential expenditure. If participants were too poor to contribute to an ISALS, they were allowed to earn money through community work to raise their first instalment. Thus those too poor to contribute were enabled to join and save together with those who could afford to join initially.

Case management; Caregiver-child dyads recruited to the intervention arm of the trial were supported by CCWs to access paediatric (and adult) HIV services within a continuum of care through the case management system. CCWs within the local communities (also referred to as village health workers) with home-based care experience, received an additional one-week training in ECS and providing adherence support. Home visits by CCWs supported adherence to ART and retention in care, attendance of caregivers and children at fortnightly meetings, as well as monitoring uptake of parenting skills training within the home environment. These activities complemented the monthly review and adherence support provided at the health facility.

In each community, the ECS community worker was responsible for the overall coordination and implementation of the intervention, assisted by the community nurse, ISALS facilitator, and CCW as required. All cadres were expected to attend all intervention group meetings.

Outcome measures

The primary outcome measures were:

1. **Cognitive development**

The age-standardized Early Learning Composite (ELC) score was assessed for all infants at baseline and endline. Trained assessors (independent of the implementers) used the Mullen Scales of Early Learning focusing on the four cognitive scales (visual reception, fine motor, receptive language, and expressive language). The Mullen Scales of Early Learning Tool is an individually administered comprehensive measure of cognitive functioning for infants and preschool children from birth through 68 months [34]. Scores were adjusted based on the child's age. The number of assessors was kept to a minimum of 3, to maximise reliability of measurement. To increase validity, assessors were interchanged between intervention and control groups after each clinic pair, to ensure that there was no systematic bias between the groups. The Mullen assessments were video recorded. As quality control, a random 10% sample of videos was reviewed internally and another random 10% sample was reviewed by an independent external assessor prior to the follow up survey.

2. **Retention in HIV care**

The proportion of HIV exposed or infected children with full retention in care (>80%) of scheduled visits at 12 months.

Secondary outcomes (Table 2) include HIV infected infants viral load measurement (>1000 copies per ml at 12 months), ART adherence and retention in both HIV positive mothers and HIV infected infants, parental stress levels and mental health status of caregivers, household food security status and infant nutritional status.

Sample size

Based on data collected in our pilot study, the mean Mullen ELC Score was 110.6 (standard deviation [SD] 16.1). The coefficient of variation (k) between clusters was 0.07 but this does not take account of the clustering effect of the group-based intervention so a value for k of 0.15 was used. Using these values, assuming a harmonic mean of 16 dyads enrolled per cluster and a loss to follow-up of 20%, 15 clusters per arm were needed to provide 80% power to detect an effect size (difference in means/SD) of 1.23 for the Mullen ELC Score. The same sample size provides 80% power to detect a risk difference of 20% in retention in care, assuming retention is 65% in the control arm and k=0.2. Based on these calculations our recruitment target was 528 caregiver-child dyads in total from 30 clinics. We recruited 574 dyads to ensure a harmonic mean of 24 dyads was enrolled from the larger seven clinics and a harmonic mean of 12 dyads was enrolled from the smaller eight clinics. This was done to ensure ECS group sizes were sufficient to include 2 ISALS groups per ECS group.

Randomisation process

The imbalance between arms was minimised by using restricted randomization, minimising on the number of HIV exposed infants between 0-24 months per clinic. Mapping of all clinic clusters within the two districts was conducted before recruitment and enrolment in each district. Of all the mapped clinics, those with fewer than 30 annual deliveries were excluded from the randomization process. The remaining thirty clusters were randomly allocated to the intervention versus usual care arms. The intervention was delivered to groups of 12 dyads, and 6 health facilities of sufficient size to run one group and 9 facilities of sufficient size to run two groups were allocated to each arm (Figure 2). To maximise transparency and buy-in from key stakeholders, a public randomisation procedure was undertaken (in January 2016 in the first district and in May 2016 in the second district) involving MoHCC, and district level governance and medical representatives.

Blinding

Blinding of patients and programme implementers were not possible at baseline because the participants had to know whether they were receiving the ECS programme. At 12 months follow up, the assessments was conducted outside trial communities with participants, from control and intervention communities within the same district, seen together. The assessor was blind to community allocation. Otherwise, data collection procedures were identical.

Data collection

During the enrolment visit, all participating caregiver-child dyads were allocated a unique identifier to ensure patient confidentiality. Baseline data were collected using an interviewer-administered questionnaire and Audio Computer Assisted Survey Instrument (ACASI) for the sensitive parts of the questionnaire administered with the caregiver and a developmental assessment of the child. Caregivers received guidance on using ACASI from trained surveyors with regards to using the laptop and headphones to listen to instructions, questions, and responses that have been digitally recorded onto the ACASI platform.

The questionnaires collected information on the following domains: demographic characteristics, household characteristics, income and expenditure, food security, antenatal, delivery and post-natal care related to birth of participating child, infant and child feeding practices, maternal mental health, parental stress, HIV testing, disclosure and treatment history for self and participating child, self-reported ART adherence. Questionnaire data were entered directly onto tablets pre-programmed using Open Data Kit with range and consistency checks incorporated.

A follow up assessment was conducted among enrolled caregiver-child dyads after 12 months of programme implementation. This assessment was conducted in the same order in which the clusters were enrolled. Caregivers completed the follow up

questionnaire administered in the same way as at baseline. Children had a full developmental assessment conducted by a trained assessor.

Data management

CeSHHAR Zimbabwe was the data-coordinating centre. In the field, data were uploaded to cloud storage daily and on password-protected office servers at the end of each week. The server was only accessible to the project data manager and named study personnel, on a central computer. Other hard-copy data were stored separately and securely in the field and then locked in a secure room at the data management centre. All data were cleaned, entered, analysed and stored.

Data analysis

Given the small number of clusters in the trial, cluster-level summary methods will be used. Analysis will be intention-to-treat. Age standardised ELC scores will be calculated from a combination of scores in the four cognitive domains of the Mullen Scales at endline using a HIV negative population in this setting, or a USA reference population if a local reference population cannot be obtained. The mean age-standardised composite score for each cluster will be estimated and the difference in means between arms calculated. The 95% CI for the mean difference will be estimated using a stratified t-test, with variance estimated from the residual mean square from an analysis of variance of cluster-specific means on stratum and trial arm. Analysis will adjust as fixed effects for baseline ELC score, stratum, and the following factors if they are imbalanced between arms at enrolment: age of children and caregivers, HIV status of children, socio-economic status and caregivers' mental health. For the HIV-specific primary outcomes (proportion of children retained in care at 12 months and proportion with unsuppressed viral load) and for binary secondary outcomes, the unadjusted prevalence ratio will be estimated as the ratio of the geometric mean percentage in the intervention cluster versus the control cluster and compared using logistic regression. The main analysis will be complete case, with multiple imputation as a sensitivity analysis for the two primary outcomes, using variables associated with the outcome and with missingness. Further sensitivity analysis will use individual-level logistic regression and compare the result with the cluster-level methods described above.

Data sharing

The trial steering committee (principal investigators and investigators) will consider data sharing applications for quantitative and qualitative data. All applications for data sharing must be made through the principal investigator using a standard Data Sharing Form. The trial steering committee convenes a meeting to consider the application. There will be a good reason for turning down a request. Requests will be considered

within 4 weeks of being made, and a decision communicated to the applicant as soon as possible thereafter.

Process evaluation

The process evaluation integrates quantitative and qualitative data collection tools. In addition, key contextual factors that might affect whether the intervention will work in other settings in Zimbabwe were documented. Project documentation will be reviewed to assess whether activities were conducted as scheduled, to identify any delays or gaps, and to check for standardised comparison across intervention sites. Routine programme data were used to track participation in the intervention, complemented by qualitative research, using semi-structured in-depth interviews (IDIs) with ECS staff, case managers, clinic staff and participating caregivers conducted at 3, 6 and 12 months after the start of the programme. There were 24 CCWs, 15 community based trainers (trainers for the ISALS), 17 ECS facilitators, and 13 nurses involved in implementing the intervention.

The research team also conducted an in-depth process evaluation of the ISALS/ECS and case management programme. The process evaluation included gathering general information on programme implementation processes in intervention communities. Participant groups were randomly observed during ISALS collection / ECS sessions to provide data on programme fidelity. Project staff carry an “events diary” to make note of events that were beyond the control of the project, yet have the potential to influence implementation or outcomes (natural disasters, introduction of other ISALS/ECS services, and change in MoHCC standard of care).

IDIs with caregivers were conducted in the intervention arms at two intervals across the project (mid-implementation and end). Caregivers for the IDIs were purposively selected for specific attributes such as high or low levels of engagement in activities, users and non-users of clinical service. These interviews explored perceptions of the community programme, perceptions of clinical and other available services, and positive and negative experiences of the intervention. Semi-structured interviews, with health care staff at intervention clinics and the implementing stakeholders, were conducted to elicit perceptions of the acceptability of the intervention and their own levels of satisfaction and perspectives on its quality.

Research ethics and approval

Ethical approval has been granted by the Medical Research Council of Zimbabwe (MRCZ/A/1943), Research Council of Zimbabwe, University College London (6789/002) and London School of Hygiene and Tropical Medicine (9912). The exposed Infant register was utilised within the study. This is not a research tool. The register is part of programme data under the Zimbabwe MoHCC data provision. The data are not

publicly available and any requests to use that data are made directly to the Zimbabwe MoHCC services and considered on a case-by-case basis.

Protocol modification

Any deviation from, or changes of, the protocol will be communicated to relevant partners and funding bodies via email. Changes to the current protocol at the Pan-African Clinical Trials Registry will be updated online.

Discussion

Several studies have highlighted the effectiveness of implementing comprehensive programmes to improve ECD and nutrition outcomes [16, 35]. Research shows poorer child development outcomes in children exposed to HIV especially in resource poor settings [9, 12]. This trial aims to examine the real world effectiveness of a combined parenting and income-generating programme, with the aim of enhancing child stimulation and utilising skill based learning for economic strengthening of populations in resource-limited settings. Prior to the roll out of the trial, the intervention and research procedures were piloted to assess feasibility and acceptability and to inform the details of the final trial design.

Through the 18 ECS sessions, the ISALS training and the home visits over one year we anticipate positive development in growth and cognitive development. We also anticipate improved parental skills, caregiver-child relationships, reduced stress, improved socio-economic resilience and household food security. This trial will contribute towards understanding the effects of integrating different components of care into a comprehensive programme. It will provide useful insight and understanding in delivery methods of comprehensive services and child development in a resource-limited country.

We have used a cluster randomised design to evaluate this community-based intervention as the intervention was delivered at the level of the health facility and it would not have been practical or desirable to randomise individuals within a facility to different standards of care. The trial will determine whether the comprehensive intervention package has an impact on trial outcomes. The detailed process evaluation will allow us to determine whether the intervention was delivered as intended and will provide insights into the strengths and limitations of the different intervention components. It will, however, not be possible to disentangle the effectiveness of the individual intervention components per se. Nevertheless, findings from this trial will contribute to the literature on the effectiveness of parenting interventions and provide insight on how these interventions could be harnessed into the HIV response to maximise child outcome in resource-limited settings.

***Word count**:* 4,083

Trial status

At the time of the manuscript submission, recruitment for the trial was completed and process evaluation and data analysis ongoing.

List of abbreviations

ACASI – Audio Computer Assisted Self Interviews

ART – Antiretroviral Therapy

CCW – Case Care Workers

CeSHHAR – Centre for Sexual Health and HIV/AIDS Research

CHIDO – Child Health Intervention for Development Outcomes

ECD – Early Childhood Development

ECS – Early Childhood Stimulation

ELC – Early Learning Composite

IDIs – In-depth Interviews

ISALS - Internal Savings and Lending Scheme

MoHCC – Ministry of Health and Child Care

SD – Standard Deviation

Declarations

Ethics approval and consent to participate

The trial was carried out according to Good Clinical Practices guidelines. The trial has been approved by the Medical Research Council of Zimbabwe and Research Council of Zimbabwe approval code MRCZ/A/1943. University College London (6789/002) and London School of Hygiene and Tropical Medicine (9912) approvals were also obtained. All participants gave written informed consent prior to enrolling in the trial.

Consent for publication

Not applicable.

Availability of data and materials

At the time of publication of research, the subset of the data required for the purposes of verifying research findings will be available for sharing on request from authors. Fuller sharing of data with any group requesting access to individual records will be ensured within 12 months of completion of trial. We will aim to hold the anonymised data for sharing as original databases stored with a soft copy of the fully annotated questionnaires and the STATA files used for recoding and analysis.

Ethical clearance will be sought before data are transferred to other groups for secondary analysis.

Competing Interests

The authors declare that they have no competing interests.

Funding

The funding partners for the study are USAID-PEPFAR, funded under the Orphans and Vulnerable Children Special Initiative.

Authors' Contribution

FC, and LS, conceived and designed the study protocol. PN and FC developed the intervention programme. RC, LS, HM, and ZM, drafted and finalized the manuscript. MT, LC, HW and VS contributed to the concept formation and study design. All authors have approved the final manuscript.

Acknowledgements

Our recognition and gratitude go out to our various partners USAID-PEPFAR (funding organisation), the PEPFAR OVC Technical Working Group (technical support) and World Education Zimbabwe (implementing partner). MT is a lead investigator with the

Centre of Excellence in Human Development, University Witwatersrand, South Africa, and is supported by the National Research Foundation, South Africa.

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Figure Titles

Table Titles

Figure 1. Proposed theory of change

Figure 2: Trial Design

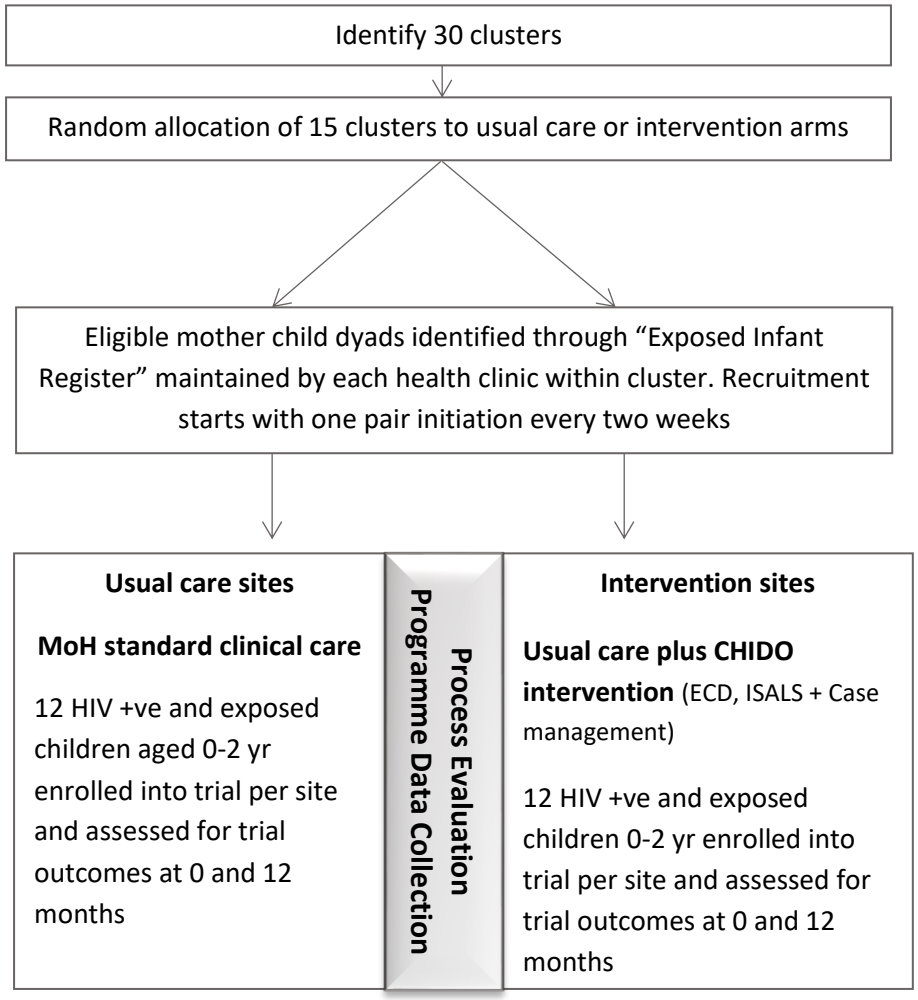

Figure 3: Intervention Schema

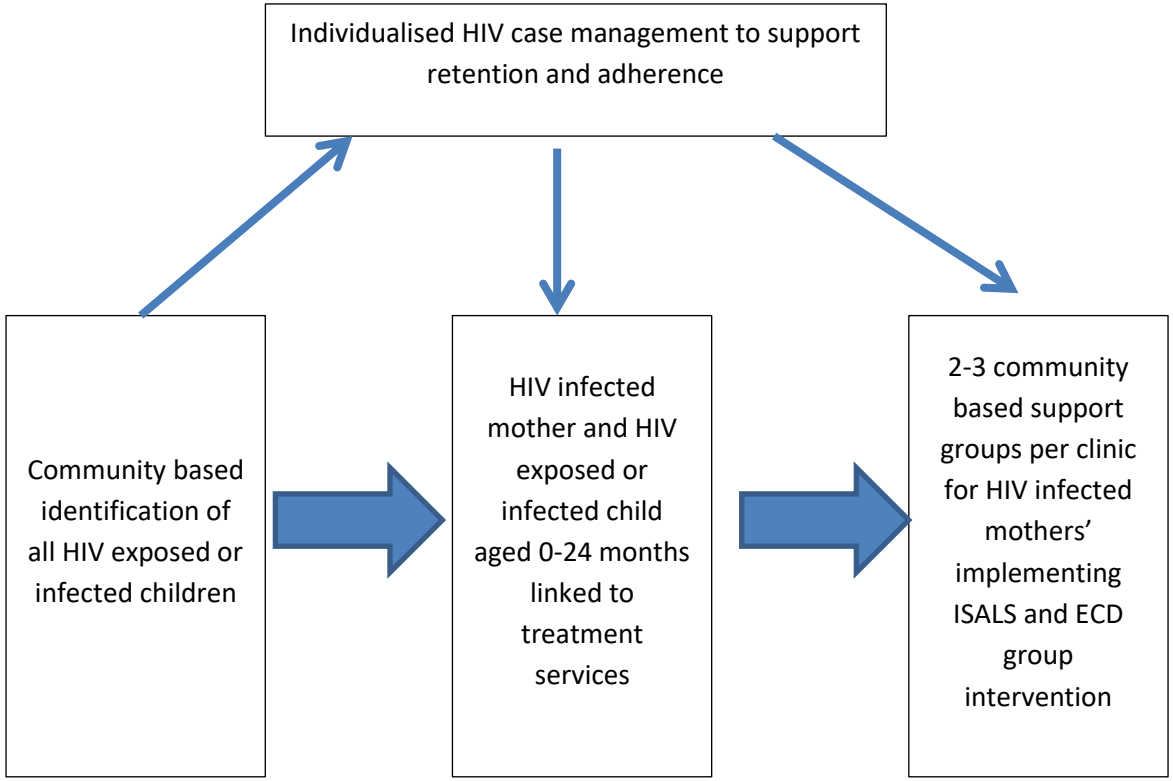

Table 1: CHIDO Trial Timeline

		Timeline													
	Communities	**Aug – Dec 2015**	**Jan – Feb 2016**	**Mar– April 2016**	**May – Jun 2016**	**July – Aug 2016**	**Sept – Oct 2016**	**Nov – Dec 2016**	**Jan– Feb 2017**	**Mar – April 2017**	**May – Jun 2017**	**July – Aug 2017**	**Sep – Oct 2017**	**Nov – Dec 2017**	**Jan – Jun 2018**
Pilot study	Non-trial communities														
Community Mapping of Clinics in 2 Districts	Trial communities														
Randomisation of clinics in the 2 districts															
Allocation of the 30 clinics to the Intervention or Control arm															
Enrolment of participants at baseline	Intervention														
	Control														

Completion of baseline assessment															
Rollout of CHIDO intervention package to the intervention arm	Intervention														
	Control														
Process evaluation	Process evaluation														
Phased 12 month follow up assessments undertaken in order of enrolment	Intervention														
	Control														
Data Analysis															

Table 2: CHIDO Trial Outcomes

	Outcome Measures	Target Group	Instrument	Administration
Primary	**Child Development Outcomes**: Mean childhood development global score	Infants	Mullen Scales for Early Learning	Child Assessment
	Child HIV Outcomes: i) Retention in care	Infants	Questionnaire	Self-report
Secondary	**Child HIV Outcomes:** i) Viral load	HIV + infants	Viral Load Tests	Clinical/Laboratory Tests
	Child Development Outcomes: i) Visual reception ii) Fine Motor iii) Receptive language iv) Expressive language	Infants	Mullen Scales for Early Learning	Child Assessment

	Nutritional Outcomes: Weight for age, height for age, weight for height (BMI) z-scores	Infants	Mid Upper Arm Circumference tape measure, height mate/board	Child Assessment
	Parenting Outcomes: Parenting Stress	Caregivers	Parental Stress Index Short Form (PSI-SF)	Interview
	Adherence Outcomes: i) Retention in care ii) Viral Load	HIV +ve mothers HIV +ve mothers	Medical Adherence Rating Scale (MARS) Viral Load Tests	Interview Clinical/Laboratory Tests
	Food Security Outcome	Caregivers	Household hunger (food deprivation) scale	Interview
	Mental Health Outcomes: i) Postnatal Depression ii) Common Mental Disorders	HIV +ve mothers Caregivers	Edinburgh Postnatal Depression Scale Shona Symptom Questionnaire (SSQ) 8	Interview Interview

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3

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APPENDIX 3: CHIDO Trial findings paper

Effects of parenting classes and economic strengthening for caregivers on the cognition of HIV-exposed infants: a pragmatic cluster randomised controlled trial in rural Zimbabwe

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Keywords: Early childhood development, Internal savings and lending scheme, HIV-exposed infants, RCT, Zimbabwe

Word count: 5,003

Abbreviations

AIDS - Acquired Immune Deficiency Syndrome

CHIDO - The Child Health Intervention for Developmental Outcomes

ECD- Early childhood development

ECS- Early childhood stimulation

ELC- Early Learning Composite

EPDS- Edinburgh Postnatal Depression Scale

HEU- HIV-exposed uninfected

ISALS- internal savings and lending scheme

SSQ- Shona Symptoms Questionnaire

PMTCT- Prevention of mother to child transmission

PSI-SF- Parental Stress Index- short form

ABSTRACT

Introduction

HIV-exposed children show signs of developmental delay. We assessed the impact of a pragmatic multicomponent intervention for caregivers of HIV-exposed children aged 0-2 years in Zimbabwe.

Methods

We conducted a cluster-randomised trial from 2016-2018. Clusters were catchments surrounding clinics, allocated (1:1) to either National HIV guidelines standard of care or standard care plus an 18-session group intervention comprising i) early childhood stimulation (ECS) and parenting training with home visits to reinforce skills and retention in HIV care; ii) economic strengthening. Primary outcomes measured 12 months after baseline (4.5 months post-intervention completion) included: i) global child development measured using the Mullen Scale of Early Learning; ii) retention in HIV care. Analysis used mixed effects regression to account for clustering and adjusted minimally for baseline prognostic factors and was by intention to treat. Trial registration number: PACTR201701001387209.

Results

Thirty clusters, 15 in each arm, were randomised. 574 dyads were recruited with 89.5% retained at follow-up. Ninety one of 281 (32.4%) were recorded as having received the complete intervention package, with 161/281 (57.3%) attending ≥14 ECS sessions. There was no evidence of an intervention effect on global child development (intervention mean-88.1 vs. standard of care mean-87.6; aMD=0.06; 95%CI: -2.68, 2.80; p=0.97) or infant retention in care (proportion of children who had missed their most recent HIV test: intervention-21.8% vs. standard of care-16.9%, p=0.18). There was weak evidence that the proportion of caregivers with parental stress was reduced in the intervention arm (aOR=0.69; 95%CI: 0.45, 1.05; p=0.08) and stronger evidence that parental distress specifically was reduced (intervention arm-17.4% vs. standard of care-29.1% scoring above the cut-off; aOR=0.56; 95%CI: 0.35, 0.89; p=0.01).

Conclusion

This multicomponent intervention had no impact on child development outcomes within 4.5 months of completion, but an impact on parental distress. Maternal mental health remains a high priority.

Word count: 297 (limit 300)

What is already known?

- HIV-exposed children in resource limited settings face multiple and complex stressors associated directly and indirectly with HIV infection.
- Early interventions for HIV-exposed children have led to documented improvements in child outcomes in the short and longer term.

What are the new findings?

- The intervention trialled here did not have an impact on child cognitive development, but reduced parental distress which could directly and indirectly impact child trajectories.
- The prevalence of reported symptoms of common mental disorder was extremely high among participating caregivers.

What do the new findings imply?

- Cognitive development outcomes may take longer to improve following parental child stimulation training.
- Comprehensive interventions to address childhood development may need to include screening and intervention for poor mental health in caregivers.

INTRODUCTION

Early childhood development (ECD) covering the first 3 years of a child's life marks a time of gradual development of a child's sensory-motor, social-emotional, cognitive and language capacities. These processes are shaped by many factors, including interactions between the child and their environment, exposure to experiences, and genetics (1). During this period of rapid physical growth, the child acquires a complex set of skills and functional competencies facilitating achievement of their potential in life and laying the foundation for long-term physical, emotional, and psychological health in child and adulthood.

During this period, children's brains develop rapidly and can be modified by their environment (2) influencing their ability to learn and develop over time (3). Thus, early childhood is a key time to maximise the opportunity for children to develop their full potential. Researchers have shown that appropriate stimulation, good quality parenting provided by a consistent, responsive caregiver, coupled with adequate nutrition and access to health and psychosocial care can contribute to optimal development (4, 5). Conversely, adversities during this period, such as poverty, malnutrition, poor health, low stimulation, exposure to stressful conditions and impoverished environment can disrupt brain development, attachment, and early learning (2).

HIV infection in both the parent and the child represents a multi-faceted life challenge (6). HIV can impact child growth and development in a variety of ways including their cognitive development (7, 8). Several studies have described the risk of developmental delay and impairment in both children living with HIV (9), and HIV-exposed uninfected (HEU) infants (7) compared to HIV unexposed infants (8), with the risk apparently heightened in low and middle income countries (LMICs) (10). Children infected with HIV perinatally face greater risk of neurological and neuropsychological deficits compared to HEU infants, either due to direct effects of HIV on the central nervous system (9), exposure to treatment or other HIV related factors. These risks can be mitigated; research illustrates the importance of early ART initiation, and virological suppression during infancy or early childhood and its association with improved neurocognitive outcomes in children with perinatally acquired HIV (11, 12). HIV can also impact the neurodevelopment of children indirectly through its influence on the child's living environment (8), including community stigma and discrimination, caregiver unemployment, caregiver illness and bereavement or caregiver mental health (10, 13, 14). However, in some cases despite facing significant adversities, HEU children can develop resiliency and demonstrate positive developmental trajectories, similar to those HIV unexposed uninfected (15).

Early interventions for disadvantaged children have led to documented improvements in child outcomes such as survival, health, growth and cognitive and social development (16). Several studies have demonstrated the benefits of caregiver or child targeted interventions over the long term and showed improvements in developmental outcomes of children from LMICs (2, 4). Home visits and support to HIV positive caregivers' by community health workers was found to improve developmental outcome for HEU children (17). Parenting and child stimulation programmes taught to the caregiver can significantly improve cognitive and motor development in young children infected with HIV (18). In addition microfinance programmes (which includes the provision of loans, savings, and insurance) in rural settings can have a positive impact on various household indicators, improve food security and the health of children (19). Research shows that combination interventions can have accelerated benefits (20, 21). Theoretical models (22) suggest that internal assets, family resources and community support can promote the resilience process and temper negative impacts of parental HIV. The need for an evaluation of more complex, broader and integrated interventions is timely.

Zimbabwe is one of the countries most severely affected by HIV globally, with prevalence estimated at 14.6% among 15-64 year olds (23). Over a million children have been orphaned due to AIDS related deaths since the start of the epidemic (24). Prevention of mother to child transmission (PMTCT) programmes have dramatically reduced perinatal transmission and ART rollout has reduced mortality and morbidity in caregivers (25). However, despite improved health and survival of infants born to mothers living with HIV, interventions to improve the wellbeing and development of these children are needed. The Child Health Intervention for Developmental Outcomes (CHIDO) trial aimed to determine the real world effectiveness of a multicomponent community-based intervention on child development and HIV.

METHODS

The methods have been previously published (26). A brief overview is provided here.

Study design and participants

The CHIDO trial is a pragmatic parallel-arm cluster randomised controlled trial conducted in 30 primary care clinic catchment areas in two districts in Zimbabwe (Goromonzi and Mudzi). Detailed mapping of all health facilities and their communities was conducted to select trial sites, which are at least 15km apart.

Community sensitisation was carried out in phases. First the local leaders (including traditional and political leaders, health and educational professionals) were given information about the study, its objectives, the target population and encouraged to ask questions or raise any

concerns. They were then invited to take part in the site randomization process. The caregivers were identified from the HIV Exposed Infant Registers kept at trial clinics and were eligible for inclusion if they were the primary caregivers (biological and non-biological), the biological mother had been living with HIV, and cared for a child aged 0-24 months. Caregivers who gave written informed consent/assent in English or Shona were enrolled into the trial, completed a baseline assessment and were followed up after 12 months. In intervention communities, caregiver-infant dyads were encouraged to engage in all CHIDO intervention activities. Whilst they attended the clinic specifically for the intervention sessions they could also attend clinic services if scheduled/required.

Extended CONSORT guidelines were followed for reporting the results of this trial.

Patient involvement

Patients and village health workers were involved in formative work undertaken at which the CHIDO intervention was developed.

Randomisation and masking

Clinics were randomised in a 1:1 allocation ratio to the CHIDO intervention or Ministry of Health and Child Care (MoHCC) standard of care. Restricted randomisation was used to ensure balance by district (20 in Goromonzi district and 10 in Mudzi district) and on the number of HIV exposed infants aged between 0-24 months per clinic by stratifying the clinics into those able to run one group of 12 dyads (12 clusters) and those of sufficient size to run two groups of 12 dyads (18 clusters). To maximise transparency and buy-in from stakeholders, a public randomisation procedure was undertaken in each district (on 19th January 2016 in Goromonzi and on 31st May 2016 in Mudzi) involving MoHCC, and district level government and medical representatives. Assessors conducting the endline survey procedures were blind to trial arm.

Intervention components

The intervention included three elements: i) an 18 session health, nutrition and early childhood stimulation (ECS) parenting programme (Table 1); ii) an internal savings and lending scheme (ISALS) with ISALS sessions held immediately after each ECS session; and iii) village health workers who visited participants at home each month (or more frequently in the case of non-attendance at group sessions or other problems). The parenting programme content evolved out of formative work and the number of sessions was set after piloting and feedback from participants about preferred length and frequency of sessions.

Insert Table 1 here

Baseline and endline assessments and data collection

Participant enrolment was conducted in parallel in intervention and standard of care communities between 16 January and 8 September 2016. At enrolment, all participating caregiver-child dyads were allocated a unique identifier. Questionnaire data which included demographic, socio-economic, maternal mental health and household food security information were collected using an interviewer-administered questionnaire with data entered directly onto tablets pre-programmed using Open Data Kit with range and consistency checks incorporated. Maternal mental health was measured using the Edinburgh Postnatal Depression Scale (EPDS) (27, 28), which is a diagnostic tool that has been locally validated in Zimbabwe(28), plus the 8-item Shona Symptoms Questionnaire (SSQ-8), a locally developed and validated scale which determines risk of common mental disorders (including anxiety and depression) (29). Finally parental stress was measured using the Parental Stress Index Short Form (PSI-SF) (30).

The more sensitive questions were self-completed using Audio Computer Assisted Survey Instrument to maximise validity. This was followed by a developmental assessment of the child conducted by one of two trained research nurses. Developmental assessments were videoed, and a small randomly selected sample was reviewed by a highly experienced assessor. This was done as part of quality control and assurance, and to minimize differences between assessors.

Intervention implementation commenced within three months of participant enrolment in all communities and ran over 12 months between 7th March 2016 and 7th July 2017.

An endline assessment was conducted between 10 April 2017 and 18 January 2018 among enrolled caregiver-child dyads 12 months after the baseline survey and within 0-5 months after completion of intervention delivery. The endline survey was conducted in parallel, with pairs of intervention and control trial sites being assessed at the same survey venue to minimise unblinding of assessors. Survey procedures were as described at baseline.

At endline a dried blood spot sample was collected from all biological mothers to determine HIV viral load and infants to test for HIV antibody status and viral load. Programme attendance records and village health care worker diaries were reviewed, and data double entered into password protected Access databases.

Laboratory assessments

Dried blood spot samples were air dried, stored at room temperature and submitted weekly to the respective laboratories. Infant samples were sent to the National Microbiology Reference

Laboratory in Harare for HIV-1 antibody testing using COBAS® AmpliPrep/COBAS® TaqMan. Samples confirmed HIV positive were sent for viral load testing. Caregiver samples were sent to Flow Cytometry Laboratory for viral load testing using Biomerieux NucliSENS easyMag and EasyQ.

Outcome measures

There were two primary outcomes for the trial, i) change in the mean age-standardized Mullen Early Learning Composite (ELC) score (31) of children; ii) the proportion of HIV exposed or positive children with full retention in care (>80%) of scheduled HIV treatment and care visits at 12 months. In the absence of locally validated robust child development measures, the Mullen ELC score was chosen as it had been used to determine impact of caregiver interventions over a similar time period in Africa (32, 33). We assessed seven pre-specified secondary endpoints as previously reported, reflecting factors intended to be affected by the intervention, which were analyzed with the same analytical framework as the primary outcome (see Table 2).

Insert Table 2 here

Statistical analysis

Our sample-size calculations have been described previously (26). We estimated that we would need 15 clusters per arm with a harmonic mean of 16 caregiver child dyads per cluster at endline, and assuming 20% loss to follow-up over 12 months to have 80% power to detect an effect size (difference in means/SD) of 1.23 for the Mullen ELC Score and 82% power to detect a risk difference in retention in care of HIV exposed children of at least 17% assuming 65% are retained in the control arm. The overall recruitment target was therefore 528 caregiver-child dyads in total from 30 clinics. We recruited 574 dyads to ensure a harmonic mean of 24 dyads was enrolled from the larger seven clinics (to allow 2 groups to run at these sites) and a harmonic mean of 12 dyads was enrolled from the smaller eight clinics, where just one ECS/ISALS group was run.

The statistical analysis followed a pre-specified analytical plan differing from the published protocol by using individual-level analysis (see supplementary materials) which allowed for greater flexibility. Data were analysed in STATA v.15.1 (StataCorp LP, College Station, Texas, USA) using intention to treat principles incorporating random effects for clusters and adjusting minimally for baseline prognostic factors. Mean differences and 95% confidence intervals (CI) were used to estimate the effect of the intervention for quantitative outcomes using mixed effects linear regression. Odds ratios (OR) and 95% CI were used to estimate the effect of the

intervention for binary outcomes using mixed effects logistic regression. Mental health questions were categorised as at risk or not at risk, with cut-points of 12/30 for the EPDS (28), 6/8 for the SSQ-8 (29), and at the 90th percentile of the reference range for PSI-SF domain and total scores (30). Baseline factors adjusted for a priori were the baseline measurement, strata in Goromonzi (two groups based on the number of children on the clinic register), district (Goromonzi or Mudzi), infant age (0-<6 months, 6-<12 months and 12-24 months) and for quantitative Mullen outcomes, a categorical covariate representing the assessor at baseline. Sensitivity analyses were performed using a cluster-level analysis for the ELC score (34). Evidence for effect modification in the ELC score was assessed by incorporating interaction terms with baseline Mullen ELC score or with baseline caregiver's mental health as measured by EPDS, SSQ-8 and PSI- SF. The effect of the intervention was also examined in a per protocol analysis comparing those in the intervention arm who attended most ECS sessions (either at least 14/18 sessions in total, or at least 7/9 sessions addressing child development) with those in the standard of care arm.

Ethics approval

The trial [registration number PACTR201701001387209] has been approved by the Medical Research Council of Zimbabwe and Research Council of Zimbabwe approval code MRCZ/A/1943. University College London (6789/002) and London School of Hygiene and Tropical Medicine (9912) approvals were also obtained.

RESULTS

All 30 clusters were randomised (15 to each trial arm) and all remained in the trial until the end (Figure 1). Number of participants recruited (n=574) exceeded target enrolment (n=528). Retention was 89.5% (514/574), (261: 91.5% in the intervention arm and 253: 85.0% in the standard of care arm) of whom 506 of 514 had endline data on the Mullen score. Six Mullen scores were missing because the child had died. The other two children were found and tested for HIV but the Mullen test was not performed. At follow-up 18 children had a different primary caregiver from the person who completed the baseline interview.

Descriptive characteristics at baseline

Baseline characteristics were generally comparable between trial arms (Table 3); the intervention arm had a greater percentage of infants aged under six months (26.3% vs. 15.0%), infants stunted at baseline (38.4% vs. 34.3%) and households of lower socioeconomic status (37.0% vs. 30.0%). Only two of seven HV infected babies had been started on ART within six weeks of birth. Almost all caregivers (562/574; 97.9%) were biological mothers, and about half

(304/574; 53.0%) had secondary education or higher. Reported food insecurity was high. Mental health of caregivers was poor with 230/574 (40.1%) caregivers at risk of common mental disorders (SSQ-8>6) and about half of mothers (284/562; 49.5%) above the threshold for postnatal depression (EPDS>12) at baseline. High parental distress (PSI-SF parental distress subscale>90th percentile) was reported by 185/574 (32.2%) caregivers.

Infants were 291/574 (50.1%) female, and 207/574 (36.1%) were stunted (WHO height-for-age z-score <-2). The mean composite score on the Mullen Early Learning Scale at baseline was 102.3 (95%CI: 98.6, 106.0), which was similar to the US reference norms (see Table 3). Characteristics of those lost to follow-up were similar to those who completed follow-up (Appendix Table 1).

Insert Table 3 here

Programme Implementation

The CHIDO intervention was initiated in all 15 intervention clusters, with 281 participants enrolled. There are missing attendance data from one cluster. In the 14 clusters with attendance data, 21 ECS groups were run with each group intended for up to 12 participants. Seven clusters ran one group and seven clusters ran two groups. Of 268 caregivers in the intervention arm from the 14 clusters with records, 232 (86.6%) attended any ECS session. There were 43/268 (16.0%) participants who attended all 18 ECS sessions, and 118/268 (44.0%) who attended 14-17 sessions. Of the nine sessions addressing child development (see Table 1 and Figure 2), 79/268 (29.5%) participants attended all nine sessions, and 79/268 (29.5%) attended 7 or 8 sessions, median per group who attended 7 to 9 child development sessions was 7.5 (IQR 6-9).

ISALS ran immediately after the ECS sessions and all women who attended an ECS session were assumed to have attended an ISALS session. Women were recorded in the ISALS register if they made a financial contribution to the ISALS (i.e. actively participated in the ISALS process). The target was for women to participate in 12 ISALS over the course of the trial. ISALS registers were not available for five clusters. Where records were kept, 184 of the 232 caregivers (79.3%) participated in at least one ISALS session and 155 (67%) made a financial contribution. The median number of sessions attended at which a financial contribution was made was 5 (IQR 2–9), and 14/232 (6.0%) made a financial contribution at least 12 times (equivalent to once monthly). Overall 198/232 (85.3%) received at least one home visit and the median number of home visits per caregiver was seven (IQR 0–9). Impact evaluation was assessed a median 134 (IQR 98 to 163) days after participants attended their last ECS session among 232 participants who attended any session and were followed up.

Among all intervention participants only 32.4% (91/281) were recorded as having received the full intervention package as devised (>14 ECS, >6 ISALS and >6 home visits), Figure 3.

Primary outcomes

Early learning composite score

At the endline survey the Mullen ELC mean score was 87.9, a reduction of 14.4 points from baseline. There was no evidence of a difference in Mullen composite score after programme implementation between trial arms (mean of 88.1 in the intervention arm and 87.6 in standard of care arm; adjusted mean difference (aMD)=0.06; 95%CI: -2.68, 2.80). The estimated coefficient of variation (k) was 0.09. Cluster-level means showed departure from normality, but results were comparable (aMD=0.11; 95%CI: -2.90, 3.11). There was also no evidence of difference in Mullen sub-scales by trial arm; Table 4. Individual child trajectories showed that 80% of infants had lower ELC scores at follow-up compared to baseline in both arms.

Insert Table 4 here

There was no evidence for effect modification for the pre-specified baseline covariates on the intervention effect on the Mullen score (Table 5). Defining adequate provision of ECS as attendance at 14 or more sessions, there was no evidence of an intervention effect among those receiving adequate provision (aMD=0.57; 95%CI: -2.39, 3.53) compared to the standard of care arm.

Insert Table 5 here

Child HIV retention in care

At follow-up, infant HIV prevalence was 3.9% (10/257) in the intervention arm and 2.4% (6/248) in the standard of care arm. Clinic attendance data were not collected. Two proxy measures for HIV care retention were used. Firstly, in HIV positive children the prevalence of virological failure (viral load>1000 copies/ml) was 4/8 (50.0%) in the intervention arm (with 2 missing test results) and 4/6 (66.6%) in the standard of care arm. The numbers were too small to detect any difference between arms in HIV prevalence or viral suppression. Secondly, the date of the most recent HIV test was recorded at baseline and follow-up. Children were recorded as not retained in care if they had missed an HIV test in the PMTCT schedule (at 6 weeks, 9 months and weaning). In the intervention arm 21.8% of infants had missed the most recent test, compared to 16.9% in the standard of care arm (adjusted odds ratio (aOR)=1.25; 95%CI: 0.77, 2.01, p=0.37).

At baseline 165/574 (28.7%) of caregivers said they did not know the child's HIV status and by follow-up only 16/506 (3.1%) said they did not know (Table 3). There was no difference between arms in reported knowledge of HIV status at follow-up. At follow-up in the intervention arm 79/85 (92.9%) of caregivers who at baseline reported not knowing child's status reported they now knew it, compared to 55/58 (94.8%) in the standard of care arm.

Secondary outcomes

Nutritional outcomes

There was no evidence of any impact of the intervention on weight for age z-score, height for age z-score or body mass index (see Table 6), although there was strong evidence that infants in the intervention arm had a reduced mean MUAC for z-score (-0.60 vs. -0.49; aMD=-0.20; 95%CI: -0.35, -0.06; p=0.01).

Parenting stress

There was weak evidence of an intervention effect on parental stress overall (aOR=0.69; 95%CI: 0.45, 1.05; p=0.08). There was strong evidence that the intervention had an impact on the Parental Distress sub-scale of the PSI (17.4% vs. 29.1%; aOR=0.56; 95%CI: 0.35, 0.89; p=0.01).

Maternal Adherence outcomes

The proportion of women with viral loads of >1000 copies per mL was similar by arm (13.4% in the intervention arm vs. 10.5% in the standard of care arm; aOR=1.33; 95%CI: 0.72, 2.46). Self-reported adherence on the Medical Adherence Rating Scale was high at follow-up and also similar between trial arms (97.6% in the intervention arm vs. 98.4% in the standard of care arm; Appendix Table 1).

Household food security

There was no evidence of difference in household food security by trial arm, with 24.9 % in the intervention arm and 21.7% in the standard of care arm reporting experiencing food insecurity (aMD: 1.19; 95%CI: 0.62, 2.26; p=0.52).

Maternal mental health outcomes

There was no evidence of a difference between trial arms in the proportion of biological mothers with at least mild post-natal depression measured using the EPDS (39.8% vs. 43.9%; aOR=0.79; 95%CI: 0.50, 1.25; p=0.32), despite symptoms of postnatal depression being

common (Table 6). There was also no difference observed among those at risk for common mental disorders (44.8% vs. 45.5%; aOR=0.90, 95%CI; 0.62, 1.32; p=0.59).

Insert Table 6 here

DISCUSSION

We undertook a pragmatic evaluation of a multi-component group intervention combining sessions addressing early childhood stimulation and more general childcare with household economic strengthening to improve food security and economic barriers to clinic attendance. We aimed to improve global child development and retention in HIV care of infants born to HIV positive mothers both by targeting these outcomes and some of their structural drivers. There was no effect of the intervention on global child development within 4.5 months of completing the intervention. HIV retention in care was almost universal in both arms of the trial by endline. Only 32% of those in the intervention arm were confirmed to have received the full intervention package. Participants reported high levels of food insecurity, symptoms of anxiety and depression and parenting stress at baseline, all factors which are likely to impede participation. The intervention had no effect on any of these secondary outcomes except parental distress. Of note, the intervention was evaluated in rural communities requiring some participants to travel considerable distances to attend sessions.

Although evidence from LMIC is limited, studies have demonstrated that ECS programmes targeting young children in these settings can improve global child development both in the short and longer term (4, 35). However, few have been delivered to HEU children. Many of these interventions have focused just on single interventions (such as nutrition, positive parenting practices) whilst this trial has looked at a more comprehensive package which addressed the wider structural barriers to early childhood development in addition to global chid development per se.

This intervention implemented by the Bantwana Initiative of World Education Inc. was innovative in seeking to reach groups of caregivers rather than individuals and combine ECS training with training on more general child care issues. In addition the intervention aimed to strengthen household economic security through ISALS both to improve food security (and thereby nutritional status of the child) and reduce economic barriers to clinic attendance. In practice, uptake of the intervention was sub-optimal possibly reflecting the acceptability of the intervention to some of the potential beneficiaries. Process evaluation suggested that using a group approach for mothers living with HIV was potentially stigmatising, in that some women feared participation might result in deductive disclosure within the community. The distance caregivers had to travel to take part in intervention sessions in some sites also undermined

attendance. In addition, although the majority of women attended ISALS sessions relatively few opted to participate in the savings and lendings process perhaps reflecting their reluctance to trust women in a group they were assigned to. Outside of the trial this intervention is offered to all mothers/caregivers of small children in a community and mothers are free to choose whether or not to join an ISALS and with whom. By evaluating the intervention we imposed artificial constraints on its delivery.

The trial occurred whilst the Zimbabwe Ministry of Health and Child Care and partners were strengthening prevention of mother to child transmission programmes. Option B+ was scaled up across Zimbabwe in 2014 and several studies have shown increasing engagement of mothers with services although engagement of infants in the care cascade has been less marked. Our findings suggest substantial improvements in knowledge of infant HIV status over the trial with knowledge of status near universal after 12 months in both arms. Reassuringly few children are HIV positive (3%) post-breastfeeding, although among the few with HIV, a substantial proportion in both arms had a detectable viral load, implying suboptimal engagement with care. Over 90% of women in both arms were virologically suppressed, higher than among women living with HIV in Zimbabwe generally (86%) (36). This suggests that Zimbabwean mothers are optimally engaged in care and that our intervention could not substantially contribute to this.

There was some evidence of an intervention effect on parenting stress overall and distress specifically. However the intervention did not affect risk of other common mental disorders. Of note the intervention was not designed to address maternal mental health specifically. Caregivers in this trial had a high prevalence of risk of common mental disorder symptoms; around 50% of women were above the cut-off for mild post-natal depression at baseline and endline. Previous studies suggest that maternal depression negatively impacts both parenting and child development and this may have undermined our ability to demonstrate an impact. Future interventions may need to incorporate a specific mental health component. The treatment gap for mental health in much of Africa is extremely high Community-based lay health worker problem solving therapy, such as the Friendship Bench which has been widely scaled up in urban Zimbabwe present a method of closing the gap. Implementation of an adapted Friendship Bench through primary health clinics in rural areas is currently being explored.

We assessed global child development using the Mullen Early Learning Scale, which is widely used but not validated or normed among African children of this age. It is a complex instrument and despite comprehensive training and limiting the number of trained assessors our independent review of instrument implementation found that assessment of children was

suboptimal. Of note though, the Mullen ELS has been successfully used elsewhere in Africa to determine the impact of a caregiver intervention after 12 months (32). When compared to normative data (USA-based), the baseline data on child development score ranges were comparable, but by 12 months follow-up the scores were lower than normative groups. All children in the study were, by definition, HIV-exposed and there is a solid evidence base that both HIV exposure and infection are associated with child development challenges.

Although there were no short-term effects on cognitive development for children, the fact that the endline data collection occurred a median of 4.5 months after intervention completion may be important. The child development benefit of parenting training may need more time to influence child development outcomes, particularly as the child stimulation components of the course were scheduled at the end of the package and the impact of reduced parental stress on parenting behaviours may take time to be observed.

Strengths of our study included that we piloted research and intervention components to optimise our implementation and evaluation approach. We ran a large trial and had a high retention rate (90%) over 12 months. The trial was conducted independently of programme implementers. We measured child development outcomes using assessors blinded to trial arm and undertook an independent validation of these measures. HIV retention in care was validated using biological markers. Mental health outcomes were all assessed using locally validated scales.

However, there are some limitations. By recruiting from the HIV-exposed infant registry, children who were not engaged in care were not included. This could have introduced some bias, excluding those least engaged in care and potentially most vulnerable. Measurement of global child development was suboptimal and we are uncertain as to what impact this has had on the global child development outcomes. However, we minimised number of Mullen ELC assessors and assessors determined outcomes in intervention and control arms. More time and resources for training and validation of assessment procedures was required. Programme uptake was measured using programme implementer data and the apparently low programme uptake may reflect incomplete data collection by lay facilitators rather than poor attendance. As outlined above the intervention design was adapted to fit the constraints of the trial evaluation design which may have adversely affected outcomes. A shorter ECS programme may be more practical to implement. The nature of the intervention was ambitious both in complexity and duration. Our study suggests that fidelity to the lengthy programme may be a challenge, but that the intertwining of interventions was feasible. Single interventions may flounder when real life complexity is not addressed. Parenting in poverty and the presence of HIV is a complex reality. Our hypothesis was that a multicomponent intervention which

addresses both ECD and its structural drivers was feasible and acceptable to some; the data on attendance can serve as a guide to future intervention planning. HIV specific interventions, even if they are not labelled as such, may be stigmatising and may hinder attendance.

Our trial has important implications for programmers and policy makers. Causes of poor child development in HIV affected children are clearly multifactorial, but the feasibility and scalability of addressing multiple factors in a single multi-component intervention is challenging. Given the high rates of poor mental health, effective community based mental health interventions need to be scaled up beyond urban areas and potentially run alongside ECS interventions. Design and implementation of evaluations of real-world interventions face several challenges including fitting within donor funding cycles, limited by implementer priorities, and political realities, all of which are crucial factors.

Acknowledgement

Our recognition and gratitude go out to our various partners USAID-PEPFAR (funding organisation), the PEPFAR OVC Technical Working Group (technical support) and World Education Zimbabwe (implementing partner), CESSHAR, Mavambo and UCL. We would like to thank Professors Lucie D. Cluver, Mark Tomlinson, and Michael J Boivin for their contribution during the initial stages of trial design. We would also like to thank the families and children who participated in the trial.

Funding

The funding partners for the study are USAID-PEPFAR, funded under the Orphans and Vulnerable Children Special Initiative. HAW, VS and AR received support from the Medical Research Council (MRC) and the Department for International Development (DFID UK) under the MRC/DFID Concordat (K012126/1).

Competing interests

The authors declare that they have no competing interests.

Contributions

LS and FMC led the trial design, with involvement from VS and HAW. FC, and LS, conceived and designed the study protocol. PN and FMC developed the intervention programme. FMC, RC, PN, RM, and ZM led the trial implementation, data collection and process evaluation. AMR carried out the statistical analysis. VS and HAW oversaw trial analysis and data interpretation. LS and FMC led data interpretation with involvement from HAW, VS, AMR, HM, RC, and ZM. HM, LS and FMC wrote the paper and all authors were involved in the review of drafts. All authors have approved the final manuscript.

Data sharing

At the time of publication of research, the subset of the data required for the purposes of verifying research findings will be available for sharing on request from authors. We will aim to hold the anonymised data for sharing as original databases stored with a soft copy of the fully annotated questionnaires and the STATA files used for recoding and analysis. Ethical clearance will be sought before data are transferred to other groups for secondary analysis.

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639 *Figure 1: Recruitment and enrolment*

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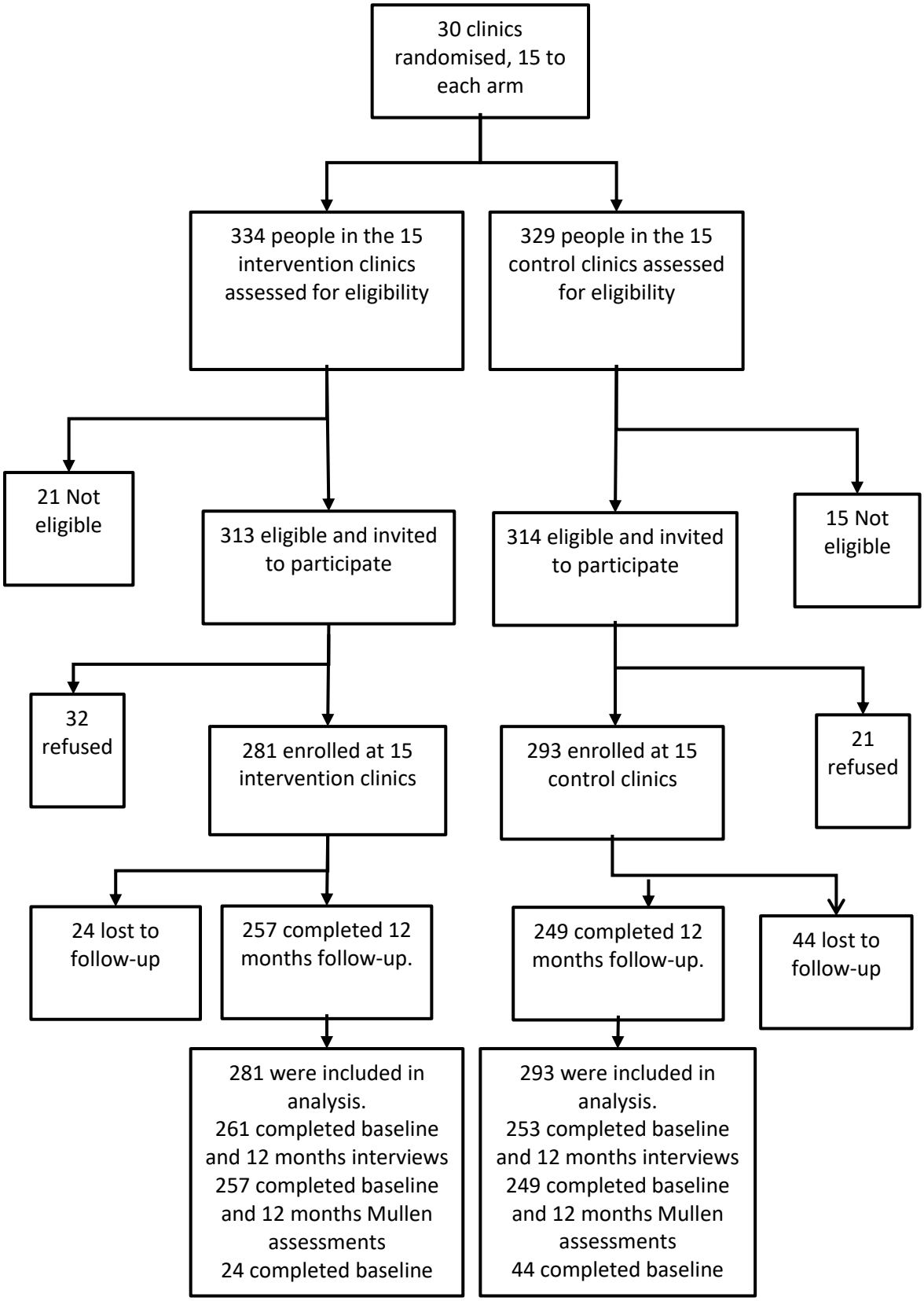


Figure 2: ECS session attendance. Orange bars indicate sessions focusing on child development. (n=281 all trial participants; n=268 trial participants in communities that recorded ECS; n=232 who ever enrolled in a session)

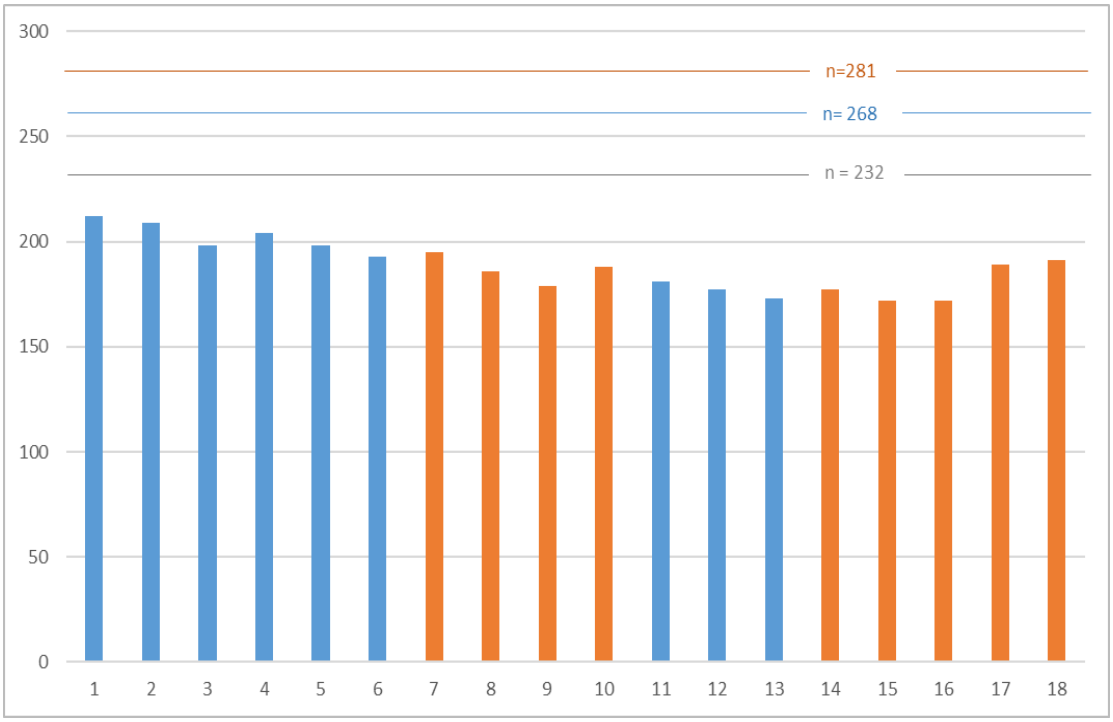
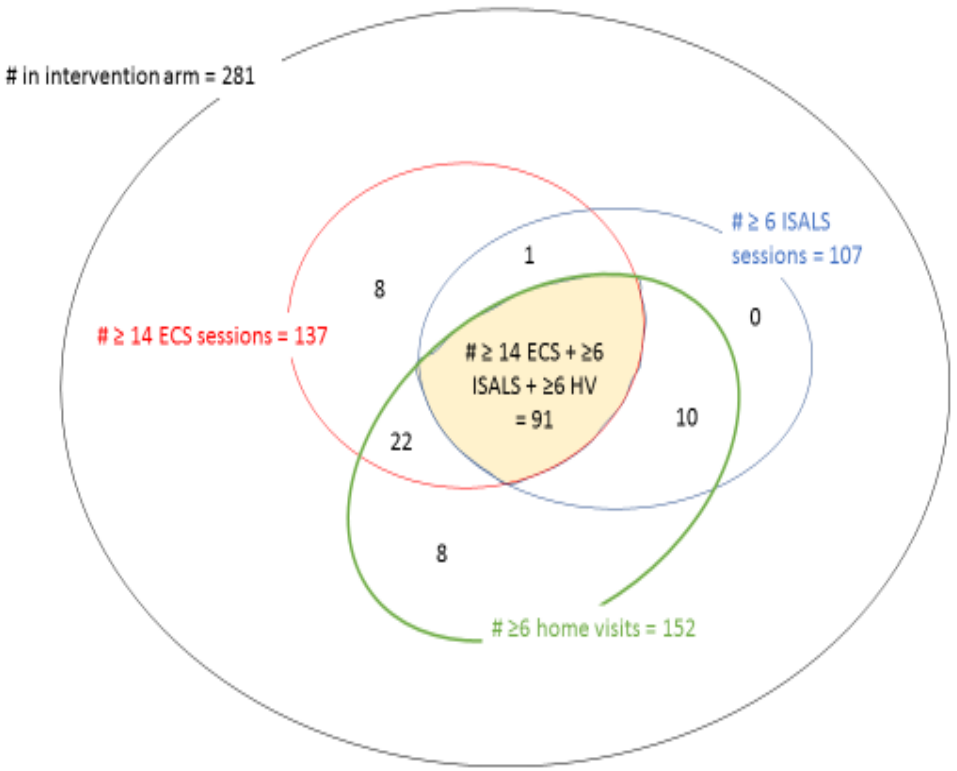


Figure 3: Venn diagram of trial participant attendance at intervention sessions



652 *Table 1: Parenting programme content*

Session number	Delivered by	Parenting programme content
1	CHW	Relationships with people around you and your child
2	CHW	The role of good parent – responsive parenting practices (session I)
3	CHW	The role of good parent - responsive parenting practices (session II)
4	Nurse	A healthy infant and young child (session I)
5	Nurse	A health infant and young child (session II)
6	Nurse	A well-nourished infant and young child
7	CHW	Physical/motor development (session I)
8	CHW	Physical/motor development (session II)
9	CHW	Social and emotional development (session I)
10	CHW	Social and emotional development (session II)
11	Nurse	A health infant and young child (focus on PMTCT and treatment adherence)
12	Nurse	Complementary feeding (session I)
13	Nurse	Complementary feeding (session II)
14	CHW	Communication and language development (session I)
15	CHW	Communication and language development (session II)
16	CHW	Developing thinking and understanding of the world (cognitive)(session I)
17	CHW	Developing thinking and understanding of the world (cognitive) (session II)
18	CHW	Positive discipline

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654 *Table 2: Secondary outcomes of the CHIDO trial*

Outcome Measures	Assessment tools used
1. Child HIV Outcomes: Viral load	Viral Load Tests conducted using Biomerieux NucliSENS easyMag and EasyQ on dried blood spot samples
2. Child Development Outcomes: • Visual reception • Fine Motor • Receptive language • Expressive language	Mullen Scales for Early Learning
3. Nutritional Outcomes: Weight for age, height for age, weight for height (BMI) z-scores	Mid Upper Arm Circumference tape measure, height mate/board
4. Parental Stress	Parental Stress Index Short Form (PSI-SF)
5. Adherence Outcomes: • Retention in care • Viral Load	Medical Adherence Rating Scale Viral Load Tests conducted using Biomerieux NucliSENS easyMag and EasyQ on dried blood spot samples

6. Food Security Outcome	Household hunger (food deprivation) scale-modified HFIAS (one item from each domain of the scale (i)uncertainty about household food supply; ii)) insufficient quality; and 3)insufficient food intake
7. Mental Health Outcomes: • Postnatal Depression • Common Mental Disorders	Edinburgh Postnatal Depression Scale Shona Symptom Questionnaire (SSQ) 8

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656 *Table 3: Descriptive characteristics of participants at baseline by trial arm*

	Measure and Level	**Intervention arm**	**Standard of care arm**
Total	N (% of total)	281 (49.0%)	293 (51.0%)
Infant's characteristics			
Age (years)	Median (IQR)	1.04 (0.48, 1.49)	1.00 (0.68, 1.47)
Age	0-<6m	74 (26.3%)	44 (15.0%)
	6-<12m	61 (21.7%)	100 (34.1%)
	12-24m	146 (52.0%)	149 (50.9%)
Sex	N (%)		
	Male	141 (50.2%)	142 (48.5%)
	Female	140 (49.8%)	151 (51.5%)
HIV status as reported at baseline	N (%)		
	True positive	2 (0.7%)	3 (1.0%)
	False positive	7 (2.5%)	1 (0.3%)
	Unconfirmed positive	3 (1.1%)	2 (0.7%)
	True negative	155 (55.2%)	184 (62.8%)
	False negative	6 (2.1%)	2 (0.7%)
	Unconfirmed negative	11 (3.9%)	31 (10.6%)
	Prefers not to say	2 (0.7%)	0 (0%)
	Unknown	95 (33.8%)	70 (23.9%)
HIV status as reported at 12 months	N (%)		
	True positive	5 (1.8%)	4 (1.4%)
	False positive	1 (0.4%)	2 (0.7%)
	True negative	236 (84.0%)	231 (78.8%)
	False negative	5 (1.8%)	2 (0.7%)
	Unconfirmed negative	1 (0.4%)	2 (0.7%)
	Prefers not to say	1 (0.4%)	2 (0.7%)
	Unknown (negative)	9 (3.2%)	7 (2.4%)
	Lost to follow-up	23 (8.2%)	43 (14.7%)
HIV status as known at 12 months	N (%)		
	Infected	10 (3.6%)	6 (2.0%)

	Measure and Level	Intervention arm	Standard of care arm
	Exposed uninfected	247 (87.9%)	242 (82.6%)
	Unknown	1 (0.4%)	2 (0.7%)
	Lost to follow-up	23 (8.2%)	43 (14.7%)
Birth weight (kg)	Mean (95% CI)	2.99 (2.90, 3.08) n=272	2.93 (2.86, 3.00) n=283
Weight-for-age z-score	Mean (95% CI)	-0.86 (-1.15, -0.57)	-0.86 (-0.99, -0.72)
Underweight (z-score <-2)	Yes	44 (15.7%)	43 (14.7%)
	No	237 (84.3%)	250 (85.3%)
Length-for-age z-score	Mean (95% CI)	-1.56 (-1.87, -1.25)	-1.46 (-1.71, -1.21)
Stunted (z-score<-2)	Yes	107 (38.4%)	100 (34.3%)
	No	172 (61.7%)	192 (65.8%)
Body mass index (BMI) z-score			
Low BMI z-score	Yes	15 (5.4%)	17 (5.8%)
	No	264 (94.6%)	275 (94.2%)
Mid-upper arm circumference z-score			
Low MUAC z-score <-2	Yes	14 (6.0%)	15 (5.8%)
	No	218 (94.0%)	246 (94.3%)
Mullen scales (T-scores)	Mean (95% CI)		
	Expressive language	52.4 (49.7, 55.1)	53.1 (51.3, 55.0)
	Fine Motor	51.1 (47.9, 54.4)	50.2 (47.4, 53.0)
	Gross Motor	50.1 (47.7, 52.6)	50.8 (49.2, 52.4)
	Receptive language	47.6 (44.5, 50.8)	47.6 (44.8, 50.4)
	Visual reception	53.5 (49.3, 57.8)	52.6 (50.2, 55.1)
	Early learning composite score	102.6 (96.5, 108.7)	102.0 (97.8, 106.3)
Caregiver's Characteristic			
Caregiver type	N (%)		
	Mother	272 (96.8%)	290 (99.0%)
	Other	9 (3.2%)	3 (1.0%)
Age (years)	Median (IQR)	32 (27, 36)	32 (27, 36)
Marital status	N (%)		
	Married	227 (81.1%)	228 (77.8%)
	Divorced/separated	32 (11.4%)	42 (14.3%)
	Widowed	16 (5.7%)	15 (5.1%)
	Never married	5 (1.8%)	8 (2.7%)
Education	N (%)		
	Secondary or above	152 (54.1%)	152 (51.9%)
Employment	N (%)		
	Employed	90 (32.0%)	120 (41.0%)
SES	N (%)		
	Lowest	104 (37.0%)	88 (30.0%)
	Middle	100 (35.6%)	91 (31.1%)
	Highest	77 (27.4%)	114 (38.9%)

	Measure and Level	Intervention arm	Standard of care arm
Parental stress score (PSI-SF)	N (%)		
Parental distress subscale n=565	Not stressed (<90th percentile)	188 (68.4%)	192 (66.2%)
	Stressed (>=90th percentile)	87 (31.6%)	98 (33.8%)
Parental child interaction dysfunction subscale n=565	Not stressed (<90th percentile)	169 (61.2%)	182 (63.0%)
	Stressed (>=90th percentile)	107 (38.8%)	107 (37.0%)
Difficult child subscale n=563	Not stressed (<90th percentile)	241 (87.3%)	240 (83.6%)
	Stressed (>=90th percentile)	35 (12.7%)	47 (16.4%)
PSI-SF total score n=564	Not stressed (<90th percentile)	180 (65.7%)	185 (63.8%)
	Stressed (>=90th percentile)	94 (34.3%)	105 (36.2%)
Mother's viral load copies/ml* N=485	Geometric mean (SD)	126.2	108.0
	N (%) Failure (>=1000 copies/ml)	33/246 (13.4%)	25/239 (10.5%)
Maternal mental health(EPDS)* n=562	N (%)		
	Not depressed (score 0-11)	132 (48.5%)	146 (50.3%)
	Depressed (score>=12)	140 (51.4%)	144 (50.0%)
Common mental disorders (SSQ-8) n=573	N (%)		
	No CMD (score 0-5)	168 (60.0%)	175 (60.0%)
	CMD (score 6-8)	112 (40.0%)	118 (40.0%)
Household food security (HFIAS)	N (%)		
	Little to no hunger	116 (41.3%)	126 (43.0%)
	Moderate to severe hunger	165 (58.7%)	167 (57.0%)
Medical adherence rating scale n=560	Not adherent	8 (3.0%)	5 (1.7%)
	Adherent	263 (97.1%)	284 (98.3%)

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Table 4: Primary outcomes

Outcome	Intervention arm	Standard of care arm	Adjusted mean difference* (95% CI)	Measure of effect (95% CI)	K
Mullen scales (T-scores), mean (95% CI), adjusted mean difference	N=257	N=249			
Early learning composite score	88.1 (84.0, 92.2)	87.6 (83.1, 92.1)	0.06 (-2.68, 2.80) p = 0.97	-	0.09
Expressive language Mullen scale	44.9 (43.1, 46.7)	45.3 (43.3, 47.3)	-0.44 (-2.03, 1.14) P = 0.58	-0.44 (-2.03, 1.14) P = 0.58	
Receptive language Mullen scale	45.3 (43.1, 47.5)	45.8 (43.1, 48.4)	-0.11 (-1.82, 1.60) P = 0.90	-0.11 (-1.82, 1.60) P = 0.90	
Fine Motor Mullen scale	41.7 (39.3, 44.2)	41.0 (38.5, 43.6)	-0.23 (-2.38, 1.92) P = 0.83	-0.23 (-2.38, 1.92) P = 0.83	
Gross Motor Mullen scale	50.2 (47.7, 52.6) N=196	48.2 (45.4, 51.0) N=201	1.99 (-0.54, 4.51) P=0.12	1.99 (-0.54, 4.51) P=0.12	
Visual reception Mullen scale	42.8 (40.1, 45.5)	41.5 (38.6, 44.4)	0.84 (-1.44, 3.12) P = 0.47	0.84 (-1.44, 3.12) P = 0.47	
Child retention in HIV care	201/257 (78.2%)	207/249 (83.1%)	-	OR = 0.73 (0.47, 1.14, p=0.16	
Virological failure children as proportion of those HIV positive	4/8 (50%)	4/6 (67%)	-	-	
Virological failure mothers	33/246 (13.4%)	25/239 (10.5%)	-	OR = 1.33 (0.72, 2.46), p=0.36	

* Positive mean difference indicates that those in the intervention arm have higher Mullen scores

Table 5: Effect modification of the intervention effect by baseline characteristics

		Mean Mullen ELC after programme implementation		
Covariate	**Level**	**Intervention arm**	**Standard of care arm**	**p-value for effect modification**
Baseline ELC score	Below average (Mullen ELC <85)	78.5	79.2	
	Average + (Mullen ELC>=85)	90.1	89.1	0.91

Baseline EPDS	Not showing signs of depression (EPDS score <12)	89.7	88.5	
	Showing signs of depression (EPDS score >=12)	86.5	86.5	0.78
Baseline SSQ-8	No CMD (SSQ-8<6)	89.7	88.6	
	CMD (SSQ-8>=6)	85.7	86.1	0.51
Baseline PSI Parental Distress Sub-scale	Not showing signs of distress (PSI-PD<90th percentile)	87.7	88.3	
	Showing signs of distress (PSI-PD>=90th percentile)	89.2	85.9	0.54
Baseline infant's age	0-<6m	88.5	89.1	
	6m-<12m	89.6	86.7	
	12m-24m	87.3	87.8	0.70

662 *Table 6: Secondary outcomes*

Outcome	**Intervention arm n=257**	**Standard of care arm n=249**	**Measure of effect (95% CI)**
Weight-for-age z-score, mean (95% CI), adjusted mean difference	-0.96 (-1.09, -0.84)	-0.85 (-0.97, -0.72)	-0.13 (-0.28, 0.03) P=0.10
Underweight, n (%), adjusted odds ratio			
No	224 (86.8%)	222 (88.8%)	1
Yes	34 (13.2%)	28 (11.2%)	1.24 (0.62, 2.47) P=0.54
Height-for-age z-score, mean (95% CI), adjusted mean difference	-1.36 (-1.61, -1.12)	-1.34 (-1.49, -1.20)	-0.06 (-0.24, 0.11) P=0.49
Stunted, n (%), adjusted odds ratio			
No	184 (71.3%)	189 (75.6%)	1
Yes	74 (28.7%)	61 (24.4%)	1.23 (0.79, 1.93) P=0.36
BMI-for-age z-score, mean (95% CI), adjusted mean difference	-0.16 (-0.48, 0.15)	-0.01 (-0.20, 0.18)	-0.14 (-0.39, 0.10) P=0.26
Low BMI-for-age z-score, n (%), adjusted odds ratio			
No	239 (92.6%)	237 (94.8%)	1
Yes	19 (7.4%)	13 (5.2%)	1.45 (0.68, 3.05) P=0.34
MUAC-for-age z-score, mean (95% CI), adjusted mean difference	-0.60 (-0.75, -0.45)	-0.49 (-0.61, -0.38)	-0.20 (-0.35, -0.06) P=0.006
Low MUAC-for-age z-score, n (%), adjusted odds ratio			
No	245 (95.0%)	244 (97.6%)	1
Yes	13 (5.0%)	6 (2.4%)	1.63 (0.53, 496) P=0.39
PSI-SF percentile>=90%, n (%), adjusted odds ratio			

Outcome	Intervention arm n=257	Standard of care arm n=249	Measure of effect (95% CI)
No	185 (71.7%)	161 (63.6%)	OR= 1
Yes	73 (28.3%)	92 (36.4%)	OR = 0.69 (0.45, 1.05) P =0.08
PSI-SF percentile, mean (95% CI), adjusted mean difference	76.8 (73.0, 80.4)	76.2 (70.5, 81.9)	0.44 (-5.18, 6.05) P=0.88
Parental Distress sub-scale percentile>90%, n (%), adjusted odds ratio			
No	213 (82.6%)	178 (70.9%)	OR= 1
Yes	45 (17.4%)	73 (29.1%)	OR = 0.56 (0.35, 0.89) P=0.01
Parental Distress sub-scale, mean (95% CI), adjusted mean difference	65.0 (60.1. 70.0)	66.6 (60.2, 72.9)	-0.15 (-7.16, 6.86) P=0.97
Parent-Child Dysfunctional Interaction sub-scale percentile>=90%, n (%), adjusted odds ratio			
No	157 (60.6%)	152 (60.1%)	OR = 1
Yes	102 (39.3%)	101 (39.9%)	OR = 1.00 (0.63, 1.59)
Parent-Child Dysfunctional Interaction sub-scale, mean (95% CI), adjusted mean difference	74.0 (68.3, 79.7)	72.7 (65.8, 79.6)	-0.02 (-6.16, 6.12) p= 0.99
Difficult Child sub-scale percentile>=90%, n (%), adjusted odds ratio			
No	203 (78.3%)	186 (73.5%)	OR = 1
Yes	56 (21.6%)	67 (26.5%)	OR = 0.79 (0.46, 1.38) P= 0.41
Difficult Child sub-scale, mean (95% CI), adjusted mean difference	70.0 (65.5, 74.5)	70.0 (66.0, 73.2)	0.73 (-4.34, 5.79) P= 0.78
High EPDS, n (%), adjusted odds ratio			
No	148 (60.2%)	134 (56.1%)	1
Yes	98 (39.8%)	105 (43.9%)	0.79 (0.50, 1.25) P=0.32
High SSQ-8, n (%), adjusted odds ratio			
No	144 (55.2%)	138 (54.6%)	1
Yes	117 (44.8%)	115 (45.5%)	0.90 (0.62, 1.32) P=0.59
Household food security HFIAS, n (%), adjusted odds ratio			
Little to no hunger	196 (75.1%)	198 (78.3%)	1
Moderate to severe hunger	65 (24.9%)	55 (21.7%)	1.19 (0.62, 2.26) P=0.52

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APPENDIX 4: CHIDO Trial questionnaire

Captured automatically by ACASI:

- Participant ID
- Date of Interview
- Gender
- Time interview started and ended

SECTION 1: TO BE FILLED BY THE SURVEY ASSISTANT

Q No.	Question			Responses			Instructions	Comments/skip rule
1	Name of child Zita remwana	Age in months and years Zera remwana mumwedzi nemakore	Record gender of child Munhuyi?	Relationship with caregiver Hukama nemuchengeti wemwana Mother/father 1 Sister /brother 2 Aunt/ Uncle 3 Grandmother/ father 4	Mother took PMTCT (ANC, delivery & breastfeeding) Mai vemwana vakapinda here muchirongwa chePMTCT Yes 1 No 2 Don't know 3	HIV status Mamiriro yemwana maererano nehutachiona hweHIV Positive 1 Negative 2 Not yet tested 3 Don't know 4	Please ask for all children below 18 years. In Q1 record the child in the study. *Ndapota nyorai vana vari pasi pemakore gumi nesere. PaQ1 nyora mwana apinda muongororo.*	Data Officer: Please link with c1.

Q No.	Question	Responses	Instructions	Comments/skip rule
	1 M / Y B/G 2 B/G 3 B/G 4 B/G 5 B/G 6 B/G 7 B/G 8 B/G 9 B/G 10 B/G			
2	Do you have the maternity record of your baby's biological mother (from the hospital)? Mune kadhi rekusikero raamai here?	Yes seen Yes not seen No Skip to 9	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	For not seen and No Skip to Q7
3	May I see this maternity record? Ndingarionewo here card rekusikero iri?	Yes (1) (Hongu) No (0) (Kwete) I cannot find the booklet at the moment (Ndashaya bhuku)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

Q No.	Question	Responses	Instructions	Comments/skip rule
4	Did the baby's biological mother seek antenatal care during this pregnancy Mai vemwana vakaenda kusikero here vaine pamuviri?	Yes/ Hongu No/ Kwete **Don't know/ handizive**	***To the surveyors:*** **Fill in information from this section from booklet and where it is not there ask the respondent.** *Kumushandi weongororo: Pindurai mibvunzo muchishandisa zvakanyorwa mubhuku. Kana risipo ita zvekubvunza wachapinda mutsvakurudzo iyi.*	
5	The baby's biological mother received antenatal care in a health care facility? Amai vemwana vakaenda kusikero kuchipatara here kana kuclinic?	Yes Hongu No skip to 12 Kwete Nothing written on card Hapana chakanyorwa pakadhi **Don't know/** Handizive		Skip to Q7
6	Number of antenatal visits the biological mother attended during the pregnancy. Vakaenda kusikero kangani vane pamuviri.	Record antenatal visits Nyora kuti akaenda kusikero kangani. Don't know/ handizive		

Q No.	Question	Responses	Instructions	Comments/skip rule
7	When were you (biological mother) last tested for HIV? Makagumisira kuongororwa hutachiona rinhi?	Before pregnancy (last pregnancy) Ndisati ndane nhumbu. **During pregnancy** Pandaive nepamuviri/nhumbu **Following pregnancy** Mushure mekusununguka **Don't know/** handizive	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
8	What was your (biological mothers) HIV test result? Chii chakabuda muongororo yenyu (yemai vemwana uyu) yehutachiona hwe HIV?	HIV negative HIV positive Prefers not to say (Handina kusununguka kutaura) Did not collect result (Handina kutora maresults) **Don't know** (Handizive)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
9	Do you have your baby's health card? Mune kadhi remwana rekusikero here?	Yes Hongu No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	If response is No Skip to Section 2A

Q No.	Question	Responses	Instructions	Comments/skip rule
10	May I see the baby's health card? Ndingaonewo here kadhi rake?	Yes seen Yes not seen I cannot find the card at the moment	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	If response is: Yes not seen or I cannot find card then Skip to Section 2 A
11	The baby's weight at birth (in kilograms) and the apgar score Uremu hwemwana paakazvarwa (mumakg) ne apgar score (inorakidza kuti mwana akagwinya zvakadii achangobva mukusunungukwa)	Record kilograms		
12	The baby received any of these forms of treatment Mwana akapihwa here umwe wemishonga inotevera	Yes-AZT Yes-NVP syrup single dose Yes-NVP multiple doses Yes-don't know type ART (i.e. continuous) Nothing written on the card (Hapana chakanyorwa pakhadhi)	Please press ALL statements that apply to you *Dzvanya pane mitsara yose inoenderana nemi chete*	

Q No.	Question	Responses	Instructions	Comments/skip rule
13	The baby was given Cotrimoxazole. Mwana akapihwa Cotrimoxazole?	Yes (Hongu) No (Kwete) Nothing written on card (9) (Hapana chakanyorwa pakhadhi)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
14	Has the child attended growth monitoring in the last 6 months? Mwana wenyu akaenda here kusikero mumwedzi mitanhatu yakapfuura?	Yes (Hongu) No (Kwete)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to Section 2 A:

Q No.	Question	Responses	Instructions	Comments/skip rule
15	***To the surveyors:*** record vaccination date for each vaccination from the child health card Kumushandi wetsvakurudzo: Nyora zuva rekubaiwa majekiseni ese emwana ari pakadhi rekusikero.	1 BCG 2 OPV 1 3 OPV 2 4 OPV3 5 OPV4 6 Pentavalent 1 7 Pentavalent 2 8 Pentavalent 3 9 Pneumococcal 1 10 Pneumococcal 2 11 Pneumococcal 3 12 Rotavirus 1 13 Rotavirus 2 14 Measles 15 DPT **16 DT**	**Please us the number pad to tell us month and year you were born** *Ndapota shandisai gwaro remanhamba kutiudza kuti mwana akabaiwa musi upi*	
16	Does the weight line on the baby health card show good, dangerous and very dangerous growth rate Mutsara unoratidza huremu hwemwana pakadhi rekusikero uri kuratidza kuti mwana ari kukura zvakanaka here, zvinotyisa, kana kuti zvinonyanyisa kutyisa	Normal (Ari pakati nepakati) Moderate underweight (Akaderera) Severely Underweight (Akaderera zvakanyanya)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

SECTION 2:
A. SOCIODEMOGRAPHY: Tinoda kutangakubvunza mibvunzo yakananganana nehupenyu hwenyu (T205)

Q No.	Question	Responses	Instructions	Comments
A1	In what month and year were you born Makazvarwa mwedzi uye gore ripi (T1)		**Please us the number to tell us month and year you were born** *Ndapota shandisai gwaro remanhamba kutiudza kuti makazvarwa mwedzi negore ripi (T2)*	
A2	How old were you on your last birthday? *Mange mune makore mangani pabhavhadheyi renyu rekupedzisira?* *(T3)*	Number pad	Please use the number pad to tell us how old you are. If you are uncertain, enter your best guess. *Ndapota shandisa gwaro remanhamba pakutiudza kuti une makore mangani. Kana usina chokwadi, tiudze aunofungidzira (T4)*	
A3	What tribe/ethnic group do you belong to *Rudzi rwako nderwupi?* *(T5)*	• *Shona (0)* • *Ndebele (1)* • *Kalanga (2)* • Other (4) *Rumwewo*	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete (T6)*	

Q No.	Question	Responses	Instructions	Comments
	What is your religion? *Chitendero chenyu ndechipi?* *(T7)*	Roman Catholic Methodist Anglican Lutheran Presbyterian Pentecostal Apostolic Baptist Moslem African Traditional Religion Other specify (Chimwewo) • No religion (Handina chitendero)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

Q No.	Question	Responses	Instructions	Comments
		What is the highest level of education that you have completed? Chikoro makagumira pachinhanho chipi? • (T8)	None (Handina kuenda kuchikoro) Primary school (Ndakagumira kuprimary) Secondary School (Ndakagumira Secondary School Form 4) Secondary School Forms 5 to 6 (Ndakagumira Secondary Form 5 to 6) Certificate/Diploma/Degree (Ndakagumira paCertificate/ Diploma/Degree)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*
	A4	How many people were living in your house for at least 3 days in the last week? (Include yourself, all adults and all children) (T9) Mumba menyu munowanzo kugara vanhu vangani? (Zviverengeri, vanhu vakuru vese uye nevana vese).	Number pad	Please write the number *Ndapota nyora nhamba* *(T10)*
	A5	Think about the building in your home that is the most appealing. What material is it built of? Fungai pamusoro pemba yakanaka kupfura dzimwe dzese mumusha wenyu, yakawakwa nechii? (T11)	Pole and Dagga (Mapango nemadhaka) Wood (Mapuranga) Mud bricks (Mudhindirwa) Cement blocks (Yezvidhinha zvesamende) Stones (Nematombo) Other ---Specify (Zvimwewo)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*

Q No.	Question	Responses	Instructions	Comments
A6	What type of sewage disposal system do you use? Munoshandisa chimbuzi chemhando ipi? *(T13)*	Flush Bowl System (Yekugweja) Our own Blair toilet (Bhureira yepamba) Neighbor's Blair toilet (Bhureira yemuvakidzani) Bush (Musango) Pit (Yegomba) • Other (Imwewo)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
A9	Did your village ever hold HIV testing days in the past year? Mubhuku muno makamboitwa mazuva ayiitwa ongororo dzeHIV mugore rakapfuura here? (T17)	•Yes/ Hongu • No/ Kwete Don't know / Handizive	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
A10				
A11				

B.Household Details: Income and food security/Iyezvino ndinoda kukubvunzai mibvunzo pamusoro pemawaniro emhuri yenyu mari nezvekudya(T206)

Q No.	Question	Responses	Instructions	Comments
B1	Are you employed at the moment? Pari zvino muri kushanda here? (T18)	• Yes full time Hongu nguva dzose • Yes part time Hongu dzimwe nguva • Yes informally Hongu zvekuzviitira • No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to B4
B2	What type of work do you do? Munoita basa rei? (T19)	• Professional/ managerial Repamusoro /Humaneja • Self employed Rekuzviitira • Skilled labor Randakadzidzira • Manual or unskilled Remaoko/ risina kudzidzirwa	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
B3	Approximately how much money do you earn/source each month in US dollars? Munotambira marii pamwedzi mumaUS dhora? (T20)	• $ 0 • $ 01-100 • $ 101-200 • $ 201- 300 • $301 and above /kana kupfuura	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
B4	What is your marital status? Makaroorwa/kana kuroora here? (T21)	• Married Ndakaroorwa/ ndakaroora • Divorced/Separated Takarambana • Widowed Ndiri shirikadzi/tsvimborume • Never been married handina kubvira ndamboroorwa/kuroora	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to B7 unless married
B5	Is your husband employed? Murume wenyu anoshanda here? (T22)	• Yes full time Hongu nguva dzose • Yes part time Hongu dzimwe nguva • Yes informally Hongu zvekuzviitira • No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

Q No.	Question	Responses	Instructions	Comments
B6	Approximately how much money does your partner earn/source each month in US dollars? Murume wenyu anotambira marii pamwedzi mumaUS dhora? (T23)	• $ 0 • $ 01-100 • $ 101-200 • $ 201- 300 • $301 and above/ kana kupfura	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
B7	Are you financially dependent on anyone? Munoriritirwa nemumwe munhu here? (T24)	• Yes Hongu • No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to B9 if no
B8	Who are you financially dependent on? Ndiani anokuriritirai? (T25)	• Husband/ partner Murume/mukadzi wako/shamwari yebabonde • Parents Vabereki • Mother/father in law Vamwene/tezvara • Brother/ Sister Hanzvadzi • Brother/ Sister in law Tsano/Muramu • Other relative Imwe hama • Other non-relative Mumwewo asiri wehukama	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

Q No.	Question	Responses	Instructions	Comments
B9	In the past four weeks, was there ever no food to eat of any kind in your house because of lack of resources to get food? Mumasvondo mana apfura, pane here pamakashaya chikafu chekudya mumba menyu nokuda kwekushaya? (T26)	• Yes Hongu • No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to B11 if no.
B10	How often did this happen? Zvakaitika kangani? (T27)	• Rarely (1-2 times) Kashoma kasingapfure kaviri • Sometimes (3-10 times) Dzimwe nguva dzisingapfure gumi • Often (more than 10 times) Kakawanda, kanopfura gumi	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
B11	In the past four weeks, did you or any household member go to sleep at night hungry because there was not enough food? Mumasvondo mana apfura, pane here imi kana mumwe munhu wemumba menyu pamakarara mune nzara nokuti panga pasina chikafu chakakwana? (T28)	• Yes Hongu • No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to B13 if no
B12	How often did this happen? Zvakaitika kangani? (T27)	• Rarely (1-2 times) Kashoma kasingapfure kaviri • Sometimes (3-10 times) Dzimwe nguva dzisingapfure gumi • Often (more than 10 times) Kakawanda, kanopfura gumi	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

Q No.	Question	Responses	Instructions	Comments
B13	In the past four weeks, have you had to go an entire day without eating because there was no food in your household? Mumasvondo mana apfura, pane pamakamboita zuva rese musina kumbodya nokuti panga pasina chikafu chokudya mumba menyu here? (T29)	• Yes Hongu • No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to B15 if no
B14	How often did this happen? Zvakaitika kangani?	• Rarely (1-2 times) Kashoma kasingapfure kaviri • Sometimes (3-10 times) Dzimwe nguva dzisingapfure gumi • Often (more than 10 times) Kakawanda, kanopfura gumi	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
B15a	Which grants does your household receive to support your household expenditure? Mhuri yenyu inombowana here rubatsiro rwemari kubva kuhurumende kana kumwewo here? (T30)	• Social welfare grants (Mari yekuhurufeya) • Cash transfers • BEAM • Old age pension (Yemachembere) • Other (Dzimwewo) • No (Kwete)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to B16 if no
B15b	Specify amount. Tiudzei kuti imarii. (T31)	Record amount.	Please use the number pad to tell us how much it is. Ndapota shandisai gwaro remanhamba kutiudza kuti munovana marii (T32)	

Q No.	Question	Responses	Instructions	Comments
B16	Did your household receive any other assistance in the past year? Mhuri yenyu yakambowana rumwe rubatsiro here mugore rapfuura? (T33)	• No (Hatina) • Food handouts (Takapihwa chikafu) • Inputs for nutrition gardens (Takapihwa zvekushandisa mugadeni) • Agricultual inputs (takapihwa mbeu nefeteraiza) • Clothes or blankets (takapihwa mbatya nemagumbeze) • Disability benefits (including crutches/wheelchairs etc) (Takapihwa rubatsiro nekuda kwehurema kusanganisira mawhiri cheya nemadondoro) • Other (Zvimwewo)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
B17	Is anyone in your household participating in a savings scheme for the past six months? Pane here umwe wemumhuri menyu ari mumukando kubva mumwedzi mitanhatu yadarika (T34)	• Yes Hongu • No • Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
B18	Did your household receive visits from any community workers in the last month? Mhuri yenyu yakamboshanyirwa here nevashandi vehurumende vane chekuita nezvehutano vanoshandira munharaunda menyu mumwedzi wapfura (T35)	• No (kwete) • Village Health worker (vana mbuya utano) • Case care worker • Home based care (vehome based keya) • Behaviour change facilitator	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

C. ANTENATAL CARE, DELIVERY AND POSTNATAL CARE/ Iyezvino ndinoda kukubvunzai mibvunzo pamusoro pekuvhenekwa panguva yekuzvitakura kusununguka uye mushure mekusununguka (T207)

Q No	Question	Responses	Instructions	Skip / Comments
C1	Record baby's age Nyora mwedzi yemwana yekuzvarwa.	Record of month	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Insert child age selected from for the study in Section Q1 line 1
C2	Record baby's sex. Nyora kuti mwanai? (T36)	Boy (Mukomana) Girl (Musikana)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
C3	Is the respondent the selected infant's biological mother? Apinda muchirongwa ndiye mai vemwana here? (T37)	Yes Hongu No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to C5 if yes Link with section E
C4	What relationship is the respondent to the infant? Mune hukama hwakadini nemwana wamuri kuchengeta (T38)	Father/stepmother Baba/mainini 1 Sister/ brother Mukoma/hanzvadzi 2 Aunt Tete/Maiguru/mainini 3 Uncle Sekuru/babamukuru 4 Grandmother Mbuya 5 Other specify Vamwewo 6	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

C5	Does the child have biological siblings? Mwana ane hanzvadzi, vakoma kana vanin'ina vemudumbu rimwe naye here? (T39)	Yes Hongu No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to C7 if no
C6	How many siblings does the child have? Ane vakoma, vanin'ina kana hanzvadzi ngani dzemudumbu rimwe naye? (T40)	Record number.	Please use the number pad to tell us how many sibling does the child have *Ndapota shandisa gwaro remanhamba pakutiudza kuti mwana ane vanin'ina kana vakoma kana hanzvadzi ngani (T41)*	
C7	Did you go to a clinic at some point after the birth of your baby so that your baby could receive immunizations? Makaenda here kukiriniki mushure mekunge mazvara mwana wenyu kuti anobaiwa? (T42)	Yes Hongu No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to C9 if yes

C8	Why did you not go to a clinic to have your baby immunized? Nemhaka yei musina kuenda kukiriniki kunoti mwana abaiwe? (T43)	I forgot Ndakakanganwa Drug Stock outs Kwange kusina mishonga Husband refused Murume wangu akaramba Religious reasons Nekuda kwechitendero Other (specify) Chimwewo chikonzero (tsanangura)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
C9	Was the baby ever tested for HIV? Mwana akamboongororwa hutachiona hweHIV here? (T44)	Yes Hongu No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to C13 if yes

C10	Why did you not test your baby for HIV? Nemhaka yei mwana wenyu asina kuongororwa hutachiona hweHIV? (T45)	I was not offered to have my baby tested for HIV Handina kumbopihwa mukana wekuti aongororwe. I was scared to find out the result Ndaitya kuziwa maresults acho. My husband would not let me Murume wangu aisandibvumidza. The test was too expensive Ongororo yacho yaidhura. I did not go back to a clinic after the baby was born Handina kudzokera kukiriniki ndaongororwa. The clinic was too far away Kiriniki yanga iri kure. Did not feel comfortable around the clinic staff Handina kusununguka nevashandi vehutano. I could not take time away from home/work to go to the clinic Ndakashaya nguva yekubva pamba/kusiya basa kuti ndiende kukiriniki. I knew I was HIV negative Ndanga ndichiziva kuti handina hutachiona. My church does not allow me to Chechi yangu hainditendere kudaro. It never occurred to me/ never thought about it Hazvina kumbopinda mupfungwa. Other Chimwewo chikonzero	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
C11	Do you plan to test your baby for HIV? Mune hurongwa here hwekundo ongororesa mwana uyu HIV (T46)	Yes Hongu No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to C13 if no

C12	When do you plan to test your baby for HIV? Muri kuronga kuenda zvarini (T47)	Record time	Please use the number pad to record months and year. *Ndapota shandisa gwaro remanhamba pakutiudza gore nemwedzi wamunoda kunomuongororesa (T48)*	
C13a	Was the baby ever tested for HIV? Mwana akamboongororwa hutachiona hweHIV here? (T44)	Yes Hongu No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to C28 if no
C13b	In what month and year was the baby **last** tested for HIV? (MM/YYYY) Mwana akagumisira kuongororwa hutachiona hweHIV mumwedzi upi uye gore ripi? (T49)	Record months and year	Please use the number pad to record months and year. *Ndapota shandisa gwaro remanhamba pakutiudza gore nemwedzi waakaoongororwa (T50)*	
C14	How old was the baby when **last** tested for HIV? (in months) Mwana paakagumisira kuongororwa hutachiona hweHIV anga ave nemwedzi mingani yekuzvarwa? (T51)	Record weeks/months	Please use the number pad to record weeks or months. *Ndapota shandisa gwaro remanhamba pakutiudza masvondo kana mwedzi paakagumisira kuongororwa hutachiwana hweHIV (T52)*	

C15	Did you receive the results of your baby's HIV test? Makapihwa here zvakabuda muongororo yemwana yehutachiwana hweHIV? (T53)	Yes Hongu No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
C16	What was the result of your baby's HIV test? Zvii zvakabuda muongororo yemwana yeHIV? *(T54)*	HIV negative Akaonekwa asina hutaciwana hweHIV HIV positive Akaonekwa ane hutachiwana hweHIV Prefers not to say Ndosarudza kusazvitaura Don't know (3) Handizive	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to C28 if HIV negative or don't know
C17	Was a viral load test ever done on your child? Mwana wenyu akambotorwa viral load here? Viral load iongororo yekuona uwandu hweutachiwana muropa? (T55)	Yes, and I know the results. Hongu uye ndinoziva dudziro dzacho Yes. My child has had a viral load test but I don't know the result. Hongu, mwana wangu akaitwa ongororo yeviral load asi handizivi dudziro dzacho. No My child has never had a viral load test. Kwete, mwana wangu haana kuitwa ongororo yeviral load. .	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to c19 if Yes do not know the result & No, my child has bever had a viral load test.
C18	What is your child's latest viral load result? Ndiudzeiwo dudziro yeviral load yemwana wenyu yekupedzisira?	***Record what is on the card*** *Nyorai sezviri pacard* copies/ml	Please use the number pad to record viral load result *Ndapota shandisa gwaro remanhamba pakutiudza uwandu hweutachiona huri muropa remwana (nyorai sezviri pacard)*	

C19	Did health staff recommend that your baby is put on treatment for HIV infection, specifically on ART drugs? Vashandi vehutano vakambokukurudzirai kuti muise mwana pachirongwa chemishonga yeHIV, zvikurukuru mishonga yeART here? (T58)	Yes Hongu No Kwete Don't know Handizivi	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
C20	How old was the baby when baby was put on treatment for HIV infection specifically on ART drugs? (MM) Mwana ange ane mwedzi mingani paakaiswa pamushonga weHIV tichinyanyotarisa weART? (T59)	Record months Nyora mumwedzi Not yet initiated Haasati aiswa pamushonga	Please use the number pad to record how old baby was *Ndapota shandisa gwaro remanhamba pakutiudza kuti mwana ange ane mwedzi mingani (T60)*	Skip to C28 if not yet initiated
C21	What are the names of ART drugs your child was prescribed? Ndiudzeiwo mazita emishonga YE HIV yakapihwa mwana wenyu (T61)	Neverapine 1 Combivar 2 Zidovudine/ Lamuvidine 3 Abacavar 4 Efaverinz 5 Lopinavir/ritonavir (Aluvia) 6 Other Mimwewo 7	Please tick all that apply to you Ndapota sarudzai mishonga yose yaari kunwa (T62)	

C22	Was your baby given the treatment as directed by the health facility, in terms of the number of days and dosage? Makapa mwana wenyu mushonga sezvamakanzi muite kuchipatara, tichitarisa mazuva neuhwandu hwemishonga yacho? (T63)	Yes Hongu No Kwete Don't know Handizivi	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
C23	Who administers the ART drugs your child was prescribed? Ndiyani anonyanya kupa mwana wenyu mushonga yakanzi anwe T64	Primary caregiver Muchengeti wake wemazuva ose Siblings vana vemudumbu rimwe chete naye Father/stepmother Baba/mainini Sister/ brother Mukoma/hanzvadzi Aunt Tete/Maiguru/mainini Uncle Sekuru/babamukuru Grandmother Ambuya Other Vamwewo	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
C24	Are you still giving your baby ART treatment as directed by the health facility Muchiri kupa mwana wenyu here mishonga yema ARVs sezvamakataurirwa kukiriniki (T65	Yes Hongu No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
C25	Did the baby ever stop or miss taking the treatment you were given? Mwana akamborega here kana kudarikira kunwa mishonga yaamainge mapihwa? (T66	Yes for one day Hongu kwezuva rimwe Yes for a week Hongu kwesvondo Yes for a month Hongu kwemwedzi No Kwete	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to C28 if no

C26	What were the main reasons for missing treatment? Zvikonzero zvipi zvakaita kuti mwana adarikire kana kuti asanwe mishonga yake (T67)	Forgot to give medication Ndakakanganwa kumupa mishonga. Didn't want my child to take the medication Ndanga ndisingade kuti mwana wangu atore mishonga. Didn't trust the medication Handivimbi nemishonga yacho Had visited and forgot the medication Ndakashanya ndikakanganwa mishonga yacho. Didn't want people to see me giving the medication Ndakanga ndisingade kuti vanhu vandione ndichimupa mishonga Child not sick Mwana anga asingarware Other specify Chimwewo chikonzero	Please tick all that apply to you You are allowed to tick more than one response Ndapota sarudzai mhinduro dzese dzinoenderana nemi Munotenderwa kutipa mhinduro dzakawanda (T68)	
C27	What was the main reason for stopping treatment altogether? Nemhaka yei akaregedza mishonga yacho? (T69)	Baby would not take it Mwana aisabvuma It made the baby sick Yairwarisa mwana. I forgot Ndakakanganwa A household member told me not to Ndakaudzwa nevandinogara navo kuti ndisamupe I ran out of the medicine too quickly Mishonga yacho yaikakasika kupera The treatment was too expensive Mushonga wacho yaidhura Other Chimwewo chikonzero	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

C28	Has the baby ever spent the night in a clinic or hospital **after** being discharged from birth facility? Mwana akamborara here mukiriniki kana muchipatara mushure mekunge abuda muchipatara achizvarwa? (T70)	Yes (Hongu) No (Kwete) Don't know/remember (Handizivi/handicharangarira)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to D1 if no or don't know
C29	How many times has your baby been hospitalized? Mwana wenyu akapihwa mubhedha kangani? (T71)	1 time Kamwe chete 2 times Kaviri 3 times Katatu 4 times Kana 5 times or more Kashanu kana kupfura Don't know/ remember (Handizivi/Handicharangarira)	Please use the number pad to record how many times baby was hospitalised *Ndapota shandisa gwaro remanhamba pakutiudza kuti mwana wenyu akapihwa mubhedha kangani (T72)*	

D: Infant and child feeding practices Iyezvino ndakudakukubvanzai pamusoro petsika dzokupa vana vacheche chikafu (T208)				
Q No	**Question**	Responses	**Instructions**	**Skip / Comments**
D1	Was this child breastfed? Mwana akayamwiswa here? (T73)	Yes exclusive (Hongu mukaka wemuzamu chete) Yes mixed (Hongu mukaka wemuzamu nekumwe kudya) No (Kwete) Don't know/remember (Handizivi/Handichacharingarira)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	skip to E1 if child not breastfed

D2	Are you still breastfeeding this child? Muchiri kuyamwisa mwana uyu here? (T74)	Yes (Hongu) No (Kwete) Don't know/remember (Handichazivi/Handicharangarira)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	Skip to D4 if Don't know/remember
D3	For how many months was the child breastfed after s/he was born. Mwana uyu akayamwa kwenguva yakareba sei kubva pakuzvarwa (T75)	Record Months Don't know (Handizivi)	Please use the number pad to record how many months child was breastfed *Ndapota shandisa gwaro remanhamba pakutiudza kuti mwana wenyu akayamwiswa mwedzi mingani (T76)*	
D4	Did you ever exclusively breastfeed your baby? (did you feed the baby only breast milk and nothing else for any period of time) Pane here nguva yamakayamwisa mwana chete musingamupe kumwe kudya? (T77)	Yes (Hongu) No (Kwete)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

D5	For how many months was the child breastfed exclusively? (milk only) Mwedzi mingani yamakayamwisa mwana chete musingamupe kumwe kudya? (T78)	Record Months (Nyora mwedzi) Don't know (Handizivi)	Please use the number pad to record how many months child was exclusively breastfed *Ndapota shandisai gwaro remanhamba pakutiudza kuti mwana wenyu akapihwa mukaka wemuzamu chete pasina kumwe kudya kwemwedzi mingani (T79)*	
D6	Did anyone at the health facility instruct you on how to feed your baby? Pane akambokudzidzisai here kuchipatara kuti mwana anofidwa sei? (T80)	Yes (Hongu) No, no one instructed me (Hapana akandidzidzisa)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

E: Biological mothers (skip to F if C3 is no)				
Maternal Mental Health Iyezvino ndakudakukubvanzai mibvunzo yakanangana nezvamainzwa mushure mekunge masununguka (T209)				
QNo	**Question**	Responses	**Instruction**	**Skip/comment**
E1 (T81)	For some women being a mother can be wonderful and rewarding but some women find it difficult to cope with the demands of a new baby. How did you feel during the first two weeks after birth? Kune vamwe vakadzi kuve amai chinhu chakanaka asi kune vamwe vakadzi vanoona iri nguva yakavaomera nekuda kwezvinounzwa nemwana mucheche. Imi makanzwa sei muvhiki mbiri dzekutanga muchangobva kusununguka?	Easy to cope (Zvirinyore) Fairly difficult to cope (Zvakaoma zvirinani) Very difficult to cope (Zvakaoma zvachose)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

E2 (T82)	After giving birth did you feel that you had advice and support from family or close friends? Mushure mekusununguka makanzwa here sekunge maiwana mazano uye rutsigiro kubva kuhama ne shamwari?	Yes full support (Hongu ndakabatsirwa mune zvose) Yes partial support (Hongu, dzimwe nguva) No support (Handina kubatsirwa) Don't know (Handizivi)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E3 (T83)	Who are the people who supported you? Ndevapi vanhu vakakutsigira?	Husband /partner (murume/shamwari yepabonde Mother/ Father (mai/baba vekubereka) Mother /father in law (vamwene/tezvara) Brother/ sister (hanzvadzi/mukoma/munin'ina) Brother /sister in law (mukoma/munin'ina/hanzvadzi yemurume/mukadzi) Aunt (tete/mainini/maiguru) Uncle (bamukuru,bamunini, sekuru) Neighbor (Muvakidzani) Other relatives specify (Dzimwe hama) Friend (shamwari)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
Edinburgh Postnatal Depression Scale (EPDS)				
E4 (T84)	I have been able to laugh and see the funny side of things? Ndaikwanisa kuseka nekuona zvinhu zvinosekesa?	As much as I always could (Kazhinji kacho kandaikwanisa) Not quite so much now (Kashoma pane zvandaimboita) Definitely not (Kana) Not at all (Kana zvachose)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E5 (T85)	I have looked forward with enjoyment to things? Ndavakutarisira ndine mufaro kune zvinhu zvakawanda?	As much as I ever did (Sezvandisati ndamboita) Rather less than I used to (Kashoma pane zvandaita) Definitely less than I used to (Kashoma kupfura zvandaita) Hardly at all (Kure nekure)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

E6 (T86)	I have felt scared or panicky for no good reason. Ndinonzwa kutya kana kuvhunduka pasina chikonzero.	Yes, quite a lot (Hongu, kazhinji kacho) Yes, sometimes (Hongu, dzimwe nguva) No, not much (Aewa, kure nekure) No, not at all (Aewa, kana)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E7 (T87)	Things have been overwhelming me. Zvinhu zvange zvichindikurira.	Yes, most of the time I haven't been able to cope at all Hongu panguva dzakawanda ndanga ndisingakwanise kuzvikunda. Yes, sometimes I haven't been coping as well as usual Hongu, dzimwe nguva ndaisakwanisa kukunda. No, most of the time I have coped quite well Kwete, ndaikwanisa kuzvikunda kakawanda kacho. No, I have been coping as well as ever Kwete, ndiri kukwanisa kukunda kupfura pamwe pese.	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E8 (T88)	I have been so unhappy that I have had difficulty sleeping? Ndange ndisina mufaro zvekuti ndainetseka kuwana hope.	Yes, most of the time (Hongu, kazhinji kacho) Yes, sometimes (Hongu, dzimwe nguva) Not very often (Kwete kazhinji kacho) No, not at all (Kwete, kana)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E9 (T89)	I have blamed myself unnecessarily when things went wrong. Ndaizvipomera mhosva pasina kana zvinhu zvisinga fambi zvakanaka.	Yes, most of the time (Hongu nguva dzakawanda) Yes, quite often (Hongu, dzimwe nguva) Only occasionally (Pano nepano) No, never (Kwete)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

E10 (T91)	I have been anxious or worried for no good reason. Ndainzwa kukarira nekushushikana pasina.	No, not at all (Aiwa, kana) Hardly ever (Zvine mazuva ari kure) Yes, sometimes (Hongu, dzimwe nguva) Yes, very often (Hongu, kazhinji kacho)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E11 (T90)	I have felt sad or miserable. Ndainzwa kusafara nekushushikana.	Yes, most of the time (Hongu nguva dzakawanda) Yes, quite often (Hongu, dzimwe nguva) Only occasionally (Pano nepano) No, never (Kwete)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E12 (T92)	I have been so unhappy that I have been crying. Ndainzwa kushaya mufaro zvekuti ndaimbochema kana kunzwa kuda kuchema.	Yes, most of the time (Hongu nguva dzakawanda) Yes, quite often (Hongu, dzimwe nguva) Only occasionally (Pano nepano) No, never (Kwete)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E13 (T93)	The thought of harming myself has occurred to me. Pfungwa dzekuda kuzvikuvadza dzaimbouya mandiri.	Yes, quite often (Hongu, kakawanda) Sometimes (Dzimwe nguva) Hardly ever (Zvine mazuva ari kure) Never (Kana)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
From the following statement indicate how much the statement applies to you Pamitsara inotevera ndiudzei kuti zvinoenderana nemi zvakadini (T210)				
E14 (T94)	My family is always there for me. Mhuri yangu inomira neni nguva dzose.	Always (Nguva dzose) Most of the time (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana) Not applicable Hazvipindirane neni		

E15 (T95)	I have good friends who support me. Ndine shamwari dzakanaka dzinonditsigira.	Always (Nguva dzose) Most of the time (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana) Not applicable/Hazvipindirane neni	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E16 (T96)	My husband /partner helps me a lot. Murume wangu /shamwari yangu yepabonde inondibatsira kakawanda.	Always (Nguva dzose) Most of the time (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana) Not applicable Hazvipindirane neni		
E17 (T97)	There is a lot of conflict with my husband/ partner. Pane kusawirirana kwakawanda pakati pangu nemurume /shamwari yangu yepabonde.	Always (Nguva dzose) Most of the time (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana) Not applicable Hazvipindirane neni		
E18 (T98)	Even though being a parent can be rewarding I am frustrated now while my child is at his/her present age. Kunyangwe zvazvo kuita mubereki kuchifadza ini ndinonzwa kusvotekana pazera rine mwana wangu.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuzivi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose		

E19 (T99)	I go to bed the same way I wake up in the morning, feeling I have not accomplished a whole lot. Ndinoenda kunorara ndichinzwa zvimwechetezvo zvandinonzwa ndichimuka kunzwa kunge pasina zvikuru zvandaita.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuzivi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E20 (T100)	My mother/father was better prepared to be a good mother/father than I am. Amai vangu kana baba vangu vaive vakagadzirira kuva vabereki vari nani kupfuura ini.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuzivi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose		
E21 (101)	Being a parent is manageable and any problems are easily solved. Kuva mubereki chinhu chinogoneka uye matambudziko anogadziriswa nyore nyore.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuzivi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose		

E22 (102)	I meet my own personal expectations for expertise in caring for my child. Ndinozadzikisa zvandinotarisira pakuchengeta mwana wangu.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuzivi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E23 (T103)	My talents and interests are in other areas, not being a parent. Zvandinoda nezvandinogona zviri kune zvimwewo kwete kuva mubereki	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuzivi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose		
E24 (T104)	I honestly believe I have all the skills necessary to be a good mother. Ndinovimba kuti ndine ruzivo rwese runodikanwa pakuita amai vakanaka.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuzivi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose		

E25 (T105)	Being a parent makes me feel tense and anxious. Kuva mubereki kunoita kuti ndinzwe kusagadzikana nekushushikana.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuzivi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
E26 (T106)	I wish the old days when I had no baby would come back. Ndinoshuvira kuti dai mazuva ekare andange ndisina mwana aidzokerwa.	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		
E27 (107)	Things would be a lot better if my parents were alive to support me. Zvinhu zvingadayi zviri nani dai vabereki vangu vari vapenyu kuti vandibatsire.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi Disagree Handibvumiraninazvo Strongly Disagree Handibvumirani nazvo zvachose Not Applicable Hazvipindirane neni		

E28 (T108)	I feel close to my baby. Ndinonzwa kuva pedyo zvakanyanya nemwana wangu.	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		
E29 (T109)	I regret having this baby. Ndinokungura kuti ndakaitirei mwana uyu.	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		
E30 (T110)	My baby is the most beautiful baby in the world. Mwana wangu ndiye akanakisa pasi rose.	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		

F. Shona Symptom Questionnaire (SSQ8)				
F1 (T111)	There were times in which I was thinking deeply or thinking about many things. Pane pandaimboona ndichinyanya kufungisisa kana kufunga zvakawanda.	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
F2 (T112)	I sometimes failed to sleep or lost sleep. Pane pandaimbotadza kurara kana kushaya hope.	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		

F3 (T113)	There were moments when I felt life was so tough that I cried or wanted to cry. Pane pandaimbonzwa kuomerwa nehupenyu zvekuti ndaimbochema kana kunzwa kuda kuchema.	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		
F4 (T114)	I felt run down (tired). Pane pandaimbonzwa kuneta	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana))	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
F5 (T115)	At times I felt like committing suicide. Pane pandaimboita pfungwa dzekuda kuzviuraya	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		
F6 (T116)	I was generally unhappy with things that I would be doing each day. Ndainzwa kusafara nezvinhu zvandaiita zuva nezuva	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		
F7 (T117)	My work was lagging behind. Basa rangu rainge rava kusarira kumashure	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		

F8 (T118)	I felt I had problems in deciding what to do. Ndainzwa zvichindiomera kuti ndizive kuti ndoita zvipi	Always (Nguva dzose) Very often (Kazhinji kacho) Quite often (Nguva dzakawanda) Sometimes (Dzimwe nguva) Rarely (Pano nepano) Never (Kana)		

G: Biological mothers (skip to F if C3 is no)				
HIV Testing, disclosure and Treatment history Iyezvino ndakudakukubvanzai mibvunzo yakanangana nezvekuongororwa ropa, kuudza vanhu zvabuda muongororo pamwe nezvenhoroondo pamushonga (T211)				
Q No	**Question**	Responses	**Instructions**	**Skip/comment**
G1 **(T119)**	How old were you when you first tested HIV positive? Manga mune makore mangani pamakatanga kuudzwa kuti mune hutachiona hweHIV?	Record age in completed years	Please use the number pad to record how old you were when you first tested HIV positive. *Ndapota shandisa gwaro remanhamba kutiudza kuti mange mune makore mangani* pamakatanga kuudzwa kuti mune *hutachiona hweHIV.* **(T120)**	
G2 **(T121)**	What made you go for an HIV test? Chii chakaita kuti muende kunoongororwa HIV?	Was sick/ ndairwara Advised by the health care worker/ ndakaudzwa nemushandi wezve hutano Pregnancy/ ndaive nepamuviri/ nhumbu Decided to get tested/ ndakangodawo kuongororwa ropa Other specify/ Zvimwewo		
G3 **(T122)**	Have you told anyone the results of your test? Pane munhu here wamakaudza zvakabuda muongororo yenyu?	Yes (Hongu) No (Kwete)		

G4 **(T123)**	I am going to read to you the people you could have told. Please tell me if you have told them and these should not include people who knew about it. Ndava kukuverengera vanhu vamungaday makaudza. Ndapota ndiudzeyi kana pane vanhu amakataurira uye vanofanira kunge vari vanhu vanga vasingazive nezvavo.	• Spouse/partner (Murume kana mukadzi wako) • Parents (Vabereki) • Brother(s) (Hanzvadzi/ Munin'na/Mukoma) • Sister(s) (Hanzvadzi/ Munin'na/Mukoma) • Sister or brother in law (Munin'na kana mukoma wemukadzi/murume wako) • Other family relatives specify (Vamwe vehukama)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
G5a **(T124)**	Were you ever inititiated on ARVs Makamboiswa pamushonga here wemaARVs	• Yes (Hongu) • No (Kwete		skip to H1 if no
G5b **(T125)**	Are you currently taking ARVs? Pari zvino muri pamushonga here we maARV?	• Yes (Hongu) • No (Kwete		
G6a **(T126)** G6b	Did you know your CD4 count when you started taking ARVs? Munoziva kuti CD4 count yenyu yakange iri papi pamakatanga kuiswa pamushonga wema ARVS What was it? Yanga iri chiii? **(T127)**	• Yes/Hongu • No/ kwete • Record number of copies/ml • Ndapota nyorai nhamba yenyu yeCD4 **(T128)**		

G7a G7b G7c	Do you know your recent CD4 count? What is it? When was it taken? Munoziva here CD4 count yenyu yekupedzisira**(T129)** Yange iri chii? **(T130)** Makapedzisirwa kutorwa riinhi**(T131)**	• Record number and date of last CD4 test • Ndapota shandisai manhamba kunyora mwedzi negore ramakapedzisira kutorwa CD4 count (T132)		
G8 **(T133)**	How long did it take you to be put on ART since the first time you were tested? *(Tick where applicable)* Zvakatora nguva yakareba sei kubva panguva yamakaongororwa HIV kusvika yakamazoiswa pamushonga?	• Same day I was tested (zuva rimwe chete randakaongororwa) • Within a week of testing (Musvondo rimwe chete randakaongororwa) • Between 1 - 11 months (Pakati pemwedzi mumwe chete nemwedzi gumi nerimwe) • Between 1 -5 years (Pakati pegore rimwe kusvika makore mashanu)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
G9 **(T134)**	Which treatment center do you currently go to? Pari zvino munoenda kuchipatara kupi?	• Local clinic (Kukiriniki yemunharaunda) • Local hospital (Kuchipatara chemunharaunda) • Parirenyatwa hospital (Kuchipatara cheParirenyatwa) • Harare hospital (Kuchipatara cheHarare – Kugomo) • Nazareth/Beatrice hospital (Chipatara cheNazareth) • Other (Chimwewo chipatara/kiriniki)		

G10 **(T135)**	How long is it since you first took these drugs (ARVs)? Pava nenguva yakareba seyi kubva pamakatanga kunwa mishonga iyi (maARVs).	• Record number of years or months if less than a 1 years Ndapota shandisai gwaro remanhamba kunyora makore kana musati masvitsa gore nyorai mwedzi (T136)		
G11 **(T137)**	Have you stopped taking these drugs (ARVs)? Makamira here kutora mishonga iyi (ARVs)?	• Yes (Hongu) • No (Kwete)		skip to G13 if no
G12 **(T138)**	Why have you stopped taking these drugs (ARVs)? Chikonzero chipi chakaita kuti mumire kutora mishonga iyi (ARVs)?	• Didn't want them anymore (Ndanga ndisisangaade) • Not available at the clinic (Anga apera kukiriniki) • Advised not to take them at my church (Ndakanzi ndisaamwe kuchechi) • Side effects (Aindirwarisa) • Not needed: in good health (Ndapora) • Other specify (Chimwewo chikonzero)		

G13 (T139)	Some people may miss taking their medication not because they don't want to, talking about you how often do you miss taking your ARVS on average? Vamwe vanhu vanokundikana kunwa mapiritsi avo sezvavanotariswa kunge vachiita asi kusiri kuda kwavo takatarisa imi mungati kangani pamunodarikira kunwa mapiritsi enyu?	• Once a day (Kamwe pazuva) • Twice a week (Kawiri pasvondo) • Once a week (Kamwe pasvondo) • Once every two weeks (Kamwe pamasvondo maviri) • Once a month (Kamwe pamwedzi) • Other (Imwewo nguva) • Never (handisati ndambodarikira)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
G14 (140)	In the last 7 days how many doses have you missed? Musvondo rapfuura makakanganwa kunwa mapiritsi kangani?	• Record no of doses • Ndapota shandisai gwaro remanhamba kunyora kuti makakanganwa kangani (T141)		
G15 (142)	In the last 7 days how many doses did you not take on time? Musvondo rapfuura mapiritsi mangani amusina kunwa nenguva?	• Record no of doses • Ndapota shandisai gwaro remanhamba kunyora kuti kanngani pamusina kunwa nenguva (T143)		
G16 (T144)	Have you experienced any unpleasant side effects since you started taking treatment? Makambotadza kuwirirana nemushonga here?	• Yes a lot of times • Hongu kakawanda • Yes a few times • Hongu kashoma • No • Kwete		

G17 (T145)	Have you received any of the following as part of your treatment for HIV? Makamboita here zvimwe zvezvinotevera mukurapwa kwenyu HIV?	• Changes in ARVs due to complications (Makambochinjirwa mushonga ye HIV here mushure mekunge yakurwarisai • TB treatment (kurapwa TB) • Treatment for other OI (kurapwa tumwe tuzvirwere tunokonzerwa ne HIV) • Cotrimoxazole (kupiwa mamacotri) • Hospital admission (kupihwa mubhedha) • Other/ Zvimwewo		
G18 (T146)	Did you receive any treatment to take **yourself** to prevent the baby from getting infected with HIV? Makambopiwa mishonga here yekuti mudzivirire mwana kuti asabatire utachiwana hweHIV?	Yes AZT Yes NVP single dose Yes other (specify) No Don't know Was already on ART		

H: Health-related quality of life (EQ-5D) – Adult			
Please indicate which statements best describes your own health state today Ndapota taridzai mitsara inonyatsotsanangura zvamuri kunzwa maererano nehutano hwenyu muzuva ranhasi (T212)			
H1 **(147)**	Mobility 1 = I have no problems in walking about 2 = I have some problems in walking about 3 = I am confined to bed 1 = Handina matambudziko pakufamba 2 = Ndine matambudziko pakufamba 3 = Handitokwanisi kufamba zvachose ndinongogara ndirere	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	

H2 **(148)**	Self-care 1 = I have no problems with self-care 2 = I have some problems washing or dressing myself 3 = I am unable to wash or dress myself 1 = Handina matambudziko nekuzvichengeta 2 = Ndine dambudziko nekuzvigeza nekuzvipfekedza 3 = Handitokwanisi kuzvigeza nekuzvipfekedza zvachose		
H3 (149)	Usual Activities (e.g. work, study, housework, family or leisure activities) 1 = I have no problems with performing my usual activities 2 = I have some problems with performing my usual activities 3 = I am unable to perform my usual activities 1 = Handina dambudziko nekuita mabasa angu emazuva ose 2 = Ndinoita matambudziko pakuita mabasa angu emazuva ose 3 = Handitokwanisi kuita mabasa emazuva ose		
H4 **(**150)	Pain/Discomfort 1 = I have no pain or discomfort 2 = I have moderate pain or discomfort 3 = I have extreme pain or discomfort 1 = Handina panondirwadza uye ndakagadzikana 2 = Ndinonzwa kurwadziwa uye kusagadzikana 3 = Ndinonzwa kurwadziwa zvakanyanya uye kusagadzikana zvakanyanya		
H5 (T151)	Anxiety/Depression 1 = I am not anxious or depressed 2 = I am moderately anxious or depressed 3 = I am extremely anxious or depressed 1 = Handishushikane neramangwana kana kunzwa kushungurudzika mupfungwa zvakanyanya 2 = Ndinonzwa kushushikana neramangwana zvishoma uye kushungurudzika mupfungwa zvishoma 3 = Ndinonzwa kushushikana neramangwana zvakanyanya uye kushungurudzika mupfungwa zvakanyanya		

Biological mothers (skip to J if C3 is no)
Medication Adherence Ratings Scale (MARS) Iyezvino ndoda kukubvanzai mibvunzo maererano nemanwiro amunoita mushonga (T213)

Q No	Question	Responses	Instructions
I1 **(T152)**	Do you ever forget to take your medicine? *Pane pamunombokanganwa kumwa mushonga here?*	Yes (Hongu) No (Kwete)	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*
I2 **(T153)**	Are you careless at times about taking your medicine? *Munomboshaya hanya here maererano nekumwa mushonga wenyu?*		
I3 **(T154)**	When you feel better, do you sometimes stop taking your medicine? *Pamunenge muchinzwa zviri nani munomborega here kumwa mushonga yenyu?*		
I4 **(T155)**	Sometimes if you feel worse when you take the medicine do you stop taking it? *Dzimwe nguva pamunonzwa kunge makunyanya kurwara muchinwa mushonga munomborega here kuumwa?*		
I5 (T156)	I take my medication only when I am sick. *Ndinomwa mushonga wangu pandinenge ndichirwara chete.*		
I6 (T157)	It is unnatural for my mind and body to be controlled by medication. *Pfungwa dzangu nemuviri wangu hazvina kujaira kushandisa mushonga.*		

I7 (T158)	My thoughts are clearer on medication. *Pfungwa dzangu dzakajeka kana ndiri pamushonga.*		
I8 (T159)	By staying on medication, I can prevent getting sick. *Ndikaramba ndiri pamushonga, ndinokwanisa kudzivirira kurwara.*		
I9 (T160)	I feel weird, like a 'zombie', on medication. *Ndinonzwa kuzungaira kunge dununu kana ndiri pamushonga.*	Yes (Hongu) No (Kwete)	
I10 (T161)	Medication makes me feel tired and sluggish. *Mushonga unoita kuti ndinzwe kuneta nekurukutika.*		

J: Parental Stress Index/ **Iyezvino ndoda kukubvanzai mibvunzo yakanangana nekushungurudzika mupfungwa kwevabereki (T214)**			
Q No	Question	Responses	Instruction

J1 (T162)	I often have the feeling that I cannot handle things very well. Ndinowanzo kunzwa sekunge pane nguva yandisingatambire zvinhu zvakanaka.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*
J2 (T163)	I find myself giving up more of my life to meet my children's needs than I ever expected. Ndinoona ndichizvipira kakawanda muhupenyu hwangu kupfura zvandaifungidzira kuti ndikwanise kuriritira vana vangu.		
J3 (T164)	I feel trapped by my responsibilities as a parent. Ndinonzwa sekunge ndakabatikana nokuda kwezvandinofanira kuita semubereki.		
J4 (T165)	Since having this child, I have been unable to do new and different things, Kubvira pandakaita mwana uyu, ndakutadza kuita zvinhu zvitsva kana zvakasiyana-siyana.		Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*

J5 (T166)	Since having a child, I feel that I am almost never able to do things that I like to do. Kubvira pandakaita mwana, ndinonzwa sekunge handichakwanisa kuita zvandinofarira kuita.		
J6 (T167)	I am unhappy with the last purchase of clothing I made for myself. Handisi kufara nembatya dzandakazvitengera.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*
J7 (T168)	There are quite a few things that bother me about my life. Pane zvinhu zvishoma zvinondinetsa pamusoro pehupenyu hwangu.		
J8 (T169)	Having a child has caused more problems than I expected in my relationship with my spouse (male/female friend). Kuita mwana kwakakonzera matambudziko andaisatarisira mukuwirirana kwangu nemurume wangu kana shamwarikadzi yangu).		
J9 (T170)	I feel alone and without friends. Ndinonzwa sekunge ndakaraswa sekunge ndisina shamwari.		

J10 (T171)	When I go to a social gathering, I usually expect not to enjoy myself. Pandinowanzo kuenda kumabiko, ndinowanzo tarisira kusafara.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	
J11 (T172)	I am not as interested in people as I used to be. Handichisina hanya nevanhu sezvandaisimboita.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*
J12 (T173)	I do not enjoy things as I used to. Handichanakidzwe nezvinhu sezvandaimboita.		
J13 (T174)	My child rarely does things for me that make me feel good. Kashoma mwana wangu achiita zvinhu zvinoita kuti ndinzwe kufara.		
J14 (T175)	Sometimes I feel my child doesn't like me and doesn't want to be close to me. Dzimwe nguva ndinombonzwa sekunge mwana wangu haandifarire uye haadi kunge ari pedyo neni.		
J15 (T176)	My child smiles at me much less than I expected. Mwana wangu haasekerere kwandiri sezvandaitarisira.		

J16 (T177)	When I do things for my child, I get the feeling that my efforts are not appreciated very much. Pandinoitira mwana wangu zvimwe zvinhu, ndinonzwa sekunge zvandinoita haazvikoshese zvakanyanya.		Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*
J17 (T178)	When playing, my child doesn't often giggle or laugh. Kana achitamba mwana wangu haawanzo sekenyeka kana kuseka.		
J18 (T179)	My child doesn't seem to learn as quickly as most children. Mwana wangu anoita seasingabate zvinhu nekukasika sevamwe vana.		
J19 (T180)	My child doesn't seem to smile as much as most children. Mwana wangu haawanzo sekerere kakawanda sevamwe vana.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	
J20 (T181)	My child is not able to do as much as I expected. Mwana wangu haakwanise kuita zvinhu zvakawanda sezvandaiitarisira.		
J21 (T182)	It takes a long time and it is very hard for my child to get used to new things. Zvinotora nguva yakareba, uye zvinonetsa mwana wangu kuti ajairire zvinhu zvinyowani.		
For the next statement, choose your response for the choices "1" to "5" below. Pane mubvunzo unotevera, sarudza mhinduro pakati pemhinduro shanu dzakapihwa pasi .(T215)			

J22 (T183)	I feel that I am: Ndinonzwa sekunge:	1. Not very good at being a parent Handisikugona pakuvamubereki. 2. A person who has some trouble being a parent. Ndiri munhu arikunetsekana pakuvamubereki. 3. An average parent. Sendingori mubereki ari pakati nepakati. 4. A better than average parent Sendiri mubereki ari nani pane ari pakati nepakati. 5. A very good parent Sendiri mubereki akanaka.	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*
J23 (T184)	I expected to have closer and warmer feelings for my child than I do and this bothers me. Ndaitarisira kuti ndinenge ndine rudo rwakawanda kune mwana wangu kupfura zvandiri kuita saka zvinondishungurudza.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	Please press on one box only

J24 (T184)	Sometimes my child does things that bother me just to be mean. Dzimwe nguva mwana wangu anoita zvinhu zvinondibhowa achida.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	*Ndapota dzvanya mubhokisi rimwechete chete*
J25 (T186)	My child seems to cry or fuss more often than most children. Mwana wangu anongochema kana kunetsa kupfura vamwe vana.		
J26 (T187)	My child generally wakes up in a bad mood. Mwana wangu anombomuka akapfundumwara.		
J27 (T188)	I feel that my child is very moody and easily upset. Ndinoona sekuti mwana wangu anongopfundumwara achikasika kutsamwa.		
J28 (T189)	My child does a few things which bother me a great deal. Pane zvimwe zvinhu zvishoma zvinoitwa nemwana wangu zvinondibhowa zvisingaite.		
J29 (T190)	My child reacts very strongly when something happens that my child doesn't like. Mwana wangu anotsamwa kana pane chinoitika chaasingafarire.		
J30 (T191)	My child gets upset over the smallest thing. Mwana wangu anotsamwira zvinhu zvidiki-diki.		

J31 (T192)	My child's sleeping or eating schedule was much harder to establish than I expected. Nguva yekurara nekudya yemwana wangu yakanetsa kuti ibatire kupfura zvandaifungira.		
For the next statement, choose your response for the choices "1" to "5" below. Pane mubvunzo unotevera, sarudza mhinduro pakati pemhinduro shanu dzakapihwa pasi			
J32 (T193)	I have found that getting my child to do something or stop doing something is: Ndinoona sekuti kuti mwana wangu aite chimwe chinhu kana kuti aregera kuita chimwe chinhu:	1. Much harder than I expected Sekunge zvakaoma pane zvandaitarisira. 2. Somewhat harder than I expected. Sekunge zvakatiomei kupfura zvandaitarisira. 3. About as hard as I expected. Sekunge zvakaoma sezvandaitarisira. 4. Somewhat easier than I expected. Sekunge zvakapfawa zvishoma pane zvandaitarisa. 5. Much easier than I expected. Sekunge zvakapfawa kupfura zvandaitarisira.	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*

For the next statement, choose your response from the choices "10+" to "1-3". **Pane mubvunzo unotevera, sarudza mhinduro pakati pemhinduro dzakapihwa pazasi (T216)**			
J33 (T194)	Think carefully and count the number of things which your child does that bother you. Fungai zvakanaka muverenge zvinhu zvinoitwa nemwana wenyu zvinokunetsai.	10+ 8-9 6-7 4-5 1-3 0	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*
J34 (T195)	There are some things my child does that really bother me a lot. Pane zvimwe zvinhu zvinoitwa nemwana wangu zvinokushungurudza zvakanyanya.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	
J35 (T195)	My child turned out to be more of a problem than I expected. Mwana wangu idambudziko kupfura zvandaitarisira.	Strongly Agree Ndinobvumirana nazvo zvakapfurikidza Agree Ndinobvumirana nazvo Not Sure Handinyatsokuziwi	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*

J36 (T197))	My child makes more demands on me than most children. Mwana wangu anoda zvakawanda kubva kwandiri kupfura vamwe vana.	Disagree Handibvumirana nazvo Strongly Disagree Handibvumirani nazvo zvachose	

	K: ALCOHOL USE DISORDERS IDENTIFICATION TEST (AUDIT)/ Iyezvino ndoda kuubvunzai mibvunzo maererano nekunwa hwahwa ((T217)			
Q No	Questions	**Responses**	**Instructions**	**Comments**
K1 (T198)	How often do you have a drink containing alcohol? Kangani muchimwa zvimwiva zvinehwahwa?	Never Handina kumbobvira ndambomwa Monthly or less Zvisingasviki kuita mwedzi wega wega 2-4 times per month Kaviri kusvika kanokwana kuita kana pamwedzi. 2-3 times per week Kaviri kana katatu pasvondo 4+ weeks Masvondo mana zvichipfurira.	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	**skip to K6 if no**

K2 (T199)	How many bottle of alcohol you drink on a typical day when you are drinking? Munomwa mabhodhoro mangani ehwahwa pazuva ramunowanzomwa?	1-2 3-4 5-6 7-9 10+ (T200)		
K3 (T201)	How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year? Kangani pamakamwa mabhodhoro matanhatu (kana muri munhukadzi), masere (muri munhurume) pazuva rimwe mugore rapera?	Never Kana Less than monthly Zvisingasvike mwedzi wega wega Monthly Mwedzi wega wega Weekly Pasvondo rega rega Daily or almost daily Zvinokwanisa kusvika pazuva rega rega.	Please press on one box only *Ndapota dzvanya mubhokisi rimwechete chete*	
K4 (T202)	How often during the last year have you failed to do what was normally expected from you because of your drinking? Kangani mugore rakapera pamakatadza kuita zvamaitarisirwa kuita nekuda kwekudhakwa kwenyu?			
K5 (T203)	How often during the last year have you been unable to remember what happened the night before because you had been drinking? Kangani mugore rapera pamusina kukwanisa kuyeuka zvakaitika madeko apfura nekuda kwekuti manga makadhakwa?			
K6	**Record time**			

Thank you for your time Maita basa nenguva yenyu (T204)

APPENDIX 5: CHIDO Trial ethical approval letters

RESEARCH COUNCIL OF ZIMBABWE

Cabinet Office
11 Stafford Road
Mount Pleasant
P.O. Box CY294, Causeway
Harare, Zimbabwe
Tel 263-4-304733
Fax 263-4-304851
Email secretary@rcz.ac.zw

Website www.rcz.ac.zw

Leadership, Innovation and Development

REF SC/9

29 June 2016

The Chairperson
Medical Research Council of Zimbabwe
Josiah Tongogara / Mazowe Street
P. O. Box CY 583
Harare

Dear Madam

Application for Renewal of Registration: A Trial to Determine the Effects of a Comprehensive Community Based Multi-Component Intervention on Early Childhood Development, Household Economic Resilience, and Adherence and Retention in Paediatric HIV Care and Treatment Programs: MRCZ/A/1943: Prof. Frances Mary Cowan

The above mentioned application was considered by the Research Council of Zimbabwe (RCZ) and it was approved.

Please find attached the research registration certificate (number 02804) for Prof. Frances Mary Cowan.

Yours sincerely

[redacted]

For Executive Director

Board Members: Dr. M. J. Tumbare (*Chairman*), Prof. I. Sithole-Niang (*Vice Chairperson*), Mrs. D.M. Chasi, Mr. S.C. Chigwamba, Prof. H. Chinhundu, Ms. M. Chitsiko, Dr. D. Garwe, Mrs. J. Gambe, Mrs. D. Hikwa, Mr. D.E.H Murangari, Prof. A. Murwira, Mr. S. Nyirenda, Mr. C.A. Samkange, Prof S Sibanda.
Executive Director: Mrs. S. Muzite

G.P. & S. 42914-V.

FORM RA.3

Research Act, Section 26A.

№ 02804

RESEARCH ACT, 1986

RESEARCH COUNCIL OF ZIMBABWE

CERTIFICATE OF REGISTRATION

Name Prof. FRANCES M COWAN

Nationality: BRITISH Passport No.: [redacted]

Institution of Affiliation in Zimbabwe: MINISTRY OF HEALTH AND CHILD CARE
MUKWATI BUILDING
HARARE

Residential Address in Zimbabwe: [redacted]

The bearer has been registered to conduct research in the field of INTERNATIONAL SEXUAL HEALTH, AIDS, HIV

in terms of section 26A of the Research Act, 1986.

Expiry date: 28 JUNE 2017

Signature of Bearer

[redacted]
Issuing Officer
Research Council of Zimbabwe

Date: 29 JUN 2016

RESEARCH COUNCIL OF ZIMBABWE
CABINET OFFICE
TECHNICAL OFFICE
P.O BOX CY 294
CAUSEWAY, HARARE

This receipt is not valid unless it is stamped

TITLE: A TRIAL TO DETERMINE THE EFFECTS OF A COMPREHENSI
COMMUNITY BASED MULTI-COMPONENT INTERVENTION ON
EARLY CHILDHOOD DEVELOPMENT, HOUSEHOLD ECONOMIC
RESILIENCE AND ADHERENCE AND RETENTION IN
PAEDIATRIC HIV CARE AND TREATMENT PROGRAMS.
MRC2/A/1943

Telephone: 791792/791193
Telefax: (263) - 4 - 790715
E-mail: mrcz@mrcz.org.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazoe Street
P. O. Box CY 573
Causeway
Harare

APPROVAL

REF: MRCZ/A/1943

25 June 2015

Prof F M Cowan
[redacted]

RE: A trial to determine the effects of a comprehensive, community based, multi component intervention on early childhood development, adherence and retention in paediatric HIV care and treatment programs.

Thank you for the application for review of Research Activity that you submitted to the Medical Research Council of Zimbabwe (MRCZ). Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your application to conduct the above titled study.

This approval is based on the review and approval of the following documents that were submitted to MRCZ for review:-

a) Protocol Version 8.0 dated 25 April, 2015.
b) Parental Informed Consent Forms for Formative phase Version 2 dated 15 April, 2015 (English)
c) Parental Informed Consent Forms for Formative phase Version 2 dated 16 April, 2015 (Shona)
d) Implementers qualitative Informed Consent Forms for Formative phase Version 2 dated 16 April, 2015 (English)
e) Implementers qualitative Informed Consent Forms for Formative phase Version 1 dated 16 March, 2015 (Shona)
f) Parental Informed Consent Forms for Developmental assessment (Formative phase) Version 1 dated 15 April, 2015 (English)
g) Parental Informed Consent Forms for Developmental assessment (Formative phase) Version 1 dated 25 April, 2015 (Shona)
h) Formative evaluation: Parent/Guardian Topic Guide Version 2 dated 16 April, 2015 (English and Shona)
i) Formative evaluation: Stakeholders Topic Guide Version 2 dated 17 April, 2015 (English and Shona)
j) Main trial Questionnaire Version 2 dated 16 April, 2015 (English and Shona)

- **APPROVAL NUMBER : MRCZ/A/1943**

This number should be used on all correspondence, consent forms and documents as appropriate.

- **TYPE OF MEETING : Full Board**
- **EFFECTIVE APPROVAL DATE : 25 June 2015**
- **EXPIRATION DATE : 24 June 2016**

After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted three months before the expiration date for continuing review.

- **SERIOUS ADVERSE EVENT REPORTING**: All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices or website.
- **MODIFICATIONS**: Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices or website.
- **QUESTIONS**: Please contact the MRCZ on Telephone No. (04) 791792, 791193 or by e-mail on mrcz@mrcz.org.zw

Other

- Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
- You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.
- Please note that the approval is for the formative phase only.

[redacted]

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2015 -06- 25
APPROVED
P.O. BOX CY 573 CAUSEWAY, HARARE

PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH

G.P. & S. 42914-V.

FORM RA.3

Research Act, Section 26A.

№ 02577

RESEARCH ACT, 1986

RESEARCH COUNCIL OF ZIMBABWE

CERTIFICATE OF REGISTRATION

Name PROF FRANCES MARY COWAN

Nationality: BRITISH Passport No.: [redacted]

Institution of Affiliation in Zimbabwe: MINISTRY OF HEALTH AND CHILD CARE
AIDS AND TB UNIT
MUKWATI BUILDING, HARARE

Residential Address in Zimbabwe: [redacted]

The bearer has been registered to conduct research in the field of INTERNATIONAL SEXUAL HEALTH AND HIV

in terms of section 26A of the Research Act, 1986.

Expiry date: 24 JUNE 2016

Signature of Bearer

Issuing Officer
Research Council of Zimbabwe

Date: 25 JUN 2015

RESEARCH COUNCIL OF ZIMBABWE
CABINET OFFICE
TECHNICAL OFFICE
P.O. BOX CY 294
CAUSEWAY, HARARE

This receipt is not valid unless it is stamped

TITLE: A TRIAL TO DETERMINE THE EFFECTS OF A COMPREHENSIVE COMMUNITY BASED MULTI-COMPONENT INTERVENTION ON EARLY CHILDHOOD DEVELOPMENT, HOUSEHOLD ECONOMIC RESILIENCE, AND ADHERENCE AND RETENTION IN PAEDIATRIC HIV CARE AND TREATMENT PROGRAMS:
MRC2/A/1943

UCL RESEARCH ETHICS COMMITTEE
ACADEMIC SERVICES

13 July 2015

Professor Frances Cowan
Centre for Sexual Health and HIV Research
UCL

Dear Professor Cowan

Notification of Ethical Approval
Project ID: 6789/002: A trial to determine the effects of a comprehensive community-based multi-component intervention on early childhood development, household economic resilience and adherence and retention in paediatric HIV care and treatment programs

I am pleased to confirm in my capacity as Chair of the UCL Research Ethics Committee (REC) that your study has been approved by the REC for the duration of the project, until July 2017.

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form':

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

   Reporting Non-Serious Adverse Events
   For non-serious adverse events you will need to inform Helen Dougal, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

   Reporting Serious Adverse Events
   The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

16 January 2017

To Whom It May Concern:

RE: A trial to determine the effects of a comprehensive community based, multi-component intervention on early childhood development, household economic resilience and adherence and retention in paediatric HIV treatment and care programmes.

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 **PACTR201701001387209**

Please be advised that 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, post or fax) 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

APPENDIX 6: Characteristics of caregiver interviewed at endline and lost to follow-up

Caregiver's Characteristic	**Measure and Level**	**Lost to follow-up** N=60 (10.5%)	**Interviewed at follow-up** N=514 (90.0%)	**P value**
Age (years)	Mean	29 (27, 31)	32 (32, 33)	<0.01
Caregiver type	N (%)			0.23
	Mother	60 (100.0%)	502 (97.7%)	
	Other	0 (0.0%)	12 (2.3%)	
Marital status	N (%)			0.49
	Married	51 (85.0%)	404 (78.8%)	
	Divorced/separated	7 (11.7%)	67 (13.1%)	
	Widowed	2 (3.3%)	29 (5.7%)	
	Never married	0 (0.0%)	13 (2.5%)	
Education	N (%)			0.74
	Secondary or above	33 (55.0%)	271 (52.7%)	
Employment	N (%)			0.79
	Employed	21 (35.0%)	189 (36.8%)	
SES	N (%)			<0.01
	Lowest	8 (13.3%)	184 (35.8%)	
	Middle	21 (35.0%)	170 (33.1%)	
	Highest	31 (51.7%)	160 (31.1%)	
PSI-SF total score n=504	Not stressed (<90th percentile)	40 (66.7%)	325 (64.5%)	0.74

	Stressed (>=90th percentile)	20 (33.3%)	179 (35.5%)	
Maternal mental health (EPND)	N (%)			0.36
	Not depressed (score 0-11)	33 (55.0%)	245 (48.8%)	
	Depressed (score>=12)	27 (45.0%)	257 (51.2%)	
Suicidal ideation at baseline	N (%)			0.06
	Suicidal	12 (20.0)	159 (31.7)	
	Non-suicidal	48 (80.0)	343 (68.3)	
Common mental disorders (SSQ8)	N (%)			0.77
	No CMD (score 0-5)	37 (61.7%)	306 (60.0%)	
	CMD (score 6-8)	23 (38.3%)	207 (40.0%)	