NEURODEVELOPMENTAL OUTCOMES AT PRESCHOOL AGE: A 5 YEAR FOLLOW UP STUDY OF A COHORT BORN TO MOTHERS PARTICIPATING IN THE PMTCT PROGRAM IN HARARE, ZIMBABWE.

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June 2008

Thesis submitted as a part of the

Master of Philosophy Degree in International Community Health

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
BINS	Bayley Infant Neurodevelopmental Screener
ELISA	Enzyme Linked Immunosorbent Assay
HAZ	Height for age Z score
HIV	Human Immunodeficiency Virus
MSCA	McCarthy Scales of Children's Abilities
PMTCT	Prevention of mother to child transmission
SPSS	Statistical package for social sciences
WAZ	Weight for age Z score
WHO	World Health Organization
WHZ	Weight for Height Z score
GCI	General cognitive index
HAART	Highly active antiretroviral therapy.

DEFINITION OF TERMS

HIV infected child: a child is considered infected if antibodies for HIV persist beyond 15 months.

Seroreverter: a child born to an HIV positive mother whose HIV antibody test is negative by age 15 months.

Infant: age from birth to 12 months.

Preschool age: chronological age of between 2 and 5 years.

Intelligence: measured by Kaufman`s short form of McCarthy Scales of Children `s Abilities and reported as General Cognitive Index (GCI).

Neurodevelopment impairment: Refers to conditions which are characterized by either developmental delay or regression of previously acquired milestones.

BINS level of risk for developmental delay: Categorized as low, moderate or high risk according to summary score.

Cognitive impairment: a GCI $\geq$1 SD below the average score ($\leq$ 84).

Screening: a test conducted on a population to identify those at risk. In this study those at risk are sent for definitive diagnosis and intervention of the particular type of disability.

Morbidity: refers to the occurrence in the previous 3 months of any of the following illnesses: cough, diarrhea, fever, ear discharge, vomiting or admission to hospital with any other diagnosis.

WHO paediatric clinical staging of HIV / AIDS: for children with confirmed HIV infection and based on the presence of various symptoms: Stage 1= asymptomatic; Stage 2= mild symptoms; stage 3=advanced symptoms; stage 4 =severe symptoms.

ABSTRACT

Background and purpose. The relationship between paediatric HIV infection and neurodevelopment has been studied largely in developed countries even if the burden of paediatric HIV is in Sub -Sahara Africa. This study assessed cognitive outcome at preschool age in Zimbabwean children, enrolled from a national PMTCT program, with vertically transmitted HIV type 1 infection who had been followed up for 5 years.

Methods. We assessed cognitive function in 278 preschool children with Kaufman short form of McCarthy Scales of Children`s Abilities (MSCA). Four groups were identified: 25 with HIV infection, 94 HIV negative born to HIV positive mothers (seroreverter), 126 HIV negative born to HIV negative mothers (controls) and 33 with unknown status. All children had been previously screened in infancy for neurodevelopment using Bayley Infant Neurodevelopmental Screener [BINS]; 115 had received prophylactic single dose Nevirapine at delivery, but none were on antiretroviral treatment.

Results. Cognitive impairment was observed in 24 children (8.6%) without significant difference between the groups. The family income of less than 30 US dollars per month, having a teenage mother and renting a house was associated with cognitive impairment. Mean General Cognitive Index(GCI) subtests scores were significantly lower between seroreverter and HIV negative children in specific subtests representative of verbal, perceptual performance and quantitative performance.HIV infected children were significantly more stunted , had more skin disorders, and lymphadenopathy compared to their uninfected peers. Maternal age was predictive of lower GCI scores. Correlation between BINS high risk score and GCI was observed between the ages 3 to 4 months.

Conclusion. The Kaufmann short form of MSCA is a simple cognitive screening tool for preschool children, however it should be complemented by a good neurodevelopmental screening tool in the first year of life.HIV infected children who survive to preschool age did not manifest lower cognitive scores than established child norms. Chronic malnutrition as indexed by stunting was associated with poor cognitive function at preschool age. BINS if performed in the first 6 months of life, was predictive of later cognitive performance particularly in HIV infected children. Therefore comprehensive interventions addressing early diagnosis and treatment for both childhood HIV and malnutrition could result in significant improvement in cognitive function.

Acknowledgement

This dissertation was supported by various people and organizations in Norway and Zimbabwe to whom I wish to express my heartfelt thanks.

I wish to thank the Letten Foundation for granting financial support for this study and allowing me to work with mothers and children enrolled into the Better Health for Mother and Child project and the NORAD foundation for funding the scholarship.

The University of Zimbabwe College of Health Sciences departments of Paediatrics, Obstetrics and Gynaecology for providing the research team with regular transport to the study sites (a mammoth task in present day Zimbabwe) and overseeing the smooth running of other logistics. I wish to thank my supervisors Professor Babill Stray-Pedersen, Professor Akhtar Hussain and Dr Isidore Pazvakavambwa for taking me through the paces of research. Special thanks to the statistician Lien Diep for helping with some of the data analysis. The UZ-UNO staff namely professor M Chirenje, Professor S Rusakaniko, M Munjoma, E Kurewa, F Gumbo, K Duri, M Nhembe and S Madzime for providing brutal honesty and encouragement in appraising the progress of the study. I wish to express my heartfelt gratitude to the drivers, nurses and counselors in the clinics who sometimes walked many kilometers in the scorching sun to local participants. I wish to thank Mrs Leslie Gregory, clinical psychologist, for providing training on the adaptation of the research tool to the research team despite her busy clinic schedule in public service. Thank you to my special friend Jill Almvang for proof reading the manuscript.

To the participating families and children in this study, your patience was humbling. My sincere gratitude for the dedication you portrayed during the study period.

Finally I wish to thank members of my family, especially my husband and young children for their support and tolerance during my absence from home. Your trust made it all worthwhile.

CHAPTER. 1 INTRODUCTION

The period from conception to the first six years of life have been shown to set a basis for the coping skills in learning, behavior and health in adulthood(1). In developing countries it was estimated that more than 200 million children under the age of 5 years do not reach their cognitive developmental potential due to preventable risk factors such as infections, malnutrition and inadequate cognitive stimulation(2).These early adverse childhood experiences influences brain development and have social, economic and political ramifications for the future(3).

Globally there are 2.5 million children younger than 15 years living with HIV/AIDS and 90% acquired the infection from their mothers during pregnancy, labour, delivery or postnatally through breast feeding. An estimated 500 000 new infections in children less than 14 years occurred in 2006 and at least 90% live in Sub-Sahara Africa(4). Due to premature deaths in the adult population the number of AIDS orphans and child –headed households is also increasing(5). The relationship between paediatric HIV infection and neurodevelopment has largely been studied in developed countries(6) when the burden of paediatric HIV is in Sub -Sahara Africa. HIV type1 infection is associated with poorer child neurodevelopment. Conflicting evidence exist on the prevalence of neurodevelopment impairment in HIV exposed and infected children(7-10). The different methods used by various researchers in equally diverse populations dilute the generalisability of the results(11-13).

Zimbabwe, once the bread basket of southern Africa has one of the highest adult HIV-1 seroprevalences in the world. In 2004 data from the national surveillance system estimated the adult prevalence at 21% (14). In response to HIV / AIDS Zimbabwe rolled out the Prevention of Mother to Child transmission of HIV (PMTCT) program according to HIVNET 012 recommended guidelines(15). In the absence of HIV prevention measures, approximately 35 % of children born to HIV positive mothers will contract the virus and are at risk of poor neurodevelopmental outcomes. This study is important because there is a dearth of knowledge on the relationship between perinataly acquired

HIV infection and cognitive abilities at preschool age in African children. Infected children are surviving beyond infancy even in resource limited countries. Disability among children was estimated at 2 % in Zimbabwe(16), but no documented evidence exist on the contribution of HIV-1 .

This sub-study is part of a larger study on mother to child transmission of HIV(17). The children born to mothers of the initial cohort have been followed up from birth to assess risk for neurodevelopmental impairment during infancy and at preschool age. The aim of this study was to compare cognitive function at preschool age in a paediatric sample of infected and uninfected children born to mothers who participated in the national PMTCT program. The information from this study may contribute to existing knowledge on the subject of child development in developing countries as well as aid in formulating guidelines in the screening for neurodevelopmental impairment and care of HIV exposed children.

1.1 OBJECTIVES

1.1.1 Main objective

The main purpose of this study is to describe cognitive performance (according to McCarthy Scales of Children `s Abilities), at preschool age, in children born to HIV infected and uninfected mothers who participated in the national PMTCT program.

1.1.2 SPECIFIC OBJECTIVES:

1) To characterise cognitive performance using the McCarthy Scales of Children `s Abilities in a cohort of children.

2) To identify predictors of cognitive impairment at preschool age in these children.

3) Compare cognitive function at preschool age with early neurodevelopment outcomes according to Bayley Infant Neurodevelopment Screener (BINS).

CHAPTER. 2 BACKGROUND INFORMATION

2.1 CHILD DEVELOPMENT

Child development involves the acquisition of physical, cognitive, motor, social, language and sensory integration skills at predictable stages. This is necessary for later age- appropriate interaction with the environment. Exposure of the developing child to biological and psychological factors may result in undesirable alteration in the global or specific cerebral structure and function(18). Functional limitations that result from disorders of central nervous system describe neurological impairment. In children it is important to monitor early development because although the developing brain is vulnerable to insults, unlike in adults, recovery is possible with early diagnosis and interventions, averting permanent disabilities(19).Therefore screening children ascertains if a child has acquired developmental milestones appropriate for his or her age.

2.1.1 RISK FACTORS FOR POOR NEURODEVELOPMENTAL OUTCOMES

Evidence abounds that early years of development from conception set the base for coping skills in learning, behavior and health throughout adult life(1). Brain differentiation occurs in a chronological order starting with cell proliferation, migration, synaptic connection, myelination and pruning (20) and can be affected by a variety of biological and psychological factors at each developmental stage. Established biological risk factors include infections, malnutrition, neurotoxins and micronutrient deficiencies. The timing of the injury has consequences on the pattern of neurological impairment(10).

2.1.1.1 Environmental and psychological factors

The family unit usually forms the first immediate environment that a child is reared in. The relationship between the quality of home environment and later achievement in school is well documented(21-24). The quality of parenting a child receives namely "cognitive stimulation, care-giver sensitivity, responsiveness to the child and caregiver `s affect" influences cognitive and social competence(25). Simple touch has been suggested to exert long lasting cognitive effect in preterm infants through stimulation of cortical growth and synaptic proliferation(26). Studies done in the developed countries

reported higher cognitive function in children who received additional stimulation compared to those who did not(18). A study from South Africa also reported non cognitive benefits such as improvement in social behavior, confidence and positive affect(25). In most of the studies designs maternal responsiveness and sensitivity were not controlled for, making it difficult to attribute the improvement to cognitive stimulation only.

2.1.1.1.1 Child stimulation and cognitive function

Poverty in the home has adverse effects on the child development. Poverty is correlated with increased maternal stress or depression and inadequate child stimulation in the home(2). Studies demonstrated that the electrical brain activity of newborns of depressed mothers show reduced ability to learn from the environment(27).Maternal depression is linked to poor cognitive and language development in the children (27).Interventions to diagnose and treat maternal depression may reduce cognitive disorders in their children. In the context of HIV infection, maternal mental health disorders will compromise the parent –child interaction influencing cognitive stimulation.

2.1.1.1.2 Home environment

The characteristic of the home environment also has an impact on child cognitive ability. Unfavorable home environmental factors such as unstable caregiver, maternal alcohol or drug abuse, poverty or maternal low education put children at risk for developmental dysfunction(21;24). The physical environment exerts an important effect on neuronal development. Children with fewer stimulating play materials in the home were found to be more at risk for low intelligence later in life than children with more stimulating play materials(21). Contaminants in domestic water such as lead, manganese and arsenic have been documented to have detrimental neurological outcomes. In a meta analysis by Lanphear non toxic level of lead exposure was associated with decrement in Intelligent Quotient(28) .

2.1.1.2 Biological factors

2.1.1.2.1 Growth and development

Growth and development in children is influenced by a multitude of interlinked risk factors. Intrauterine growth restriction (IUGR), birth weight of <2500 g at ≥ 37 weeks gestation has been demonstrated to be associated with lower developmental levels by school going age in a European cohort(29). The neurophysiological explanation is a reduction in neuronal cell number, size, with an overall lower brain weight (30). In paediatric HIV, when other risk factors for poor growth such as social environment are considered, faltering growth parameters may be used as markers of HIV disease progression(31). Those with growth failure have earlier onset of neurodevelopment delay(32;33). Mechanisms proposed to explain the growth failure in HIV include inhibition of growth hormone-releasing factor, decreased peripheral sensitivity to growth hormone and decreased levels of insulin like growth factors(34).

Reduced head circumference for age (an indirect measure of brain size assessed by measuring the occiputofrontal circumference) has been associated with developmental delay(35). In a study to investigate the relationship between head circumference at birth and later intelligence quotient(IQ) in Chilean school age children, an association was found between low head circumference and decreased IQ by school age(35). In a review article by Wachsler-Felder, exposure to perinatal HIV infection was suggested to be associated with reduced brain growth and neurological decline in HIV infected children(36).The detrimental effect of HIV on central nervous system was maintained to 24 months of age in a study by Macmillan C et al(37). In Zimbabwe the underlying causes for developmental delay still need to be explored in the context of a developing country. Monitoring children's growth parameters is therefore essential to identify those that digress from the optimal growth curves and institute timely intervention.

2.1.1.2.2 Nutrition and cognitive development

Micronutrients deficiencies such as iodine, iron, zinc and n-3 fatty acids also affect central nervous system development through various patho- physiological mechanism .Iron deficiency in infants has been suggested to be associated with poor mental and

motor performance which improves on supplementation of iron(18). A survey conducted in Zimbabwe in 1998 estimated the prevalence of iron deficient anaemia in preschool children at almost 20%.(38). There is lack of information on the contribution of iron deficiency and other nutrients to preschool cognitive performance in Zimbabwe. Families living with HIV tend to divert economic resources to the care of the chronically sick parent leaving little for nutritional needs.

2.1.2 HIV AND COGNITIVE DEVELOPMENT

HIV virus is neurotrophic and affects children cognitively and developmentally due to the susceptibility of their immature immune and central nervous system (CNS). In perinatally infected children cognitive, motor and behavioral disorders have been show to be related to the direct infection of the CNS by the virus as the disease progresses. The virus targets areas responsible for tactile, visual, expressive speech, memory and intellectual processes, rhythm, acoustic-motor and writing(36). There is inhibition of myelination and associate fiber development in the frontal and prefrontal areas which results in neurological deficits in processing speed, visual motor integration and sustained attention. Nozyce et al documented that mental and motor impairments appear more in HIV infected children who develop a serious AIDS defining illness in the first 2 years of life(39). Fishkin and Blanchette investigated preschool and school age children respectively. There were no gross cognitive differences between infected and uninfected peers from similar backgrounds(8;40). Older children tend to exhibit motor impairments characterized by progressive corticospinal tract signs with loss of previously acquired motor milestones. Paediatric HIV and its influence on child development can be prevented. PMTCT interventions may prevent perinatal transmission of HIV by up to 50 % in a breastfeeding population (15).

2.1.3 ANTIRETROVIRAL TREATMENT AND NEURODEVELOPMENT

The interaction between perinatal HIV 1 infection and ARV prophylaxis on neurodevelopment is largely unknown. Studies have documented the pharmaco-dynamics of the antiretrovirals on the central nervous system, but few have looked at the long term

the impact of ART prophylaxis or treatment on child neurodevelopment. A study comparing neurodevelopment outcomes in a Canadian cohort of HIV uninfected children exposed to combination highly active antiretroviral therapy in pregnancy versus those not exposed did not establish any difference in developmental outcomes(11). Other studies have suggested clinical improvement when antiretrovirals are started early in the treatment of HIV infection.

2.1.4 PURPOSE OF NEURODEVELOPMENTAL SCREENING

Neurodevelopment screening aims to identify children at risk of developmental impairment or delay and refer them for further assessment(41;42).

The exact nature of neurological deficits in children exposed to HIV is still unclear because previous studies had a wide variety of methodological problems that influenced interpretation. Different screening tests were employed since there is no gold standard test(43;44). Within some studies the form of the same test differed between age groups complicating interpretation(7;11). The screening tests used so far in African populations have been translated from English bringing in the issues of cultural bias, validity and reliability. Sadly routine screening for developmental delay is not practiced widely in resource limited settings despite the ability to identify infants at risk who may benefit from referrals for assessment and early therapy.

2.2 ZIMBABWE, COUNTRY PROFILE

2.2.1 Geography

Zimbabwe lies in southern Africa sharing borders with Zambia in the north, Mozambique in the east, South Africa on the south and Botswana in the south west. It has one of the highest HIV prevalence rates in the Sub-Sahara region. The landlocked country stretches over 390 759 square kilometers and is inhabited predominantly by Africans: Shona 82%, Ndebele 14% and other ethnic groups 2%. Caucasians and Asian constitute the remaining 2%. Zimbabwe is divided into 10 administrative provinces, which are further divide into districts, wards and then into smallest units, villages in rural areas or ten house units in towns.

2.2.2 Population Demographic Characteristics

The population of Zimbabwe was 13 076 000 in 2002 (Population census 2002). Females constituted 51.2% and males 48.8%. Over 70% of the population resides in the rural areas and population density is estimated to be 32.3 per square meter. Children under 15 years of age make up 45 % of the population. The projected annual growth rate is 3.7% and the average fertility rate is 4.5 per woman.

The health parameters for the country are poor. The infant mortality rate is estimated at 68 per 1000 live births and life expectancy is 37 years for men and 34 years for women. However, the literacy rate is about 90%, amongst the highest in Africa(45).

2.2.3 Economy

Zimbabwe, once the bread basket of Southern Africa is going through an economic crisis. More than 80% of the population is living below the poverty line. A myriad of factors are been implicated in the economic meltdown including a succession of droughts, land reforms, and ill conceived government policies. The International Monetary Fund estimates the country `s inflation at above 160 000%, the highest in the world for a country which is not at war. The Zimbabwe gross national product (GPN) has stalled. The main sources of revenue are mining, tourism, and commercial farming (Zimbabwe Financial Gazette 2008).

2.2.4 Health infrastructure

At the time of this study, the health system in Zimbabwe had collapsed due to perennial poor funding, poor communication infrastructure, drug and health personnel shortages. Historically the public sector, through the Ministry of Health and Local government provided health services to both rural and urban areas. A four tier referral system still exists where the first level is the primary health care centre, the second the district hospital or mission, the tertiary the provisional hospital and the quaternary level the central hospitals. On average an individual lives within 8 miles of a health centre. A total of 106 government hospitals and 1500 primary health care clinics used to provide comprehensive services in maternal and child care, curative services and environmental health promotion.

2.2.4.1 Child follow-up clinic

Immunization, growth monitoring, opportunistic infection prophylaxis and nutritional counseling are some of the services offered at the maternal and child health clinics. In the first 2 years of life recommended vaccines are provided at birth, 3, 4, 5, 9 and 18 months. Concurrently gross motor development is assessed by enquiry. Those perceived as developmental delayed are referred to the next referral centre .The period between 18 to 60 months is quiescent as there is no scheduled interaction between health services and children occurs unless the children are unwell. Developmental monitoring and screening is not offered as part of follow up of children.

2.2.5 Epidemiology of Paediatric HIV.

Paediatric HIV is acquired mostly through MTCT. Estimated prevalence of HIV in women attending urban antenatal clinics was 31.1% in a study conducted in Harare, Zimbabwe (46). United Nation Children`s Fund estimates that 160 000 Zimbabwe children under the age of 14 are infected with HIV and that there are at least a million orphans whose parents have succumbed to HIV infection. Although the government has rolled out a national PMTCT program, only 10 % have access to services. No coordinated screening programs are in place to identify children early who have faltered from their growth and developmental trajectory.

2.2.6 Study Area

The study was conducted in the outskirts of Harare, Zimbabwe at 2 peri-urban areas of Chitungwiza and Epworth. Chitungwiza city is located 15 kilometers southeast of the capital of Zimbabwe, Harare. It is a residential dormitory for the capital and was formed in 1978 by amalgamation of three townships Zengeza, Seke and St Marys. It has a young population of 400 000. Epworth is located south of the capital; within a 20 kilometer radius .It is administered by a rural administrative board.

Figure 1 Map showing the cities of Harare and Chitungwiza, Zimbabwe.

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STUDY SITES

The clinics of St Marys, Seke and Epworth were selected as study sites based on the number of patients attending the health centers and feasibility of carrying out clinical research. The clinics offer a wide range of services and are used mainly by the low income population

CHAPTER.3 METHODOLOGY

3.1 STUDY DESIGN

This is part of an ongoing prospective study that has followed up mothers and their children from birth to the present day (17). Briefly, the primary study examined the role of sexually transmitted infections in Mother to Child transmission of HIV type 1 in Harare Zimbabwe during the period 2002 to 2004. The children born to women who participated in the study were assessed during infancy for neurodevelopment outcomes at scheduled intervals from 3 months to 12 months using the Bayley Infant Neurodevelopment Screener (BINS). A level of risk for neurodevelopmental delay was assigned to the children based on the BINS score.

3.2 STUDY POPULATION

Participants in this study were children who successfully completed at least 1 neuro developmental assessments by BINS during the follow up of one year and had complete longitudinal data for at least 3 years**.** In the primary study, both HIV positive and HIV negative pregnant women who had gone through the national PMTCT program at 36 and 38 weeks of gestation, who also had a documented HIV result from the national program ,were enrolled. The pregnant women were investigated for incidence of HIV type 1 and reproductive tract infections. The infants were followed up initially at scheduled visits at 6 weeks, 4 months, 9 months, 12 months and every 6 months thereafter.

3.3 SAMPLE SIZE

The sample size for the children was derived from calculations for the primary study. The calculated sample size for the pregnant women was based on 31 % HIV prevalence among pregnant women, 90% power to detect a 1.6 fold difference in HIV infection rates between the two groups, using a 2 tailed test with $\alpha = 0.05$, and allowing for a 25% loss to follow up. The estimated sample size was therefore 300 HIV positive women and 600 HIV1 negative women. For every HIV positive woman enrolled in the follow-up study, two HIV negative women were selected as controls, matched for age $\pm$2 years, parity and the area of residence. The initial study design was modified mid way to conveniently

enroll more HIV -1 infected pregnant women as their numbers were very few. During the study period 2002 to 2004 a total of 1050 pregnant women were enrolled with 496 HIV infected and 554 HIV uninfected. From a total of 1044 live births, 644 infants were assessed with the BINS instrument at least once in the first 12 months of age and therefore enrolled into the paediatric cohort. For the present study those who fulfilled the inclusion criteria were enrolled from the existing paediatric cohort.

3.3.1 INCLUSION CRITERIA

1) Participants from the primary study with at least one neurodevelopmental assessment by Bayley Infant Neurodevelopmental Screener (BINS).

2) Children who are aged 3 ½ years and above.

For children less than 3 year the MSCA is not reliable in assessing cognitive function compared to the Bayley Scales of Infant Development assessment tool(42).

3.4 FOLLOW UP OF CHILDREN AND ASSESSMENT

From the initial cohort of 644 children, 23 declined to participate for various reasons, 150 had relocated to a distant region, 58 had died, and 126 could not be traced, resulting in 287 who agreed to participate (Figure 2).

A total of 278 preschool children had complete examination (Figure 3).

Figure 2 Follow up pattern at preschool age from the original cohort of 644 children.

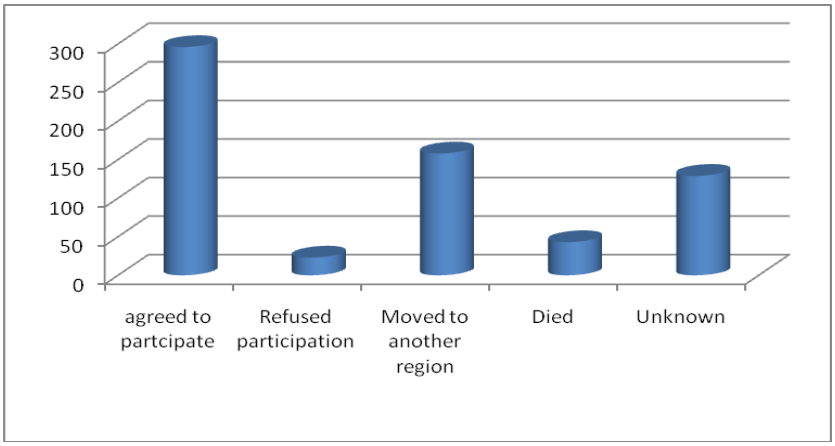
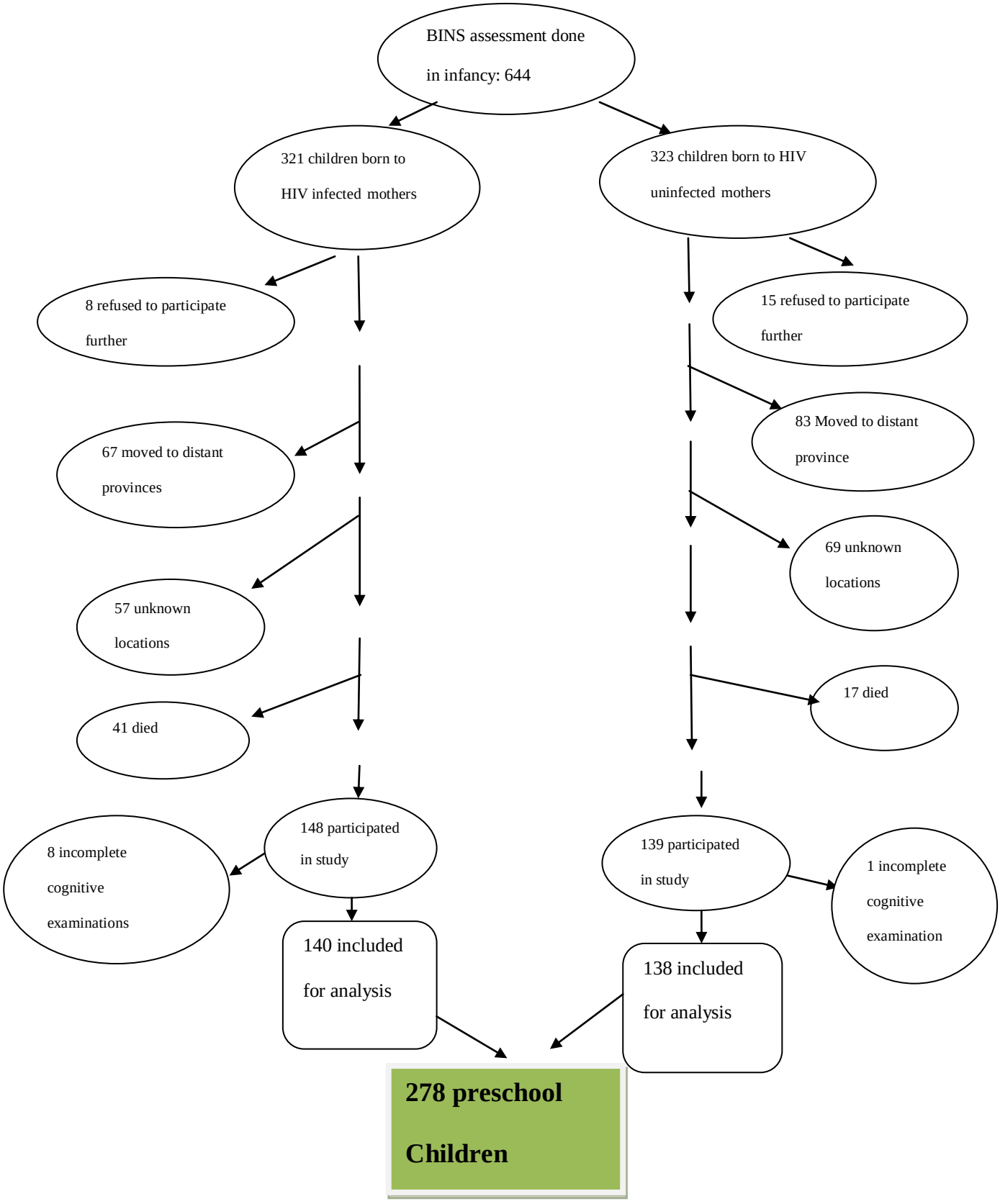


Figure 3 Flow chart showing the number of children followed up to preschool age.



3.5 PROCEDURES

3.5.1 Recruitment

Children were invited to the study sites after a field worker had visited each eligible household to inform the families about the study and request participation.

The study aims and procedures were explained to each mother or close relative accompanying the child. Written consent was obtained. They were assured that withdrawal from participation in the study would not interfere with access to treatment or other services for their child.

3.5.2 Clinical follow up

Baseline data on demographic factors, medical history, and nutritional history were collected during interviews with primary care givers using a structured interview questionnaire. Clinical and psychometric examinations were done by the medical staff that comprised 2 paediatricians and a research nurse. At each follow up visit, a history and physical examination of the children was performed. Anthropometric measurements: height, weight and head circumference were taken. Inquiry into the children's health complaints and home environment were made. If children had an acute illness, the testing was deferred until they were well. Medical care was provided to those with acute illnesses.

3.5.3 Definition and Classification of HIV -1 infection

The paediatric HIV clinical staging was assessed according to WHO algorithm(47). Those meeting the criteria for starting antiretroviral treatment were referred to tertiary hospitals where comprehensive monitoring and treatment with antiretroviral therapy for children is currently centralized.

According to the primary study protocol, laboratory criteria for diagnosis of HIV infection in the children was the detection of antibodies to HIV -1 infection in venous blood at the age of 15 months or beyond. HIV testing was performed using Abbott Determine HIV1/2 and Trinity BiotechHIV1/2 rapid tests. Positive tests were confirmed by ELISA, Vironostika HIV Uni-form11(Organon Teknika, Boxtel Netherlands). If the test was positive, the child was classified as HIV infected and if negative as HIV

uninfected. Laboratory measures of immune status such as CD4 and viral loads were not available at the time of the initial cohort.

For most children growth was assessed by measurement of weight (in kilograms) using a Salter weight scale (model Salter 9145 tracker scale) and height on a height board. Head circumference (cm) was measured by a non stretchable tape measure.

3.5.4 Neurological status

The neurological assessment included evaluation of mental status, cranial nerves, muscle tone, sensation, upper and lower extremity reflexes, balance, and rapid alternating movements. Power was tested by asking each child to push and pull the examiner`s upper limbs and opposing their movements.

All sensation tests were be performed with the child's eyes closed.

Pain was elicited by lightly touching the child with a single use disposable pin. Heat and cold tested with objects with a relatively higher or cooler temperature to the child's body temperature. Vibration was not assessed in this cohort of the children. Presence of persistent neurological abnormality was classified as abnormal.

3.6 COGNITIVE ASSESSMENT AT PRESCHOOL AGE

The Kaufman`s short form of the McCarthy scales of Children `s Abilities (MSCA) was administered cross sectional to determine the cognitive development of the children. Trained research staff blinded to the HIV status of the child, assessed the children in the presence of the parent or guardian. Children who performed poorly on any one of the 6 test items were invited for retesting within a week of the first test. They were examined only on the subset not performed adequately to limit practice effects. Efforts were made for the child to be examined by the same examiner.

3.6.1 Description of The Kaufman`s short form of the McCarthy scales of Children `s Abilities (MSCA)

The McCarthy Scales of Children`s Abilities is an assessment tool that was developed for children of ages 2 ½ through to 8½ years. It assesses children's present level of functioning in intelligence and motor ability with the aim of identifying possible

developmental delay in different skill areas. It consists of 18 subsets of cognitive and motor ability. Weighted raw scores are grouped to yield scores in 5 global areas of function: verbal, perceptual-performance ,quantitative, memory and motor .The weighted raw scores from verbal perceptual –performance and quantitative are converted to an age –related scaled score or index, and are then combined to yield a General Cognitive Index (GCI) . The mean for the GCI is set at 100, with a standard deviation (SD) of 16. Index scores for the 5 domain scales have a mean of 50 with a SD of 10 as the optimum score. Items from the verbal, perceptual-performance and quantitative are content oriented, with no subset from one domain contributing to the score of another domain. The memory and motor domains are process oriented and subsets overlap with verbal, perceptual-performance or quantitative domains. The GCI of the MSCA was correlated with the 2 standardized diagnostic tests for cognitive ability namely the Stanford -Binet Intelligent test and the Wechsler Preschool and Primary Scale for Intelligence. The GCI correlated .81 with the Stanford –Binet Intelligence test and ranged .62 to .71 with the WPPSI. Correlation between a brief version of the MCSA, the Kaufman `s short form of the MCSA and the Stanford-Binet Intelligence scales 4th Edition was .91.

For this study the Kaufman`s short form of the McCarthy Scales of Children`s Abilities was adopted in accordance with the MSCA manual instructions. It consists of a six-test abbreviated version of the General Cognitive Scale and gives a proportional representation to the verbal, perceptual-performance, quantitative and memory scales which correlates substantially with the entire McCarthy scales. It serves as a screening instrument for a wide variety of mental functions and is brief to administer and score(20 to 25 minutes).The six tests items in the Kaufman short form are puzzle solving, word knowledge, numerical memory, verbal fluency, counting and sorting and conceptual grouping. The reliability of the estimated GCI was .90 in the standardization sample and was .71 in this sample.

In this study cognitive ability was expressed as a GCI score based on age specific normative data among American children and classified as follows: GCI $\geq$ 120 superior intelligence; 85 to 119 ,average to high average; $\leq$ 84 low intelligence. All children scoring below 64 were aggregated to 64.

Modifications

Based on a pilot study (n=21), culturally appropriate modifications to some of the test items were made to make the battery of tests applicable. Test content and format was preserved .Test items were examined individually to establish which pictures and items were recognizable and to evaluate clarity of instructions. As a result of piloting we substituted some items with familiar materials. Translations of all instructions, objects and pictures were made into the local Shona language. During the assessments establishing rapport with the participants was emphasized. Detailed preparatory instructions and explanation of errors and successes seemed to enhance performance on the children. All assessments were carried out in Shona by examiners who were fluent in the language in offices situated at the quiet end of an outpatient department.

Procedures to enhance validity and reliability of data

Data were reviewed regularly to optimise quality control and inter-observer reliability specifically with the scoring criteria. Inter-tester reliability among study examiners was maintained by centralized training of all the project examiners by a senior clinical psychologist. As the MSCA was administered only once, the test retest measure was not assessed. Inter- rater reliability was enhanced by strict adherence to the scoring system Since this instrument has not been standardised in Shona speaking children, scores based on American test norms may not necessarily be equivalent for Zimbabwean children.

3.6.2 Baileys Infant Neurodevelopment Screener (BINS)

The Baileys Infant Neurodevelopment Screener (BINS) is a screening tool designed to identify infants between the ages of 3 to 24 months at risk for developmental delay or neurological impairment. Four global conceptual areas of ability are assessed: i) basic neurological function/ intactness; ii) expressive functions; iii) receptive functions and iv) cognitive functions. The 4 conceptual areas of ability can be used to determine if the neurodevelopmental impairment is global or specific. The BINS is age specific and consists of 11–13 items depending on the age of the child. Each item is scored as optimal or none optimal and the optimal responses are totaled to yield a summary score. An optimal finding has a higher predictive value for later positive outcome. The summary

score reflects the child's level of risk for developmental delay or neurological impairment, which is classified as one of the three risk groups: low, moderate, and high. In addition the BINS were analysed as a dichotomous variable HIGHRISK and LOWRISK, according to cut off points presented in the BINS manual

3.7 Definition of variables

Dependent (Outcome) variable: Intelligence: As measured by MSCA the individual's ability of solving problems and process information.

Independent (explanatory) variables:

1. Child's care giver `s socioeconomic status
2. Child `s demographic characteristics
3. Child `s HIV sero-status
4. Child `s nutritional status
5. Child `s health status
6. BINS neurodevelopment level of risk at infancy

3.8 DATA PROCESSING

The data were entered into a prepared master sheet daily in the field, cleaned, checked and corrected for inconsistencies.

3.8 DATA ANALYSIS

Only children with complete cognitive assessment data were included in the analysis. Cognitive function was classified according to the sum of the weighted scores in the six tests items of the Kaufman short form: puzzle solving, word knowledge, numerical memory, verbal fluency, counting and sorting and conceptual grouping. The General Cognitive Index (GCI) was computed from the total score. A score of 84 and below (- 1 SD below the mean) was selected as the cut-off point for cognitive impairment in this cohort. All analyses were conducted using SPSS for windows (Rel 12.0.1, 11 Nov 2003, Chicago, SPSS, Inc). Statistical analysis consisted of comparisons of proportions using the Chi square and Fischer `s exact tests for categorical data. Comparison of group averages was based on analysis of variance (ANOVA) when normality of data was

assumed otherwise Kruskal Wallis test was used (48;49). Pearson correlation was used to determine the association between the BINS scores and MSCA GCI scores. All tests were 2 tailed. A P-value of ≤ 0.05 was be considered statistically significant and only calculated for non missing data. Logistic regression was employed to generate odds ratio and predict cognitive impairment. All variables were categorized in the multivariate model. Maternal age was categorized as <20 or > 20 years. Maternal education was categorized as "less than primary school" if she did not complete 7 years of school, "primary" if she completed 7 years and "secondary" or higher if she had more than 7 years education. Maternal income was categorized into < 30 US dollars or $\geq$30 US dollars. Birth weight was categorized into < 2500 rams (low birth weight), $\geq$ 2500 grams (normal birth weight), Height, Weight,head circumference were categorized into abnormal (< 2 SD of mean for age and normal(> SD of mean for age). The number of surviving HIV infected children in this sample determined the relatively small sample size (n=25).

3.9 ETHICAL ISSUES

4.0 Approval

The study was approved by the Norwegian regional committee and Medicine Research Council of Zimbabwe. Ethical concerns in this study included the involvement of children in research, informed consent from minors, confidentiality, beneficence and standard of care. Written consent for the study was obtained on behalf of the children from their primary care-givers. The purpose and procedures of the study were explained in the local language. They were informed that participation was voluntary and that refusal would not result in any penalty or loss of benefit they previously enjoyed. They were informed of their right to withdraw from study at any time.

4.1 Confidentiality

Due to the sensitive nature of some of the questions asked, strict confidentiality was maintained throughout the study. Each child already had a unique study identification number. All data were be collected and analysed according to these numbers. The coded

numbers identifying study participants and all records were locked in a cabinet file. Any links connecting participants' identification numbers to other identifying information was stored separately in a locked cabinet with limited access.

4.2 Beneficence

Children diagnosed to have developmental delay or to have a medical condition were referred for appropriate assessment and diagnosis. A study paediatrician provided free consultation and treatment for opportunistic infections. HIV infected children satisfying criteria for starting antiretroviral were referred to the central hospital where comprehensive care was available. Attempts were made, within the limitations of the available resources to facilitate that the best available treatment was secured for those in need.

4.3 Compensation

The mothers and children were compensated for the transport costs incurred when they to came to the study clinic.

CHAPTER.4 RESULTS

4.1 FOLLOW UP

4.1.1 COMPARISON OF ENROLMENT CHARACTERISTICS BY FOLLOW UP PATTERN FOR 644 CHILDREN IN THE INITIAL COHORT

At 5 years follow up, of the 644 infants assessed for neurodevelopment during the ages 3 to 15 months, 58 were reported dead, a further 299 were lost to follow resulting in 287 who consented to participate.

The children in the 3 groups were comparable at baseline except for usage of Nevirapine prophylaxis at delivery and presence of neurodevelopmental high risk in infancy which was more frequent in the group of children who died.

Table 1 Comparison of enrolment characteristic between children who participated in the follow up study, those lost to follow up or dead.

Infant variable	Participants N=287	Loss to follow-up[$] N=299	Dead N=58	P value
Birth weight ,mean Kg± SD	3.1± 0.4	3.06± 0.4	3.06 ±0.4	0.776
Male sex	129 (44.9)	140/261 (53.6)	28 (48.3)	0.127
Nevirapine prophylaxis at delivery	128(44.6)	92 (30.8)	30 (51.1)	0.001*
Neurodevelopment high risk in infancy	13 (4.5)	13 (4.3)	8 (13.8)	0.01[α]

* participants versus those lost to follow up or died

α participants and those children that died

[$] participants who either refused to further take part in the study, moved to a distant province or whose whereabouts could not be verified.

Comparison of maternal characteristics at baseline between the study participants and the rest of the children showed no significant difference in relation to marital status, employment, years spent in formal education and occupation. Mothers lost to follow up were more likely to be HIV uninfected, younger, have less number of living children and less compliant to nutritional supplementation with Omega 3 (Table 2).

Table 2 Comparison of maternal enrolment characteristic between children who participated in the follow up study, those lost to follow up or died.

Maternal Variable	Participants N=287	Loss to follow-up Ω N=299	Dead N=58	P value
Maternal HIV-1 sero status				
Negative	139 (48.4)	167 (55.9)	17(29.3)	0.001*
Positive	148/287 (51.6)	132/299 (44.1)	40 (70.7)	
Age ,mean years ± SD	25 .3 ± 5.2	24.3± 4.7	26.1± (5.4)	0.017*
Number of living children mean value ± SD	1.4 ± 1.2	1.1 ± 1.1	1.8 ± (1.3)	0.001 §
Education, years				
0-7	54/281(19.1)	54/295(18.3)	10 (17.2)	
8-11	224/281(79.4)	233/295(79.0)	47(81.0)	0.841
>12	4/281(1.4)	8/295(2.7)	-	
Marital status				
Married	246/272(90.1)	275/294(93.5)	49 (87.5)	0.191
Single	27/272 (9.9)	19/294 (6.5)	9 (12.5)	
Formally employed	18/285(6.3)	14/295(4.7)	6 (10.3)	0.379
Omega 3 supplement in –take	54/287 (14.2)	30/299 (10)	9 (15.5)	0.002^

Ω participants who either refused to further take part in the study, moved to a distant province or whose whereabouts could not be verified.

* Participants versus those children who died.

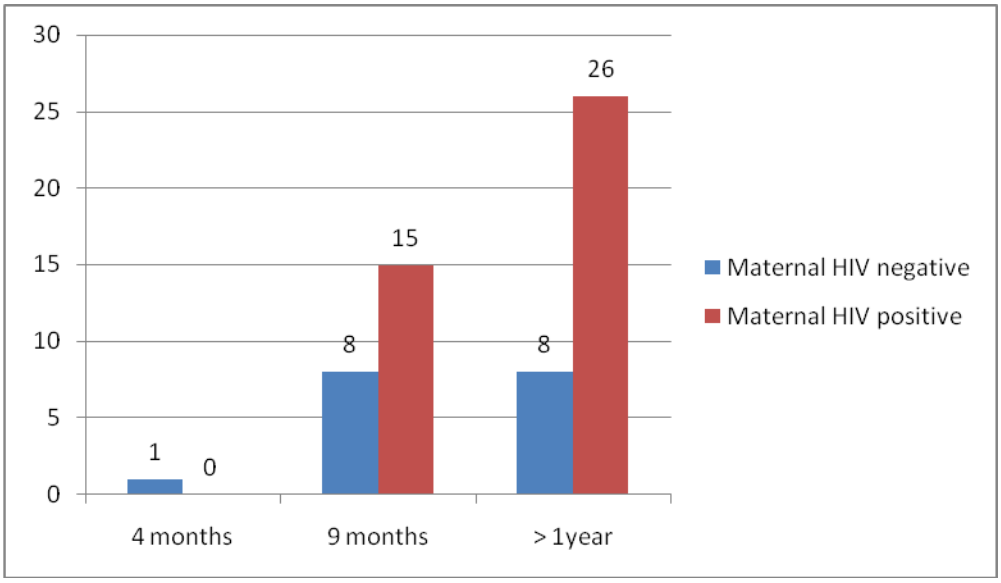
§ Participants versus lost to follow up or died.

^ Participants versus lost to follow up

4.1.2 CHILD MORTALITY DURING FOLLOW UP PERIOD

A total of 58 children, who had been assessed for neurodevelopment in infancy were, reported to have died during the 5 year follow up period. Thirty four of the deaths (34/58) occurred after the first year of life.

Figure 4 Trends in child mortality by maternal HIV status



In this cohort, beyond the age of 4 months, maternal HIV status and infants `classification into the high risk group for poor development was significantly associated with higher mortality (Table 3).

Table 3 Enrolment characteristic, maternal HIV status and neurodevelopmental outcomes in infancy of the 58 children who died during the follow up period.

Infant characteristic	Total	Deceased		P value
		Number	%	
Birth weight				
< 2500	53	3	5.7	
>2500	512	53	9.6	0.459
Sex				
Male	296	28	9.3	0.127
Female	305	30	9.6	
Nevirapine prophylaxis				
No	394	28	7.1	0.035
Yes	250	30	12	
Maternal HIV				
HIV infected	321	41	12.8	
HIV uninfected	323	17	5.3	0.001
High risk for poor neurodevelopment by BINS test				
No	610	50	8.2	0.02
Yes	34	8	23.5	

4.2 SOCIO-DEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS

The children`s primary care givers were predominantly biological parents in both groups. Extended family members included grandparents, aunts and uncles .Only one participate was living in a household headed by his fourteen year old sibling. None of the children in this study were institutionalized. Socio-demographic characteristics were comparable between children with HIV infected and uninfected mothers.

Table 4 Description of child care giver at the examination of 278 preschool children by Maternal HIV status

Maternal HIV status	HIV-1 Negative	HIV-1 Positive	
	N=138 (%)	N=140 (%)	P value
Principal primary care giver			
Biological Parents	120 (87.0)	123 (87.2)	0.821
Extended family members	18 (13.0)	17 (12.1)	
Age , mean years± SD	30.6± (9.9)	31.9± (9.4)	0.274
Male sex	2 (1.4)	5 (3.6)	0.447
Education, years			
No formal education	2 (1.4)	1 (0.7)	0.198
0-7	19 (13.8)	32 (22.6)	
8-11	114 (82.6)	106 (75.9)	
>12	3 (2.2)	1 (0.7)	
Occupation			
Not employed	63/125(50.4)	50/119(42.7)	0.39
Self employed	53/125(42.4)	57/119(46.8)	
Formally employed	9/125(7.2)	12/119(10.5)	
Total family income			
< $ 30 per month	81(58.7)	95(67.9)	0.277
>$ 30 per month	29(21)	24(17.1)	
Refused to answer	28(20.3)	21(15.0)	
Household characteristic			
Own house	32 (22.4)	39 (27.9)	0.372
Rented house	106 (76.8)	101 (72.1)	

The 278 children born to HIV negative and HIV positive mothers were similar in socio-demographic characteristics and neurodevelopmental High risk classification according to BINS test. Less mothers in the HIV infected group compared to the HIV uninfected had opted to breast feed.

There were 36 orphaned children in the cohort. Children in whom both parents had died (double orphans) were 6 whilst 30 were single orphans: 23 with father only deceased and 7 with mother only deceased.

Table 5 Socio-demographics, health, neurodevelopment risk and HIV status of 278 preschool children (aged 3 ½ - 5 ½ years).

Maternal HIV status	HIV-1 Negative	HIV-1 Positive	
	N=138 (%)	N=140 (%)	P value
Age , mean months± SD	56.1 ± 7	56.14 ± 6.1	0.851
Male sex	59(42.8)	66 (47)	0.462
Formal preschool attendance	36(30.5)	35 (29.6)	0.921
Breast fed	132(98)	122 (88)	0.001
Orphan hood	N=10	N=26	
Mother deceased	3(30)	4 (15)	0.550
Father deceased	6(60)	17 (65.4)	
Both parents deceased	1(10)	5 (19.2)	
*Morbidity in past 3 months	70 (51.6)	86 (62.3)	0.081
High risk score on BINS test in infancy	5(3.6)	8(5.7)	0.572
Child HIV status			
HIV infected	0	25	
Seroreverter	0	94	
Uninfected born to HIV infected	126	0	
*Unknown status	0	33	

* Unknown HIV status refers to those children born to HIV positive mothers who were not tested during follow up period.
* Morbidity refers to the occurrence in the previous 3 months of any of the following illnesses: cough, diarrhea, fever, ear discharge, vomiting or admission to hospital with any other diagnosis.

4.3 HEALTH STATUS

At least 30% (85/278) of the children in this cohort were stunted, while 45 (16%) were underweight. Children infected with HIV were more stunted compared to their peers in the seroreverter or HIV Negative groups. Lymphadenopathy and skin disorders were significantly more frequent in HIV infected children compared to children in the serorevertor or HIV negative groups.

Table 6 Comparison of clinical examination of 278 preschool children stratified by maternal [M] and child [C] HIV status: HIV positive (M+C+),HIV negative (Seroreverters [M+C-]) and control (M-C-).

Child indicator	**HIV infected**	**HIV uninfected**		**Unknown**	**P value**
	M+C+	**M+C-**	**M-C-**	**status**	
	N=25	N=94	N=126	N=33	
Morbidity	16/25 (64)	58/93(62.4)	66/123(53.7)	16/32(50)	0.425
Lymphadenopathy	13/24(56.5)	11/85 (12.9)	11/85 (12.9)	3/31 (9.7)	0.001
Skin disorders	9/22 (40.9)	9/84 (10.7)	19/119(16.0)	3/13 (13.3)	0.007
Dental Caries	3/22 (13.0)	4/78 (4.8)	3/118 (2.5)	4/30 (13.3)	0.70
Neurological Examination					
Abnormal	0	1	1	0	
Anthropometric					
Height					
HAZ < -2SD	11/20 (55)	28/87(32.2)	36/117(32.5)	10/30(33)	0.050
Weight					
WAZ < -2SD	5/22 (22.7)	18/82(23.2)	18/109 (16.5)	4/27(14.8)	0.603
Head circumference					
HCZ < -2SD	2	0	2	1	

Stunted; height for age less than 2 standard deviation of mean

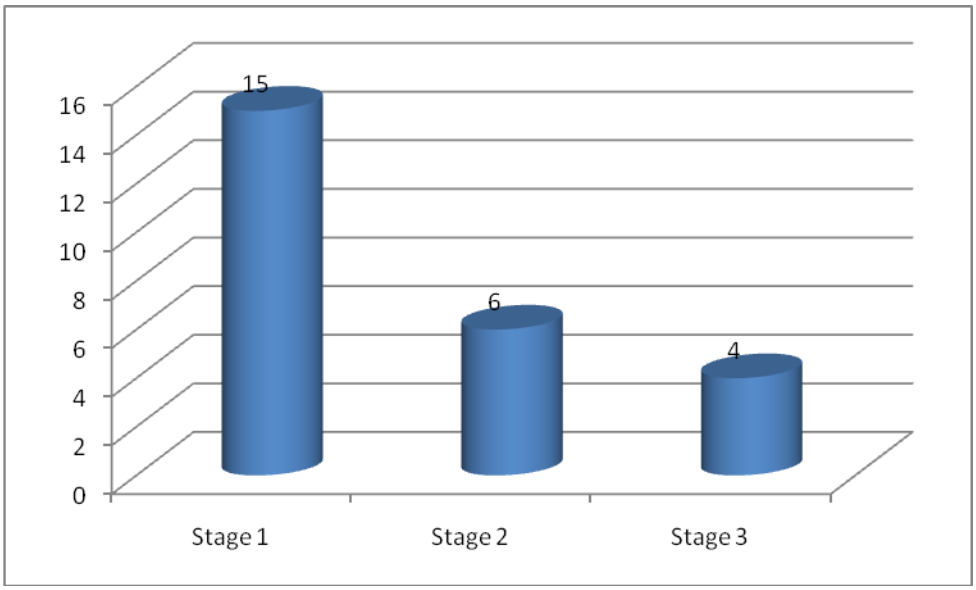
Underweight; weight for age less than 2 standard deviation of mean

Small head size; head size in centimeters less than 2 standard deviation of mean for age(50)

Paediatric HIV clinical staging

Fifteen of the twenty five HIV infected children were clinically asymptomatic (60%, [0.41-0.79] 95% confidence interval), while ten has symptoms of progressing disease (40%, [0.21-0.59] 95 confidence interval) and were referred for initiation of antiretroviral therapy at the tertiary hospital.

Figure 6 Clinical profile of 25 HIV infected children (M+C+) by WHO paediatric clinical staging.



Definition of WHO paediatric clinical staging of HIV / AIDS for children with confirmed HIV infection: Stage 1= asymptomatic; Stage 2= mild symptoms; stage 3=advanced symptoms; stage 4 =severe symptoms.

4.4 NEURODEVELOPMENT AT PRESCHOOL AGE

MSCA was completed by 278 children .The age corrected GCI scores for the total sample ranged from 64 to 136 (mean104; SD 13.9).

The means in GCI for the 4 different groups according to the child `s HIV status were all within the normal range compared to the standardization population (Table 7).

Contrary to our hypothesis, there were no significant group difference in the global cognitive function between the HIV infected and HIV uninfected children. However, some focal differences were evident in word knowledge, numerical memory, verbal fluency, counting and sorting and conceptual grouping subtests between the seroreveter and HIV negative groups. Children in the seroreverter group had lower scores compared to children in the HIV uninfected group. There was no significant difference in subtest means between the HIV infected and HIV uninfected. Child HIV clinical stage was not associated with lower GCI scores in this cohort.

Table 7 Age adjusted Subtest scores and GCI according to Kaufman short form MSCA, means , standard deviations, for children aged 3 ½ to 5 ½ years by child HIV status.

	HIV infected	**HIV uninfected**		**Unknown**	**P value**
	M+C+	**M+C-**	**M-C-**	**status**	
	N=25	N=94	N=126	N=33	
Scale/Subtest	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
GCI	100.6 (14.6)	103.7(14.2)	104.8 (14)	108.4 (13.21)	0.195
Total Weighted Scores	48.1 (12.5)	47.1 (12.7)	54.7 (13.5)	51.4 (13.5)	0.001 *
Puzzle Solving[27]	0.8 (0.8)	0.8 (1.1)	1.1 (1.2)	1.2 (1.1)	0.201
Word knowledge [29]	21.5 (4.5)	20.4 (5.3)	22.3 (4.1)	21.5 (3.9)	0.043 *
Numeric Memory [12]	5.6 (2.3)	5.7 (2.5)	6.7 (2.6)	6.5 (2.3)	0.029*
Verbal fluency [36]	14.1 (4.8)	13.1(4.7)	14.7 (4.6)	15.7 (5.8)	0.018*
Counting and Sorting[9]	4.3 (2.7)	4.1 (3.5)	5.7(2.78)	4.8 (2.8)	0.001*
Conceptual Grouping [12]	2.8 (2.0)	3.3(3.8)	4.3 (3.4)	4.8 (3.8)	0.026 *

[ ] denotes optimum weighted score for each subtest

* Post hoc test, HIV negative versus seroreverter

4.4.1 Growth and cognitive performance at preschool age

The results show a trend towards lower scores on GCI if growth is retarded. In this study children who were stunted had significantly lower means compared to those with normal height for age. This difference persisted when HIV status was considered.

Table 8 Means and standard deviations on Kaufmann short form MSCA for preschool children with and without growth restriction according to WHO growths charts

	General Cognitive Index			
	Number	Mean	± SD	P value
Height				
Stunted	85	99.7	13.0	<0.0001
Normal	170	107.7	13.5	
Weight				
Underweight	46	102	13.4	0.197
Normal Weight	196	105	14.3	
Head circumference				
Small head size	5	99.2	21.6	0.409
Normal head size	225	104	14.0	

Stunted; height for age less than 2 standard deviation of mean

Underweight; weight for age less than 2 standard deviation of mean

Small head size; head size in centimeters less than 2 standard deviation of mean for age(50).

4.4.2 Cognitive impairment

Based on the McCarthy Scales Children Abilities ` estimated General Cognitive Index, twenty 24 children (8.6 %) had a score less than 1 SD of the mean for age and were classified as cognitive impaired, 204(73%) had a normal cognitive score, and 50(18%) had a superior cognitive score.

Tables 9 and 10 show child cognitive impairment was significantly associated with, maternal younger age, low family income and living in rented lodgings. Children who were stunted or had a small head size for age, showed a trend towards being more cognitive impaired compared to children with normal growth.

Table 9 Assessment of cognitive impairment in children aged 3 ½ to 5 ½ years (n=24) and its association with child care giver socioeconomic characteristics.

Factor	Total Number N=278	Number with cognitive impairment N=24	P value	CRUDE		Adjusted Ω	
				OR	95 % CI	OR	95% CI
Maternal age ,years							
≤19	43	8	0.011	2.7	1.2- 5.9	21	2- 202
≥20	235	16		1			
Principal care giver							
Biological parents	243	22	0.75	1		-	-
Extended family	35	2		0.6	0.2- 2.5		
Education, maternal							
≤ 7 years	223	18	0.50	1.4	0.6- 3.4	-	-
>7 years	55	6		1			
Occupation, caregiver							
Not employed	112	13	0.2	1.7	0.7- 3.7	-	-
Employed	131	9		1			
Income							
< 30 USD/month	176	19	0.05	5.7	0.7- 41	-	-
>30 USD/ month	53	1		1			
Home ownership							
Own house	71	2	0.049	1	0.9- 15	-	-
Rent house	205	22		3.8			
Marital status							
Single	28	1	0.485	0.4	0.05- 2.7	-	-
Married	240	22		1			
Maternal HIV							
Infected	140	10	0.373	0.7	0.7- 3.1	-	-
Uninfected	38	14		1			

Cognitive impairment defined by GCI score < 1 standard deviation of mean

Ω Adjusted for family income, maternal HIV infection and marital status

Table 10 Assessment of cognitive impairment in children aged 3 ½ to 5 ½ years (n=24) and its association with child anthropometric outcomes, early neurodevelopment assessment HIV status, and sociodemographics characteristics.

Factor	Total Number N=278	Number with cognitive impairment N=24	P value	Crude ODDS	95% CI
Gender					
Boy	125	14	0.168	1.7	0.8-3.7
Girl	153	10		1	
Birth weight					
<2500	20	4	0.12	2.2	0.8-5.8
≥2500	220	20		1	
Nevirapine prophylaxis					
No	158	16	0.319	1.51	0.6-3.4
Yes	119	8		1	
Preschool attendance					
No	164	15	0.286	2.2	0.7-7.2
Yes	71	3		1	
Child HIV Status					
HIV infected	25	2	0.85	0.8	0.2-3.5
HIV seroreverter	94	7		0.8	0.3-2
HIV negative	126	12		1	0.3-3
Unknown status	33	3		0.9	
High risk in infancy					
No	265	23	1	1	0.1-6
Yes	13	1		0.9	
Arthropometric					
Height ,stunted	170	9	0.064	1	0.9-5.2
No	85	10		2.2	
Yes					
Weight ,underweight					
No	196	16	1	1	0.4-3
Yes	46	4		1.1	
Head circumference					
< 2SD	5	2	0.064	4.9	1.5-15
≥2SD	255	21		1	

4.5 Comparison of GCI mean scores based on BINS risk grouping

Only thirteen children classified as high risk according to BINS classification were evaluated at preschool age, 8 of whom were born to HIV infected mothers.

Table 11 Infants neurodevelopment outcomes according to BINS risk classification at baseline (3 to 15 months) for the 278 preschool children.

BINS risk	Maternal uninfected N (%)	Maternal infected N (%)	P value
3-4 months			
Low	74(94)	90(82.6)	0.036
Moderate	4(5.1)	17(15.6)	
High	0	2(1.8)	
7-10 months			
Low	44(58.7)	67(61.5)	0.811
Moderate	26(34.7)	37(33.9)	
High	5(6.7)	5(4.6)	
11-15 months			
Low	13(46.5)	9(52.9)	0.287
Moderate	15(53.6)	6(37.5)	
High	-	1(6.2)	

Preschool outcome on the GCI mean scores were compared with the three BINS risk groupings: Low risk, Moderate risk, and High risk in infancy (Table 8). Differences in mean scores between the BINS groups, were significant in the HIV infected group, only at the 3 -4 month assessment .Significant variation was in the Low and Moderate risk groups. The difference disappeared at late examinations (7- 10 months and 11 -15 moths).

Table12 Comparison of GCI mean scores at preschool age with BINS risk grouping in infancy by child HIV status.

BINS	Child (M+C+) GCI ,mean ± SD	P value		Child(M-C-) GCI,mean ± SD	P value
3-4 month					
Low risk	104(13.3)	0.031		104(14.1)	0.14
Moderate risk	100(6.9)			194(6.9)	
High risk	64			-	
7 -10 month					
Low risk	104(14.3)	0.219		110 (13.6)	0.161
Moderate risk	98(16.1)			103(15.4)	
High risk	92			102(14.0)	
11 -15 months					
Low	110 (14)	0.58		101(15.8)	0.88
Moderate	96 (22)			101(7.4)	
High	92			-	

Two level risk grouping (highrisk, lowrisk)

In the total cohort, children in the High risk at each group of the three ages had lower GCI scores than those in the Lowrisk group, though not statistically significant (Table13).

Table 13 Comparison of two level risk grouping BINS highrisk and lowrisk versus GCI mean scores in 278 preschool children

	General Cognitive Index	
	Mean (SD)	P value
3-4 month		
Lowrisk	104 (22)	0.113
Highrisk	93(14.1)	
7 -10 month		
Lowrisk	105 (14.5)	0.74
Highrisk	105 (14.3)	
11 -15 month		
Lowrisk	101(10.1)	0.671
Highrisk	99 (14.2)	

Children falling into the highrisk and lowrisk BINS status classification at 3-4, 7-10 and 11-15 months were compared with regards their preschool cognitive outcome (MSCA GCI >1SD below average was considered cognitive impaired). Cognitive impairment was frequent in the highrisk compared to the lowrisk group at preschool age, although not statistically significant. (Table 14).

Table 14 Comparison of the BINS highrisk and lowrisk grouping by Cognitive impairment in 24 preschool children.

	Total Number	Number with cognitive impairment	P value	ODDS	CI
3-4 month					
Highrisk	4	1	0.301	3.0	0.5-17.9
Lowrisk	184	15		1	
7 -10 month					
Highrisk	39	3	1.00	1.1	0.3-3.8
Lowrisk	145	10		1	
11 -15 month					
Highrisk	8	1	1.0	1.1	0.4-8.7
Lowrisk	36	4		1	

When the BINS summary (total of raw scores as a continuous scale) and risk status groping were correlated with the preschool age McCarthy Scales GCI, association were only found if the the child had been assessed at the 3-4 month time period and the child HIV infected. The correlation was in the moderate range (Table 15).

Table 15 Correlation between BINS total of raw scores as a continuous scale and risk status grouping versus GCI outcome in 278 preschool children.

	Child (M+C+) Correlation coefficient			Child (M-C-) Correlation coefficient
BINS 3-4			**BINS 3- 4**	
Score	0.62[b]		Score	0.21
Risk	-0.54[a]		Risk	-0.17
BINS 7-10			**BINS 7-10**	
Score	0.18		Score	0.19
Risk	-0.24		Risk	-0.22
BINS 11 -15			**BINS 11-15**	
Score	-0.52		Score	-0.04
Risk	0.29		Risk	0.03

[a]P<0.05

[b]P<0.01

CHAPTER.5 DISCUSSION

This study provides data on Zimbabwean preschool aged, HIV type 1 vertically infected children followed from birth for neurodevelopment and whose mothers participated in a national PMTCT program. The primary finding was that preschool aged vertically infected HIV children showed normal global cognitive function on Kaufmann short form of MSCA. This contrast with our hypothesis that there would be significant group difference in the global cognitive function between the HIV infected and HIV uninfected children with HIV infected performing lower GCI scores. Studies conducted early in the HIV epidemic described children characterized by lower scores on global function related to the degree of encephalopathy in infancy(51-53).

Our findings confirms results from previous research(7;8;39;54;55). A study investigating the effect of HIV on cognitive abilities showed that children without AIDS defining illness performed as well as uninfected children. However the children in that study were also receiving anti retroviral treatment (54), unlike in this series where HIV infected children were predominantly asymptomatic and not on treatment.

Significant focal differences were evident in the subtests of the MSCA, in particular word knowledge, numerical memory, verbal fluency, counting and sorting and conceptual grouping between the seroreveter and HIV negative children, but no difference between the infected and uninfected children.These subtests represent verbal, perceptual and quantitative performance on the full scale McCarthy. Specific cognitive impairments associated with HIV infection have been identified in previous research. These include visuospatial , motor integration, language impairment, sequential processing and adaptive functioning(56). Boivin in former Zaire, conducted research on asymptomatic HIV infected children and had with similar findings to our study. In that series their findings indicated lower scores in sequential processing, spatial memory and auditory and visual recall(12). The poorer performance by seroreverters in this study on the subtests of MSCA may be a reflection of the harsh home environment defined by having close family members, particularly the mother succumb to HIV related illness.

Partial explanation for the pathophysiolgy on the relation between HIV and cognitive function has been provided by neuro-imaging research. Neuro-imaging studies conducted on HIV infected children already on highly active antiretroviral therapy (HAART) have documented changes in the immature central nervous system, in particular the pyramidal tract, basal ganglia, frontal and prefrontal areas of the brain (40;57). Myelinopathy resulting from HIV infection has been implicated in cognitive, visuomotor, language and behavioral delays which become more prominent over time (58). Since no neuro-imaging was assessed in any of the children in this cohort, we were unable to determine whether there is structural brain changes associated with cognitive deficits.

Neurological compromise associated with paediatric HIV infection is hypothesized to be related to the direct effects of the virus on the neural tissues. The resultant CNS dysfunction manifests as HIV related encephalopathy of the progressive or static type.(55;58). Progressive encephalopathy, the worse type, is associated with impaired brain growth, loss of developmental milestones, spasticity and behavioral disorders. In static encephalopathy, there is no insidious deterioration of attained milestones; however acquisition of new skills occurs at a much slower rate for the child `s age. Cognitive impairment in children with static encephalopathy has been reported to range from low to average and high. Static encephalopathy as opposed to progressive encephalopathy has been observed in older children(55). We did not observe significant differences in motor deficits in this study. It is likely that the more affected infants with progressive encephalopathy from our cohort probably did not survive into childhood.

Our cohort represents children who survived to preschool age in the absence of highly active antiretroviral drugs. Various factors have been put forward to explain the survival selection including maternal host factors, infant host factors, viral phenotype, viral load CD4 counts, timing of transmission and disease stage. Infants with intrauterine infection were documented to have rapid disease progressive than children with intra or post partum infection(10;59). Infection by a less virulent HIV type 2 is another possibility. Although no studies have documented sole HIV type 2 infection in the Zimbabwean population, between 18 to 25% of HIV infected adults had dual infection with HIV 1 and

HIV 2 in a surveys conducted in Zimbabwe (60). There is no data on the association of a dual infection on child cognitive function. The child survivors in this study may reflect those children with the less aggressive disease.

We acknowledge that the Kaufmann short form of MSCA was modified and adopted for this study at the expense of sensitivity to identify children with cognitive impairment. There is no gold standard cognitive assessment tool standardized for Shona speaking Zimbabwean children. The computed GCI from the subtests of the short form of MSCA may not be the most sensitive and specific test to identify subtle differences in the global cognitive performance of preschool children. It is possible that the research tool was low in sensitivity to detect rare cognitive impairment in this cohort.

The number of surviving HIV infected children in this cohort was relatively small (n=25). This may have resulted in the study being low powered to detect very small differences between the group means. Other factors that explain absence of variability in cognitive performance in this cohort may be related partly to the medical, educational, and social support the children and their families received through their participation in this study.

In this study, 24 children (8.6%) were identified as cognitive impaired: 8.3% among the HIV positive children; 7.4 % among the seroreverter; 9.5% among the HIV negative and 9.1% among those with unknown status. Family income of less than 30 US dollars per month, a teenage mother and renting a house was associated with cognitive impairment in this cohort. Among the same children, earlier neurodevelopment assessment using BINS has estimated neurodevelopment impairment during infancy at 5.2%. The prevalence of cognitive impairment in this cohort is high. Previous studies in have documented cognitive impairment ranging from 6.2 to 40% (9;13;51;53).This discrepancy in reported prevalence is due to the variability in methodology between the different studies and differences in the study populations. The prevalence of neurodevelopment impairment at age 2 year was 9% in a study conducted in Rwanda and this compares with our findings(61). In another research conducted in Tanzania, among a low HIV prevalence population, the prevalence of neurodevelopment impairment in infants was 6.2%. In both

studies however neurodevelopment impairment was more frequent in the HIV positive infants compared to the HIV negative. The relatively high prevalence among the HIV uninfected in our cohort might have been confounded by survival bias were the infected children with severe disease probable died. It is plausible that there are other factors such as socioeconomic status, nutrition or home environment that are influencing cognitive abilities at preschool age even in the HIV uninfected children.

Proxy measures for socioeconomic status (house ownership and income less than 30 US dollars per month) in this study were significantly associated with cognitive impairment. Research has implicated a relationship between socioeconomic status and cognitive ability in children. A longitudinal study conducted in Ecuador investigating the effect of iron deficiency on cognitive function found an association between low socioeconomic status and cognitive scores(62). A study by Coscia et al established that the quality of the home environment mediated the relationship between socioeconomic status and child cognitive function(22) while a study conducted in Kenya among children under 3 years living in poverty reported anthropometric measures such as height and weight as mediators of the relationship between socioeconomic status and psychomotor development(63).
Regrettable we did not assess the effect of home environment on cognitive function in this study due to time and financial constraints. Based on a commonly used scale The Home Measurement of the Environment Inventory(64), it is possible to observe and evaluate home organization, play materials, parental involvement and variety of stimulation each child receives. These provide valuable information on provision of cognitive stimulation or education in the home. Only 71 (25.5%) of the children in this cohort were attending formal preschool despite early child learning services being offered for free at public schools in Zimbabwe.

Families living with extended family members are common in African populations. In addition to the social support provided by such structures, children reared in such adult - rich environments appear to get more cognitive stimulation and have higher scores on intelligence test compared to children living in homes with few adults. In a study to

predict cognitive, adaptive and behavioral function in preschool children with HIV, a low child to adult ratio was predictive of better scores on cognitive test(65).The child adult ratio was not examined in this study.

HIV infected children in this cohort had more skin disorders and generalized lymphadenopathy compared to their uninfected peers, probably as reflection of their compromised immune function. Of concern more than 50 %(155) of all the children in this cohort reported a history of serious illness in the preceding 3 months. This may indicate that the children in this population are still at risk of determinants of child morbidity and mortality experienced by children from low socioeconomic background and may confound the relationship between HIV and cognitive function.

Forty-six children (16%) in this cohort were underweight. World Health Organisation, in 1999 estimated the prevalence of underweight in Zimbabwean under 5 year olds at 11.2%. In a study conducted in Zimbabwe investigating seasonal variability of the prevalence of underweight within a clinic based growth monitoring programme, the prevalence of underweight among children less than 5 years ranged 10.7 to 11.2. Our prevalence of underweight is higher than the estimated national figure. Possible explanations for the discrepancy is the current worsening in country`s economic environment resulting in less family resources being allocated for nutritional needs. Most families are either infected or affected by HIV infection, which may result in funds being channeled towards the caring of the sick parents or guardians at the expense of feeding the family. In this study underweight was not associated with cognitive impairment, partly be due to the small sample size which made the study weakly powered to detect small differences between groups. Studies in other developing countries have different findings(63;66-68) where being underweight was related to lower cognitive scores.

In agreement with our earlier observations(17), the mortality rate in this cohort was higher among HIV infected children compared to the uninfected .Other studies have documented similar findings(59) with crude mortality ranging 10 to 40 % (53;69;70).

The third objective of this study was to compare cognitive function at preschool age with neurodevelopment outcome according to BINS risk grouping: High, Moderate and Low. In this cohort, we observed a trend for high risk classification being related to lower GCI scores at preschool age. Similar results were documented in a study by Aylward(71). In the HIV infected children, the differences in GCI means between the 3 BINS risk groups were statistical significant if the infants were examined between 3 to 4 months of age compared to the ages 7 to 10 months or 11 to 15 months. The short form MSCA seemed to fit according to BINS classification, particularly for the HIV infected children. The aim of neurodevelopment screening in infancy is to distinguish infants with current developmental problems and predict those who at risk for neurodevelopment impairment later. To this end, we have identified the period 3 to 4 months as a possible window of opportunity to initiate neurodevelopment screening for children exposed to perinatal HIV infection and coming from predominately breast feeding population.

We could not prove if BINS risk classification in infancy predicts cognitive impairment at the ages 3 ½ to 5 ½ years in this cohort although children in the High risk group in infancy manifested more cognitive impairment at preschool age. Adaptation we made to the Kaufmann short form of MSCA might have influenced the reliability of the scale underestimating the strength of the relationship between the BINS and MSCA tests. Due to the relatively small sample size and few children with high risk in infancy who took the MSCA later at preschool age, this study is weakly powered to detect very small group differences between early and later neurodevelopment assessments. Interpretation of our findings on the predictability of the BINS test for later neurodevelopment should be viewed with caution due survival bias.

The current study has proved that it is possible to follow up child neurodevelopmental outcomes in resource limited setting, utilizing simple screening tools. Although asymptomatic surviving HIV infected children have normal cognitive function compared to their uninfected peers, they are more susceptible to other childhood infections and nutritional deficiencies. The prevalence of cognitive impairment in this cohort was high

underscoring the need to address those factors that negatively influence child development if the socio-economic potential of these children is to be realized.

5.1 LIMITATIONS OF THE STUDY

1) Moderate proportions of children were lost to follow up and this might result in biased estimates of mean GCI. Since the two groups (participants and those lost to follow up) were similar in the proportion of children born to HIV infected mothers, it is unlikely that this would lead to a strong bias in the means.
2) Follow up of the children was limited by the dispersion of town communities that took place prior to this follow up study. Families perceived to be living in urban slums of Chitungwiza and Epworth were forcible evicted to the rural areas and could not be tracked due to lack of forwarding addresses.
3) Children biomedical profiles such as CD counts 4 and viral loads were not assessed, due to financial constraints. For the HIV infected children these provide an indication on the disease stage and can be used in the monitoring of clinical progress. Almost one tenth of the children born to HIV infected mother did not have confirmatory laboratory test. This decreased the number of children with known status and possible underestimated the association between HIV and cognitive function.
4) The timing of child HIV infection was not examined in this study. This might provide answers to the variation in the pattern of cognitive function at preschool age.
5) Further investigation of the components of cognitive function was not possible in this study because MSCA does not include a measure for home environment, interaction between caregiver and child or behavioral disorders.
6) The Kaufmann short form of MSCA was developed and validated in the United States and there is no normative data for MSCA in others societies. Adaptation we made to the Kausman short form of MSCA might have influenced the reliability of the test score which might have underestimated the strength of the relationship between GCI and HIV infection .It is possible that some cultural bias in the McCarthy remained.
7) Serial longitudinal measurements on cognitive function using of the full scale MSCA was not conducted for this study. Based on the Kaufmann short form of

MSCA the index score do not allow differentiation between delay in achieving new milestones and losing previously acquired milestones

5.2 CONCLUSION

The current study has proved that it is possible to screen preschool children for cognitive impairment in resource limited settings utilizing simple screening tools such as Kaufmann short form of MSCA.HIV infected children who survive to preschool age did not manifest lower cognitive scores than established child norms. The prevalence of cognitive impairment in this study was 8.6% .Chronic malnutrition as indexed by stunting was associated with poor cognitive function at preschool age. BINS if performed in the first 6 months of life, was predictive of later cognitive performance particularly in HIV infected children. Therefore comprehensive interventions addressing early diagnosis and treatment for both childhood HIV and malnutrition could result in significant improvement in cognitive function and later academic achievement.

5.3 RECOMMENDATIONS

The following recommendations are made to Chitungwiza and Harare Municipal Council health departments concerning HIV and child development.

1. The expanded program of prevention of parent to child transmission of HIV should incorporate growth and neurodevelopmental monitoring of children using standardized instruments which are appropriate for the period birth to adolescence. Children who falter on growth or developmental milestones are identified early and referred for intervention and treatment.
2. A health education policy should be developed that promotes early child stimulation by allocating resources and providing information to parents on how they can provide cognitive stimulation to their children at home.
3. The counseling of pregnant mothers who participate for PMTCT services should emphasize on the importance of knowing the HIV status of the child so that necessary monitoring for growth and neurodevelopment is started early.

Further research recommendations are related to the limitation in this study:

1. To validate the MSCA in Zimbabwe using another cognitive assessment test e.g. Kaufmann Assessment Battery for Children so that it can be used in diagnosis preschool and school children with cognitive impairment
2. Determine the predictors of cognitive impairment in HIV negative preschool and school children.
3. Determine factors that promote normal cognitive function in vertically infected children living in deprived condition .This information would be incorporated in the planning of targeted interventions in the care of HIV infected children.
4. Evaluate the role of malnutrition and micronutrients deficiency e.g. iron on cognitive function in preschool children.
5. Develop an extensive cultural appropriate assessment tool measuring motor, language, cognition and socio-emotional development.

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APPENDIX 1 Study information and consent form

STUDY ID NO: ☐

Title of Research: Neurodevelopment outcomes at preschool age: A 5 year follows up study of a cohort of children born to mothers participating in the PMTCT program in Harare, Zimbabwe.

INTRODUCTION:

You are invited to take part in a study organized by the University of Oslo in collaboration with the University Of Zimbabwe College Of Health Sciences. This is a follow up on the study that sought to determine if sexually transmitted infections increased the chance of transmission of HIV to the child and also the effect of HIV on neurodevelopment in infancy. Studies conducted in the developing countries and East Africa suggests that children's intelligence is negatively affected by HIV. Screening and early identification of developmental delay will result in referral for appropriate diagnosis and therapy. This study aims to describe cognitive performance , at preschool age, of children born to HIV infected and uninfected mothers and identify factors that may predict delay development .In order to track development comparison will be made with earlier performance as screened by the BINS.

If you agree to take part, you will be asked to sign or fingerprint this consent form in front of a witness.

Please note that:

1) Your participation in this research is entirely free
2) You may decide not to take part or to withdraw from the study at any time without losing the benefits of standard medical care from this clinic .

Procedures:

On the day that you join the study and sign the consent form .you will be asked questions about your child `s life and health. The child will be examined by a doctor for growth and development.

Exclusion criteria:

Although you may be willing to take part in the study the doctor may decide that your child is not a suitable candidate if he or she was not assessed for neurodevelopment in infancy.

Costs:

Neither you nor your child will pay for the examinations test or treatments that you will receive as a study participant. If your child needs further assessment or treatment, referrals will be organized for you at no cost to you.

STUDY ID NO: ☐

The study information has been read to me and I understand the aim of the study. By signing/placing my thumbprint on this form I agree to participate in the study of my own free will.

....

Signature of participants Date Interviewer`s signature

Person obtaining the consent

I testify that, to the best of my ability read and explained the information concerning the research study in non technical terms to (Name of participant).....

I encourage him/he to ask questions and answered them to the best of my ability.

....

Signature Date

Participant's address:.....

.....

APPENDIX 11 **Child interview guide**

NAME OF CLINIC_____

AGE AT VISIT (months)……

Date_____ Study Identification number: ___

1. Child s date of birth / __/_ / sex 1.boy 2. girl
2. How are you related to this child……
3. Who does the main care for this child

1. mother 2. baby sitter 3. siblings 4. others

4. Care taker's age in years……

5. Care taker's gender…… 1.Male 2.Female

6.Care taker 's level of education ……. .0 . No formal education 1. Primary education

2. Secondary education 3. Tertiary education

7. Care taker 's Occupation 0.Not employed 1.Formally employed 2. Self employed

8. Is Father 1. Alive… 2. Dead… If dead , cause of death ……year of death...

9. Is Mother 1 . Alive 2.Dead ….If dead cause of death …….year of death …

10. In the past 3 months has the child been ill from one of these ailments

	No	Yes
11-Diarrhoea	0	1
12-Vomiting	0	1
13-Fever	0	1
14-cough	0	1
15 Ear discharge	0	1

16.Any other problems, specify ……

17. How many times did you feed the child in the last 24 hrs …….

18. Has child completed primary immunization course 0.No 1.Yes

PHYSICAL EXAMINATION

19Height in cm ---

20. Weight in kg……

21. Weights/ Height-----

22. Head circumference------

	No	yes
23. Underweight	0	1
24 . Stunted	0	1
25. General condition	0 Normal	1 Abnormal
26. Lymphadenopathy	0	1
27. Skin disorder	0	1

28 If abnormal specify…….. …….

29. Mouth condition 0 1

30 If abnormal specify……..

31. Cardio vascular System 0 Normal 1.Abnormal

If abnormal specify findings……..

32.Respiratory system 0 Normal 1.Abnormal

If abnormal specify findings……

33. Gastro-intestinal Tract 0 Normal 1.Abnormal

If abnormal specify findings……

34.Neurological Status 0 Normal 1.Abnormal

35 abnormal specify findings……..

36 Mental status	0	1
37 Cranial nerves	0	1
38 Sensation	0	1
39 Muscle tone	0	1
40Reflexes	0	1
41Coordination	0	1

42. WHO Paediatric Clinical stage : 1 .2. 3. 4.

43 MSCA assessment Mean GCI score…….

McCARTHY SCALES OF CHILDREN'S ABILITIES

Record Form

NAME _____ AGE _____ SEX _____

HOME ADDRESS _____

NAMES OF PARENTS OR GUARDIAN _____

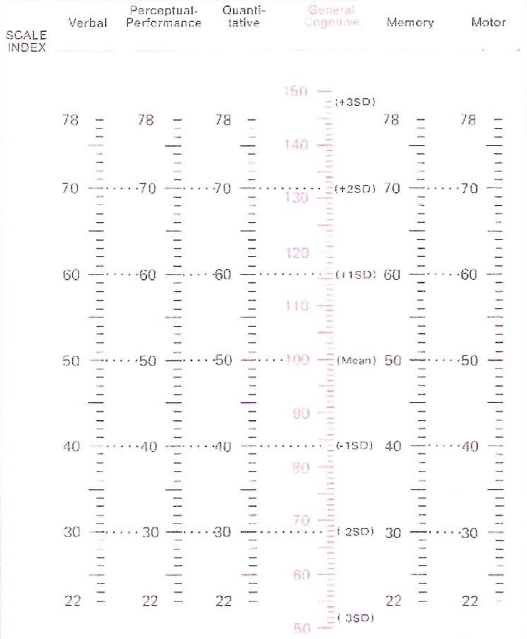
SCHOOL _____ GRADE _____

PLACE OF TESTING _____ TESTED BY _____

REFERRED BY _____

MSCA PROFILE

Enter the 6 Scale Indexes on the appropriate lines below. Then circle the mark representing the Index for each Scale. Draw a line connecting the circles. Note that the values for GC are different from those for the other Scales.



	Year	Month	Day
Date Tested			
Date of Birth			
Age			

COMPOSITE RAW SCORES AND SCALE INDEXES

Enter the composite raw scores from the back cover. *Obtain the composite raw score for GC by adding V + P + Q.* Determine the corresponding Scale Indexes from Table 16. (See page 151 of manual for detailed directions.)

Scale	Composite Raw Score	Scale Index
Verbal (V)		
Perceptual-Performance (P)		
Quantitative (Q)		
General Cognitive: Add composite raw scores V + P + Q		GCI
Memory (Mem)		
Motor (Mot)		

LATERALITY

(Enter information from Laterality Summary on page 5.)

Hand _____

Eye _____

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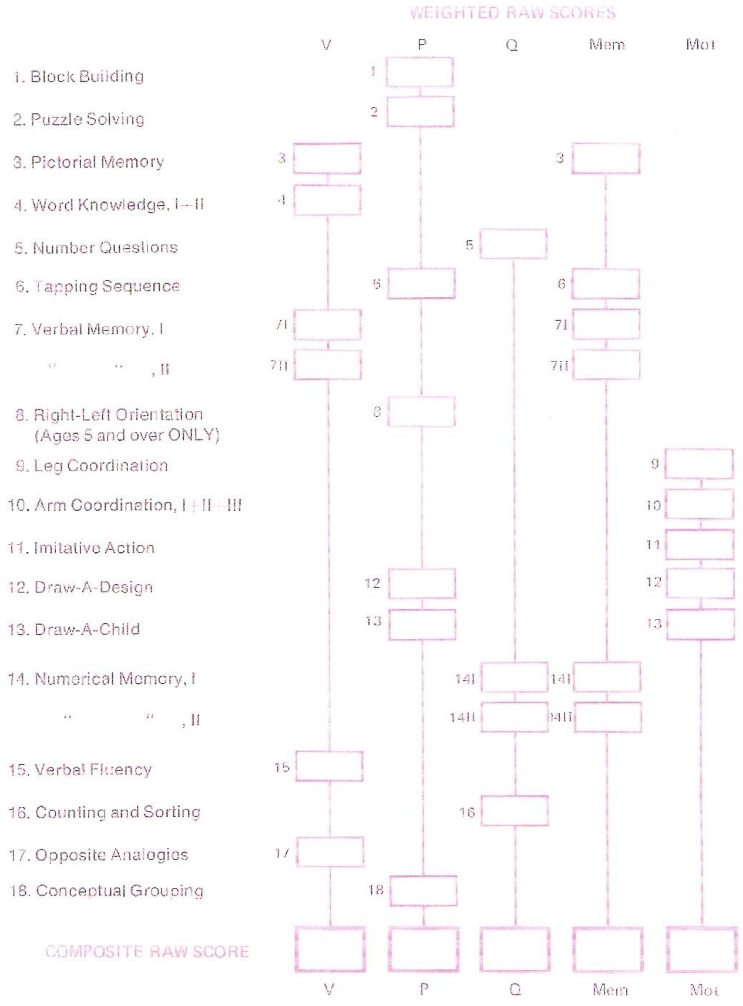
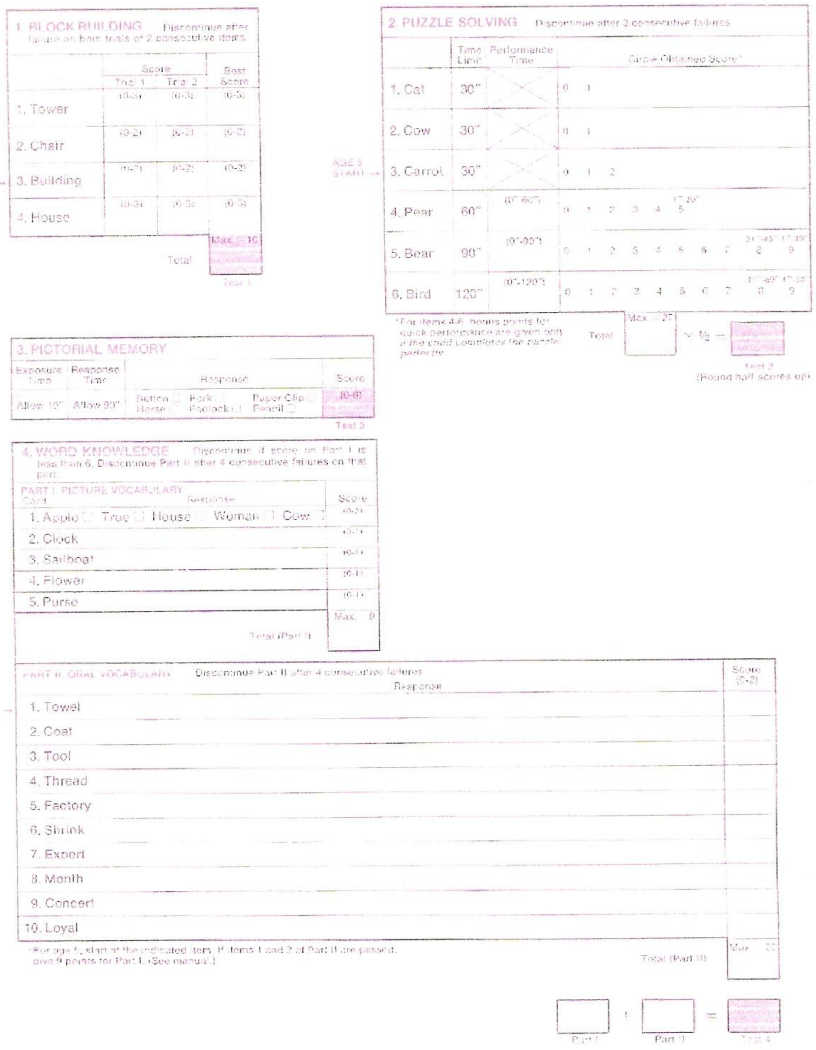
COMPUTATION OF COMPOSITE RAW SCORES

1. Enter the *weighted raw scores* which are in the shaded boxes on pages 2-7 of the record form. For each test, enter the score in the box/test bearing that test's number. (For example, the score for Test 3 is entered in 2 boxes.)
2. Sum the scores in each of the 5 columns. Enter the totals in the *composite raw score* boxes at the foot of the page.
3. Transfer the *composite raw scores* to the front cover. (Open the booklet and turn it over so that the front and back covers are side by side.) Enter the scores in the Composite Raw Score column in the box labeled "Composite Raw Scores and Scale Indexes."

(For more detailed directions on the completion of the record form, see Chapter 7 of manual.)





1. BLOCK BUILDING Discontinue after failure on both trials of 2 consecutive items.

	Score Trial 1	Score Trial 2	Best Score
1. Tower	(0-2)	(0-3)	(0-3)
2. Chair	(0-2)	(0-2)	(0-2)
3. Building	(0-2)	(0-2)	(0-2)
4. House	(0-3)	(0-3)	(0-3)

Max. = 10

Total

Test 1

Age 5 START →

2. PUZZLE SOLVING Discontinue after 3 consecutive failures.

	Time Limit	Performance Time	Circle Obtained Score*
1. Cat	30"		0 1
2. Cow	30"		0 1
3. Carrot	30"		0 1 2
4. Pear	60"	(0"-60")	0 1 2 3 4 5 (7"-20")
5. Bear	90"	(0"-90")	0 1 2 3 4 5 6 7 (21"-45") (46"-1'-20") 8 9
6. Bird	120"	(0"-120")	0 1 2 3 4 5 6 7 (21"-60") (1'-01"-2'-00") 8 9

*For items 4-6, bonus points for quick performance are given (left) if the child completes the puzzle perfectly.

Total Max. = 20 ½ =

Test 2 (Round half scores up)

3. PICTORIAL MEMORY

Exposure Time	Response Time	Response	Score
Allow 10"	Allow 90"	Button ☐ Fork ☐ Paper Clip ☐ Horse ☐ Peacock ☐ Pencil ☐	(0-6)

Test 3

4. WORD KNOWLEDGE Discontinue if score on Part I is less than 6. Discontinue Part II after 4 consecutive failures on that part.

PART I: PICTURE VOCABULARY

Card	Response	Score
1. Apple	☐ True ☐ House ☐ Woman ☐ Cow ☐	(0-2)
2. Clock		(0-1)
3. Sailboat		(0-1)
4. Flower		(0-1)
5. Purse		(0-1)

Max. = 6

Total (Part I)

PART II: ORAL VOCABULARY Discontinue Part II after 4 consecutive failures.

Response	Score (0-2)
1. Towel	
2. Coat	
3. Tool	
4. Thread	
5. Factory	
6. Shrink	
7. Expert	
8. Month	
9. Concert	
10. Loyal	

*For age 5, start at the indicated item. If items 1 and 2 of Part II are passed, give 9 points for Part I. (See manual.)

Total (Part II) Max. = 20

+ =

Part I Part II Total 4

2

14. NUMERICAL MEMORY

Discontinue Part I after failure on *both* trials of any item. If child earns 3 or more points on Part I, give Part II and discontinue after failure on *both* trials of any item.

PART I: FORWARD SERIES

	Trial 1	Trial 2	Score (0-2)
1.	5 - 8	4 - 9	
2.	6 - 9 - 2	5 - 8 - 3	
3.	3 - 8 - 1 - 4	6 - 1 - 8 - 5	
4.	4 - 1 - 6 - 9 - 2	9 - 4 - 1 - 8 - 3	
5.	5 - 2 - 9 - 6 - 1 - 4	8 - 5 - 2 - 9 - 4 - 6	
6.	8 - 6 - 3 - 5 - 2 - 9 - 1	5 - 3 - 8 - 2 - 1 - 9 - 6	

Total (Part I): Max. = 12

Test 14, Part I

PART II: BACKWARD SERIES

	Trial 1	Trial 2	Score (0-2)
1.	9 - 6	4 - 1	
2.	1 - 8 - 3	2 - 5 - 8	
3.	5 - 2 - 4 - 9	6 - 1 - 8 - 3	
4.	1 - 6 - 3 - 8 - 5	6 - 9 - 5 - 2 - 8	
5.	4 - 9 - 6 - 2 - 1 - 5	3 - 8 - 1 - 6 - 2 - 9	

Total (Part II): Max. = 10 × 2 =

Test 14, Part II

15. VERBAL FLUENCY

	Time Limit	Record Responses Verbatim	Score (0-6)
1. Things to eat Examples: bread, potatoes	20"		
2. Animals Examples: cat, bear	20"		
3. Things to wear Example: shoes	20"		
4. Things to ride Example: bus	20"		

Total: Max. = 36

Test 15

16. COUNTING AND SORTING

If child passed 9 or more items on Test 5, give full credit on Test 16. Otherwise, administer Test 16 and discontinue after 4 consecutive failures.

	Score (0-1)
1. Takes 2 blocks	
2. Takes 3 more blocks	
3. Answer: 5	
4. Puts 2 blocks on each card	
5. Answer: 2	
6. Puts 5 blocks on each card	
7. Answer: 5	
8. Point: 2nd block from left	
9. Point: 4th block from right	

Total: Max. = 9

Test 16

Telephone: 791792/791193/792747
Telefax: (263) - 4 - 790715
E-mail: mrcz@mrczimshared.co.zw

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

MRCZ APPROVAL LETTER

Ref: MRCZ/A/1399

Date : 28 June, 2007.

Gwendoline Kandawasvika
University of Zimbabwe
Department of Paediatrics
Box A178 Avondale
Harare

RE: Neuro-Developmental Outcomes At Preschool Age: A 5 Year Follow Up Study Of Children Born To Mothers Participating In A PMTCT Programme In Harare, Zimbabwe.

Thank you for the above titled proposal that you submitted to the Medical Research Council of Zimbabwe (MRCZ) for review. Please be advised that the Medical Research Council of Zimbabwe has reviewed and approved your application to conduct the above titled study. The approval is based on the following:

(a) Study protocol
(b) English and Shona Informed Consent Forms

- APPROVAL NUMBER :MRCZ/A/1399
  The above details should be used on all correspondences, consent forms and documents as appropriate.
- APPROVAL DATE : 28 June, 2007
- EXPIRATION DATE : 27 June, 2008
- MRCZ MEETING DATE : 28 June, 2007
- TYPE OF MEETING : FULL BOARD
  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 one month 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.
- 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.
- QUESTIONS: Please contact the MRCZ on Telephone No. (04) 791792, 791193 or by e-mail at mrcz@mrczimshared.co.zw.
- Other:
  Please be reminded to send in copies of your final research results for our records as well as for the Health Research Database.

Kind regards.
Mrs S. Munyati

Executive Secretary
FOR MEDICAL RESEARCH COUNCIL OF ZIMBABWE

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