Child neurodevelopment in a resource constrained setting: a 8 year follow up of children born in a high HIV prevalence community in Zimbabwe.

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Dedication

This work is dedicated to the memory of my late mother Mrs Sophie Musiyazwiriyo

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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. The University of Zimbabwe College of Health Sciences department of Paediatrics and child health 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 main supervisor Professor Babill Stray-Pedersen who made me believe in myself when the chips were down; provided shelter in her home and gave unlimited support throughout the years. Your wisdom and gentle words of encouragement in research methods has been a pillar of strength. I would also like to thank my local supervisor Professor Kusum Nathoo for critically appraising my research progress, providing worthy criticism on the third paper and the thesis manuscript. I will cherish the high standards you set as a researcher and am privileged to have worked under your guidance. I am also grateful to the late Dr Isidore Pazvakavambwa who introduced me to the field of research. Your unique mentorship is sadly missed. My sincere gratitude go to the Letten Research Centre Harare members namely Professor Chirenje, Professor S Rusakaniko, Dr M Munjoma, Dr F Gumbo, Dr P Kuona, Dr K Duri, Miss P Chandiwana, Miss M Masanganise, Mr P Mapingure, Mr Phenius Mbambo and the late Dr E Kurewa, for providing brutal honesty and encouragement in appraising the study progress. 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 locate participants. I also wish to thank Mr Alfred Chingono and Mrs Leslie Gregory, clinical psychologists for providing training on the adaptation of the research tool to the research team despite their busy clinic schedule in public service. 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 Tafadzwa and young children, Munashe, Makomborero and Ruvarashe for their support and tolerance during my absence from home. Your trust made it all worthwhile.

Thesis summary

Background: Globally, an estimated 780 million children younger than 15 years fail to reach their developmental potential due to preventable causes including HIV infection. Of the 3.4 million children living with HIV infection worldwide, 91% live in sub -Saharan Africa, but many questions remain unanswered on their neurodevelopmental function.

Aims: To document neurodevelopmental outcomes among Zimbabwean children infected, exposed uninfected and uninfected unexposed with HIV, at two different ages: in infancy and school age respectively. Secondly, to validate the McCarthy Scales of Children`s Abilities (MSCA) tool among Shona speaking 6-8 year olds in Zimbabwe.

Methods and Material: The main study was part of the "Better Health for the African Mother and Child" (BHAMC) cohort study and was conducted at 3 primary health centers in the outskirts of Harare, Zimbabwe. From 2002 to 2004, a total of 1050 pregnant women at 36 weeks of gestation with a documented HIV result, were enrolled from the national prevention of mother to child transmission of HIV (PMTCT) programme: 479 HIV infected women and 571 uninfected. The women`s baseline socioeconomic demographics at enrolment were collected. The infants` birth anthropometric measurements, feeding options and past medical history were obtained from the mothers and physical examination performed. Neurodevelopmental assessments were conducted cross sectional in infancy and again at school age using the Bayley Infant Neurodevelopmental Screener (BINS) and the culturally modified MSCA respectively The BINS` level of risk for neurodevelopmental impairment (NDI) was categorized into three risk groups: low (normal) versus moderate and high (abnormal), whilst cognitive impairment was defined as a score -2SD below the mean for MSCA for the standardization American population. For validation of the MSCA, the test was compared against the local gold standard (the educational psychologist`s assessment) at the cut off points of -2SD, -1.5 and -1SD below the mean. Ethical approved for the study was granted both in Zimbabwe and Norway.

Results: From the BHAMC cohort, 598 infants were assessed between the ages of 3 to 12 months .The overall prevalence of high risk for NDI at any time was 9.4% (95% CI 7.1–11.1%): 9.2% in males versus 9.6% in females. The high risk of NDI was higher among infants infected with HIV at 3 months (p value < 0.001) compared to 9 months of age. At univariate analysis, the high-risk category for NDI included twice as many infants infected with HIV as uninfected infants (odds ratio [OR] 2.1; 95% CI 1.0-4.3). After adjusting for

other risk factors, small head circumference for age and lack of family financial subsistence remained risk factors for NDI with an OR of 2.2 (1– 5) and 2.6 (1.0–6.4) respectively.
In validating the MSCA, a separate 101 children from the community were assessed, whose median (range) age was 97 (77-102) months and of whom 60 were female. Sensitivity rates for the MSCA were low (50% & 17 %) at -2SD and -1SD respectively compared to the specificity rates which were high (95% & 100 %) at -2SD and -1SD. The number of children identified with cognitive impairment using -2SD, -1.5SD and -1SD below the mean for MSCA as a cut-off point were 3 (3%), 7 (7%) and 13 (13%) respectively while the psychologist identified 18 (18%) children overall. The rural children tended to score significantly lower marks compared to their peers from urban areas, mean (SD) 98 (15) and 107 (15) respectively, p=0.006.

At school age, a total of 306 children from the BHAMC cohort were available and agreed to participate. Of these, 32 were HIV infected, 121 HIV exposed uninfected and 153 HIV unexposed uninfected. Overall, 49 children (16%) (95% CI 12-20 %) had cognitive impairment. Children with HIV infection scored significantly lower than the HIV unexposed uninfected children in perceptual performance domain, p value = 0.028.There was no difference in the prevalence of cognitive impairment by child HIV status. Cognitive impairment was significantly associated with parental loss, caregiver unemployment status, a history of fever three months prior to the study, and presence of moderate to severe under nutrition in univariate analysis. In the multivariate logistic regression model, caregiver unemployment status remained a risk factor for cognitive impairment after adjusting for other factors, with an odd ratio of 2.1 (95% CI 1.03-3.36) for all children. The predictive utility of the BINS high risk status in infancy for cognitive impairment at 6-8 years was assessed in only 264 children from the original cohort. The BINS high risk category had a positive predictive value of 10 % (95% CI 9-29%) and a negative predictive value 85 (95% CI 80-89%).

Conclusion: Lower socioeconomic status was associated with a high risk for NDI in infancy and cognitive impairment at 6 to 8 year of age in this study population. An early high risk classification for NDI using BINS was not associated with increased probability of later cognitive impairment. In infancy, children with HIV infection showed greater risk for NDI by age 3 months. In resource limited settings, strategies aimed at poverty alleviation and prevention of malnutrition should complement early HIV infant diagnosis and treatment of all children under 5 years old regardless of CD4 counts in order to optimize neurocognitive potential.

List of abbreviation

AIDS	Acquired Immunodeficiency Syndrome
AZT	Zidovudine
BF	Breastfeeding
BINS	Bayley Infant Neurodevelopmental Screener
BSID	Bayley Scales of Infant Development
CNS	Central Nervous System
cART	Combination Antiretroviral Therapy
ELISA	Enzyme Linked Immunosorbent Assay
GCI	General Cognitive Index
HAZ	Height for age Z score
HIV	Human Immunodeficiency Virus
MDGS	Millennium Development Goals
MSCA	McCarthy Scales of Children`s Abilities
NDI	Neurodevelopmental Impairment
NVP	Nevirapine
PMTCT	Prevention of Mother to Child Transmission of HIV
SPSS	Statistical Package for Social Sciences
SSA	Sub Saharan Africa
WAZ	Weight for age Z score
WHO	World Health Organization
WHZ	Weight for Height Z score
ZDHS	Zimbabwe Demographic Health Survey

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Papers included in thesis

1. **Kandawasvika GQ**, Ogundipe E, Gumbo FZ, Kurewa EN, Mapingure MP, Stray-Pedersen B. Neurodevelopmental impairment among infants born to mothers infected with human immunodeficiency virus and uninfected mothers from three peri-urban primary care clinics in Harare, Zimbabwe. Dev Med Child Neurol. 2011 Nov; 53 (11): 1046-52.
2. **Kandawasvika GQ**, Mapingure PM; Nhembe M, Mtereredzi R, Stray-Pedersen B. Validation of a culturally modified short form of the McCarthy Scales of Children's Abilities in 6 to 8 year old Zimbabwean school children: a cross section study. BMC Neurol 2011; 12: 147
3. **Kandawasvika GQ,** Kuona P, Chandiwana P, Masanganise M, Gumbo FZ, Mapingure MP, Nathoo K, Stray-Pedersen B .The burden and predictors of cognitive impairment among 6-8 year old children infected and uninfected with HIV from Harare, Zimbabwe: A cross sectional study: Child Neuropyschol 2015; 21(1): 106-120. Epub 2014 Jan 13.

1. INTRODUCTION

1.1 Global importance of child development

Globally, it is estimated that at least 780 million children younger than 15 years fail to reach their developmental potential due to cognitive impairment associated with brain injury (1). Various psychological, environmental and biological factors are implicated in the suboptimal neurodevelopmental outcomes in children. In low income communities, neurodevelopment is influenced by multiple factors including birth asphyxia (2), malnutrition, micronutrient deficiencies (3), inadequate stimulation (4;5), poor socioeconomic status (6;7), head injury (8), toxin exposure (9), and infectious diseases including HIV (10;11). Of the 151 million children under 5 years growing up in sub-Saharan Africa (SSA), a significant proportion are vulnerable to a constellation of these risk factors which are likely to have a negative impact on their neurodevelopment potential (12). Although HIV and environmental factors are largely preventable, these have been reported to decrease cognitive function independently in children (6;13). Children living in resource limited communities suffer the greater burden of these risk factors. However, the national health expenditure on cost- effective preventive interventions in such countries are limited (14).

1.2 Neurodevelopment and HIV

The earliest known case of infection with HIV-1 in a human was detected in a blood sample collected in 1959 from a man in Kinshasa , Democratic Republic of Congo (15). Since then, globally by 2011, an estimated 21.7 million people had died due to HIV infection whilst another 34 million were living with the infection (16). Of the 3.4 million children living with HIV infection worldwide, 91% live in SSA (17) and the majority acquired the infection through vertical transmission (18;19). HIV type 1, a neurotrophic virus, is associated with increased risk for central nervous system disease in children as the virus easily penetrates the immature blood brain barrier. CNS invasion occurs during primary infection and is often followed by compartmentalization. HIV invades cells of the lymphatic system in the nervous system by binding to the CXCR4 and CCR5 chemokine receptors, respectively. Infected monocytes and T lymphocytes pass from the lymphatic system to the CNS in order to invade the nervous system (20). The infected immune cells are thought to release numerous chemokines that either damage or kill neurons directly or stimulate other un-infected cells to produce inflammatory and neurotoxic factors. Both of these mechanisms lead to neuronal injury or death via

excitatoxicity, oxidative damage, and apoptotic pathways (20). In perinatally infected children cognitive, motor and behavioral disorders have been shown to be related to the direct infection of the CNS by the HIV virus as the disease progresses (21). HIV is thought to directly infect macrophages, microglia and to a lesser extent astrocytes resulting in neurotoxicity, neuronal damage or disturbances in cell communication (22). The postnatal period of brain development is particularly susceptible to excitatory neuronal damage due to the active synaptogenesis and pruning that takes place at this age (23). There is also increased risk to other perinatal transmittable congenital CNS infections such as, cytomegalovirus, toxoplasmosis, syphilis, tuberculosis and herpes (24). In adolescents, it hypothesized that inadequate CNS penetration of some antiretroviral drugs lead to poor HIV infection control, rendering the severe damage sustained during brain development unrepairable (25). Information on the regions of the brain affected by HIV infection is not clearly understood due to the inconsistent clinical correlation with neuroimaging studies (26;27). Autopsy data on the other hand only examines the most severe cases (28). Perhaps the use of rodent model for HIV associated neurocognitive disorders will provide more answers on the human pathobiology in the near future (29).

The relationship between paediatric HIV infection and neurodevelopment has been studied mainly in developed countries (30) and yet the greatest burden of paediatric HIV is in SSA. Studies conducted in developed countries focused on children receiving antiretroviral treatment and whose mothers were on recreational drugs, which is a different contextual setting from sub Saharan Africa where antiretroviral therapy was not universally available to all children (11). Moreover, some of the neurodevelopmental research has come from sub studies in randomized clinical trials for drug efficacy (11), the conditions of which may differ with the natural disease process in the community. The comparison of research findings on the effect of perinatal HIV infection on child neurodevelopment is hampered by the lack of standardized validated tools. Various research teams have used predominantly Western assessment tools such as the Kaufman Assessment Battery for Children and Early Childhood Screening Profiles (K-ABC) (31;32) and the Bayley Scales of Infant Development (BSID) (33) which contain test items that are unfamiliar to children of non-Western culture, have different reference values from those of the standardization population (34) or exclude important domains of development such as social skills (35). These adapted western tools may provide inaccurate findings when used in different cultural settings (18;32;36-38). A few

culturally appropriate assessment tools have been developed for a different African cultures (39;40). Although comparison between groups is possible, these tools were created for children of a specific area of residence (rural or urban) and for a limited age range, which limits interpretation of outcome measures when employed in a different setting to that of origin.

Critical periods in childhood development span from pregnancy to adolescence and are susceptible to psychological, environmental biological risk factors. There is different vulnerabilty of the developing nervous system following exposure to environmental contaminants at different developmental ages. These vulnerable periods are dependent on the temporal and regional emergence of the critical developmental processes such as proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis (41). The association between HIV infection and neurodevelopmental outcomes in infancy is determined by maternal and infant host factors both of which also influence HIV disease onset and severity. Furthermore, the timing of vertical infection influences the rate of disease progression (38;42). In a study among 114 combination antiretroviral therapy (cART) naive American infants vertically infected with HIV, intrauterine infected infants scored significantly lower than the later infected infants on measurers of mental and motor performance (38). HIV encephalopathy, as characterized by the deterioration of cognitive, motor and behavioral function was described in infants as young as 3 months of age. Active progressive HIV encephalopathy was fatal in the absence of cART while arrested progressive HIV encephalopathy was associated with residual neurological and cognitive impairment (43).

Children infected with HIV who survived to school age were found to have neurodevelopmental deficits in general cognitive impairment, visual spatial, motor, language expression, perceptive performance and executive function (13;37;44-46), depending on the type of psychometric tool used. In a recent report of neurocognitive outcomes among school age children with HIV infection, 3 out of 5 studies conducted in low income countries reported a negative association between HIV infection and general cognitive function (11). Research conducted among combined antiretroviral therapy (cART) naive children with aggressive HIV disease seemed to suggest early detrimental effects of HIV infection on neurocognitive function (10;11). This contrasts with normal cognitive function at school age described by Bagenda et al in cART naive asymptomatic Ugandan children with less aggressive HIV infection (32). The heterogeneity of study populations and the non-

comparability of neurodevelopmental measures reported limit comparison of study findings from developing countries (31;42;47).

Of note, is the lack of information on the cognitive outcome of African children exposed to, but uninfected with HIV at school age (48); a sub-population of children whose numbers are anticipated to rise as availability of more efficacious antiretroviral therapy for prevention of mother to child transmission (PMTCT) of HIV becomes more available.

1.2.1 Clinical neurological and behavioral effects associated with HIV

The prevalence of neurological complications has been identified in 20-60% of children with HIV infection who survive beyond the first year of life (30). These include HIV encephalopathy, cerebrovascular complications, peripheral neuropathy, seizures and opportunistic infections (28). HIV- related progressive encephalopathy, which is often the first AIDS defining illness in children, is the commonest neurological complication (49). In antiretroviral naïve children with advanced stages of HIV infection, HIV encephalopathy presents as a classic triad of developmental delay, acquired microcephaly and pyramidal tract deficits. Static encephalopathy on the other hand, is characterized by continued attainment of new skills, but at slower rates than is expected for age. The picture is further compounded by cerebrovascular complications, micronutrients deficiencies and possible side effects of cART. In contrast to the pattern seen in adults, HIV infection of the nervous system in children involves almost invariably the CNS, sparing the peripheral nervous system (22). As the immune suppression due to HIV progresses, the effect of the virus on the CNS is further exacerbated by the presence of opportunistic infections and neoplasms. Common opportunistic CNS infections are tuberculosis, cytomegalovirus, cryptococcus neoformans, herpes simplex virus and toxoplasmosis (24;49).

Cerebrovascular complications, which are present in 1.3% of children with AIDS, occur as a result of either ischaemic or hemorrhagic stroke, or subarachnoid bleeds (24). The structural and functional vasculature changes are mostly observed in children on protease inhibitors, due in part to the dyslipidemia effect of protease inhibitors, although changes have been reported in cART naïve children too (50). The vascular abnormalities occur due to cytotoxic effect of cytokines produced as a result of HIV infection. This leads to a panarteritis with ischaemic damage to the vasa vasorum (a network of small blood vessels that supply the wall of large vessels such as aorta) resulting in aneurismal dilatation or stenosis (24). Children with

vertically transmitted HIV infection are at risk of the cerebral vasculopathy due to the susceptibility of the immature vessels to the cytotoxic cytokines.

HIV associated behavioral problems in children remains largely unknown in developing countries (countries whose gross national income (GNI) per capita per year is US$ 11,905 or less) due to lack of adapted and validated tools for assessing behavior in these settings (51). A hospital based cross sectional study assessing the frequency of emotional and behavioral problems among Ugandan adolescent orphans infected with HIV, a reported higher than normal rates of behavioral problems in that cohort (52). Almost two thirds of the adolescents were in HIV clinical stage 111 or 1V and were not on cART. Another hospital based study in Addis Ababa Ethiopia also reported a high prevalence of behavioral and emotional problems in 39% of the 318 children aged 6-14 years who had been on cART since birth (53). Similarly, research from a multicenter randomized clinical trial in the USA reported a relatively high frequency of behavioral problems (20%) and cognitive impairment (25%) among asymptomatic antiretroviral experienced 274 children with HIV infection who were aged 2-17 years old. (37).

1.2.2 Pathology by brain region

Although there has been a lot of progress towards understanding the cell types affected by HIV, the regions of the brain damaged by HIV remain unclear for the following reasons. Firstly, the assessment of regional impairment is limited to neuroimaging studies, which are relatively nonspecific. Secondly, autopsy data though more specific, only examines the most severe cases. However, a study by Moore et al found correlation between neuropsychological deficits measured before death and neuronal damage at post mortem in both cortical and subcortical regions (54). In children neuropathological findings at autopsy corresponding to clinical disease included restricted brain growth, reactive gliosis, calcification of the basal ganglia, cerebral atrophy, ventricular enlargement and cerebral vasculature abnormalities (24).

1.2.3 Antiretroviral exposure and neurodevelopment

Combination antiretroviral therapies are directed at different stages of the HIV cycle. Main classes of antiretroviral drugs include entry, fusion, reverse transcriptase, integrase and protease inhibitors. Unlike in adults, the treatment guidelines for young children are further

complicated by age dependent dosage and formulation considerations. At the time of this study from 2002 to 2013, the Zimbabwean national HIV treatment guidelines were revised on three occasions in line with WHO recommendations**.**

The relationship between cART and child neurodevelopment is extrapolated from evidence from developed world setting where PMTCT programs are wide spread and the infants are predominantly formula fed. HIV is neurovirulent and has been demonstrated in the CSF of children irrespective of their age, CD4 count or stage of disease.(49). The initiation of cART reduced the incidence of progressive encephalopathy by 50 % in children infected perinatally with HIV, in a prospective study among 2389 American children (55). In a South African study comparing the neurodevelopment of 27 infants infected with HIV to 29 infants exposed uninfected, the use of cART, prevented further deterioration in neurodevelopment function in the HIV infected group, but did not reverse the neurological damage already present (56). The cART had been initiated from time of HIV infection diagnosis in infancy and continued for duration of at least six months. As anti HIV drugs target the different stages of the HIV life cycle, the aim of therapy is to suppress HIV replication, restore immune function and reduce HIV related morbidity and mortality. Although treatment with cART also results in decreased incidence of opportunistic infections among children with HIV infection, the eradication of HIV from the CNS still remain a challenge. Residual motor and neurocognitive deficits have been described even in clinically stable school age children who were started on cART in infancy (57). Possible explanations include inadequate treatment of HIV reservoirs, decreased effectiveness of cART in CNS, presence of other pathogens in the CNS and pharmacokinetics related factors in children (58).

Concerns remain regarding the safety of cART on the developing brain (59). Evidence on the long term neurodevelopmental effects of antiretroviral therapy exposure is largely unknown. Maternal antenatal exposure to protease containing regimens was associated with increased risk of prematurity in an American PMTCT clinical trial comparing HIV transmission rates in the protease inhibitors group versus the non-reverse transcriptase inhibitor group (60). There is paucity of information on the effect of maternal prophylactic single dose nevirapine ingestion on child neurodevelopment (61). A study comparing neurodevelopment outcomes in a Canadian cohort of HIV uninfected children exposed to cART in pregnancy versus those not exposed, did not establish any difference in developmental outcomes (11). In contrast, a review of studies investigating the impact of HIV exposure and antiretroviral therapy or

prophylaxis on neurodevelopmental outcomes reported subtle speech and language delay among children exposed uninfected with HIV (61). Due to different methodologies used in assessing the effect of maternal cART exposure on neurodevelopment, comparison of the results is limited. Further studies on the long term neurodevelopment outcomes following maternal cART exposure in children without HIV infection are needed.

Table 1: Summary of studies reporting the effect of HIV on neurodevelopment

Study	Location	Study Type	Sample size	Participants	Age (range)	Developmental scale	Exposure to ARV	Findings
Chase et al 2000(62)	US	Cohort	595	114 HIV+ 481 HIV-	0-36 mnths	BSID	Yes	HIV+ significant cognitive and motor deficits
Liorente et al 2003(63)	US	Cohort	157	All HIV +	0-36 mnths	BSID	Yes -treatment	Greater mortality in those scoring in lower quartile.
Blanchette et al 2001(64)	Canada	Cross section	50	25 HIV+ 25 M^+HIV^-	6-37mnths	BSID	Yes- treatment	HIV+, greater impairments in mental and motor development
Boivin et al 1995 (31)	DRC	Cross section	50	14 HIV+ 20 M^+HIV^- 16 HIV-	Less than 2 yrs	DDST K-ABC	No	HIV+, Motor and visual spatial deficits.
Msellati et al 1993(65)	Rwanda	Cohort	436	50 HIV+ 168 M^+HIV^- 218 HIV -	6-24 mnths	Neurological examination of (gross, fine motor language, acquisition and social skills	No	HIV , Motor deficit in 31% at 1 year, 40% at 1.5 years
Drotar et al 1998(33)	Uganda	Cross section	436	79 HIV+ 241 M^+HIV^- 116 HIV-	6-24 mnths	BSID Fagen test	No	HIV+, showed more frequent and earlier onset of motor and neurologic abnormalities
McGrath et al 2006(42)	Tanzania	Cohort	327	11 HIV+ early infection 44 HIV+ late infection	6-24mnths	BSID	No	HIV in utero infection associate with lower scores
Bisiachi et al 2000 (66)	Italy	Cross section	42	29 HIV+ 13 M^+HIV^-	6 -15 yrs	Own tests	Not stated	HIV+ ,executive function scores lower
Blanchette et al 2002(67)	Canada	Cross section	25	14 HIV + 11 M^+HIV^-	5-12yrs	WPPS	Yes treatment	HIV+, cognitive function within normal range
Fishkin et al 2000(68)	US	Cross section	80	40 HIV+ 40 M^+HIV^-	3-5yrs	WPPS	Yes	Executive function
Smith et al 2006(13)	US	Cohort	539	117 HIV+ 422 M^+HIV^-	3-7yrs	MSCA	Yes treatment	Symptomatic children had lower scores

Koekkoek et al. 2008(57)	The Netherlands	Cross section	22	HIV +	6-13.5 yrs	SON-R	Yes, on treatment	HIV+, poor executive function
Bagendi et al 2006 (32)	Uganda	Cohort	107	28 HIV+ 42 $M^{+}HIV^{-}$ 37 HIV-	6-12yrs	K-ABC	No	HIV+, no significant cognitive difference
Abubakar et al 2009 (69)	Kenya	Cross section	367	31 HIV+ 17 M+ HIV- 319 HIV-	6-35mnths	Kilifi Developmental Inventory	No	HIV+ significant cognitive and motor deficits
Lowick et al 2012 (44)	South Africa	Cross section	60	35HIV+ cART naive 30 Healthy unknown status	Preschool age	GMDS-ER	No	Developmental z-scores were <-2 in 27 (90%) HIV+ compared to 23 (76%) in the comparison group
Laughton et al 2012(70)	South Africa	RCT	90	64 HIV+ on cART 26 HIV+ cART naive	10-16 mnths	GMDS-ER	Yes Early versus deferred HAART at enrolment	Early cART initiation had better locomotor and scores
Hoare et al. 2012 (26)	South Africa	Cross sectional	24	12 HIV+ HAART naive 12HIV-	8-12 yrs	WASI	No	HIV+, poor executive function
Ruel et al 2011(71)	Uganda	Cross section	115	93HIV+ cART naive 106 HIV-	6-12 yrs	Test of Variables of Attention K-ABC, Bruininks-Oseretsky Test of Motor Proficiency	No	HIV+, cART naïve had motor and cognitive deficits
Puthanakit et al 2013 (72)	Thailand	RCT	623	284 HIV+ 155 M+HIV- 164 HIV-	1-12 yrs	WISC-Thai	Yes Early versus deferred cART at enrolment	HIV+, lower mean scores

HIV+ Child with HIV infection; HIV- Child without HIV infection; $M^{+}HIV^{-}$ Child exposed but uninfected with HIV
US - United States of America
DRC –Democratic republic of Congo
RCT - Randomised Controlled Trial
KABC -Kaufman Assessment Battery for children.
MSCA- McCarthy Scales of Children`s Abilities
SON-R -Snijders-Oomen nonverbal intelligence test for children and adolescents (abridged).
WASI -Wechsler Abbreviated Scale of Intelligence.
WPPSI- Wechsler Preschool and Primary Scale of Intelligence-Revised
WISC-R Wechsler Intelligence Scale for Children- Revised.
WISC-III & IV Wechsler Intelligence Scale for Children versions 3& 4.
WISC-Thai Wechsler Intelligence Scale for Children Thai version.
GMDS-ER Griffiths Mental Development Scales-Extended Revised Version

1.3 Risk factors for poor neurodevelopmental outcomes

From conception, brain differentiation occurs in a chronological order starting with cell proliferation, migration, synaptic connection, myelination and pruning (73), the course of which can be influenced by nature or nurture. Research from low to middle income countries implicates poverty in the most of the causal pathways for poor child neurodevelopment (4).

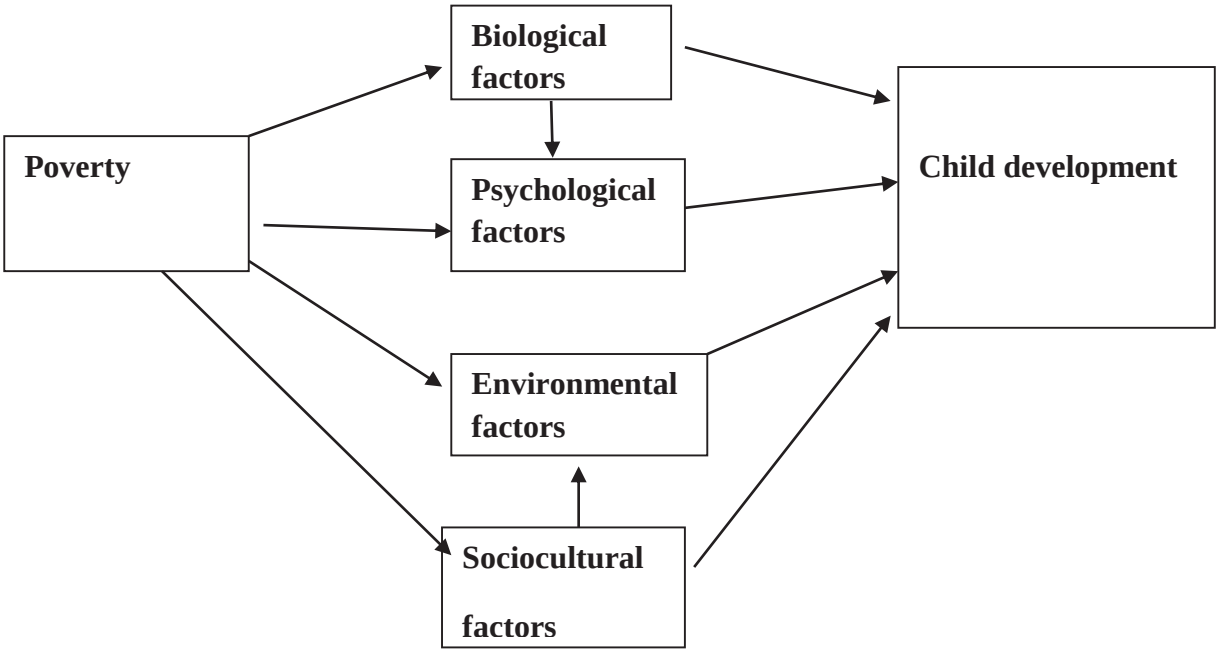

Figure 1: Conceptual framework of factors affecting child development

1.3.1 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 (74-77). 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 (78). Simple touch has been suggested to exert long lasting cognitive effect in preterm infants through stimulation of cortical growth and synaptic proliferation (4;79). Unfavorable home environmental factors such as unstable caregiver environment, maternal alcohol or drug abuse, poverty or maternal low education put children at risk for developmental dysfunction (75;76).

The physical environment exerts 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 (75). Neurotoxic contaminants in domestic water such as lead, manganese and also arsenic are a health hazard particularly in developing countries where environmental monitoring remains largely un supervised (80).

1.3.2 Nutrition and cognitive development

Of the world's under five children, 165 million were reported as stunted whilst 8 million had wasting in 2012 (81). Under nutrition (according to WHO, a weight for age, height for age and weight for height Z score of <-2 defines underweight, stunting and thinness respectively (82)) results from insufficient food intake, repeated infectious diseases or a combination of both, inflicts irreversible physical and neurodevelopmental damage. HIV infection is known to cause under nutrition in African women and their children (83). Nutrients provide the back bone of all cell functions including the nervous system (84). The Zimbabwe demographic health survey of 2010-2011 (ZDHS) estimated the prevalence of underweight and stunting in children under 5 years at 10% and 32 % respectively (85). Similar to other developing countries, the burden of under nutrition and effect on neurodevelopment in older school age children is largely unknown locally due to limited documentation. A survey conducted among 982 rural Shona Zimbabwean children age 6-17 years identified stunting and underweight among the boys and girls at ages 11-15 and 8-15, respectively, but did not report on the prevalence rate of wasting (86).

1.3.3 Anaemia and cognitive development

Micronutrient deficiencies such as iron iodine, zinc, selenium and n-3 fatty acids also affect central nervous system development through various patho-physiological mechanisms. Iron is an essential nutrient for all body tissues and is present in the brain of the developing fetus, where it is needed for proper formation of neural tissue (87) and development of brain cells (88). Iron deficiency, a common form of nutritional deficiency, results from long-term imbalance caused by an inadequate dietary iron intake; poor iron absorption or utilisation; increased iron requirements for growth during childhood or chronic blood losses. In the advanced stages of iron depletion, the haemoglobin concentration decreases, resulting in iron deficiency anaemia (89). Worldwide, approximately 600 million children of preschool and school age are anaemic. In half of the children, the cause is due to iron deficiency (90). Iron deficiency anaemia during childhood results in growth retardation, reduced school

achievement, impaired motor and cognitive development, and increased morbidity and mortality (4). In a cross sectional, household prevalence survey conducted in four or the ten administrative provinces of Zimbabwe in 1997, 17% of the preschool children surveyed had iron deficiency anaemia (91).The common cause for iron deficiency anaemia in that study was nutritional (91). The ZDHS of 2010-2011 reported that 56 percent of children under the age of 5 years suffered from some degree of anaemia (85). In a cross sectional study among 318 Zimbabwean children aged 6-10 years from this cohort, the prevalence of anaemia, iron deficiency and iron deficiency anaemia were 15%, 4% and 3% respectively (92). Similarly in a study among 604 Senegalese school children aged 5-17 years, the prevalence of anemia, iron deficiency and iron deficiency anemia was 14.4%, 39.1% and 10.6% respectively (93). Another cross sectional study among 845 school children aged 7-14 years from a coastal area in Tanzania reported an even higher prevalence of iron deficiency anaemia of 33% (94). Of note is that school children generally do not benefit from supplementary nutritional programmes in developing countries.

1.3.4 Infectious diseases and cognitive development.

In line with meeting the targets for Millennium Development Goals (MDGs) 4 and 5 for the year 2015, significant progress was reported by many countries in an effort to end all preventable deaths under 5 morbidity (81). However, in 2012 it was estimated that globally, 6.6 million children under five years died from neonatal sepsis, HIV, acute respiratory infections, diarrhoeal disease, tuberculosis or malaria (81). The long term impact of the above diseases on the neurodevelopmental potential of those children who survive is largely unknown; especially when infections mediate malnutrition, leading to poor neurodevelopmental outcomes. Furthermore, the role of neglected tropical diseases such as schistosomiasis and helminth infestation in child development remains undocumented in developing countries.

1.3.5 Sociocultural factors and cognitive development.

The structure and cultural background of a family is critical in child development. Culture influences all aspects of child development and is reflected in child rearing practices. Protective cultural practices such breastfeeding are widely practiced in the developing communities (95). It is the cultural norms that dictate the role of adults in child play, investment in child development and the degree to which society will embrace child

protective practices such as child stimulation. Unfortunately, the AIDS epidemic has resulted in an increase in orphaned children as their parents succumb to HIV related illnesses. The family structure and dynamics have changed with more AIDS orphans growing up under the care of aged grandparents, older siblings or other relatives (36). However, there is a lack of data on how the change in household composition impacts on child neurodevelopment, especially when the care givers change is due to death of a parent. In a case study among 193 Ugandan orphans aged 15-19 years, 29% continued schooling undisrupted, 25% spent time off school and 45% dropped out of school and the least chance of continuing with education was reported in those fostered by grandparents (7%) (96).

1.3.6 Poverty and child development

Although definitions of poverty vary according to social, cultural and geographical location, according to the epidemiological perspective, the meaning of low socioeconomic status, unemployment and low levels of education are the same across all cultures (97). Universally, poverty increases the risk for emotional distress in families and children which may interfere with educational achievements. Poverty was correlated with increased maternal stress or depression and inadequate child stimulation in the home (98). Studies demonstrated that the electrical brain activity of newborns of depressed mothers show reduced ability to learn from environment (99). In the context of HIV infection, maternal mental health disorders compromise the parent-child interaction influencing cognitive stimulation. Poverty also negatively impact on the family's nutritional status. 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 (100).

1.4. Neurodevelopmental assessment screening in the African context

Similar to children in developed communities, children in Africa are at risk of biological and psychosocial insults that affect brain development (1). However the magnitude of neurocognitive impairment among sub-Saharan Africa school children remains underestimated due to lack of culturally sensitive assessment tools. With over 2000 native languages spoken on the African continent (101), comparison of research findings on child cognitive development conducted across the diverse African cultures remains a challenge due to cross cultural

differences. With no data available, advocacy for the primary prevention and early intervention of cognitive impairment receives inadequate consideration from national policy makers.

In resource constrained settings, one of the reasons for lack of information on child disability is the unavailability of experts and culturally sensitive neurodevelopmental assessment tools. The assessment of neurodevelopment in children is difficult due to potential confounders such as the characteristics of the home environment, infectious diseases, environmental toxins or birth complications. A few developmental assessment tests which were created in developed country, have been used in developing countries (102). Ideally, assessment tools should reflect the intended constructs, demonstrate reasonable reliability and validity, sample a broad range of abilities and be standardized against an age appropriate population (103;104). However instruments produced and standardized in the Western context are not directly applicable to a setting that is different from that of the original target population (103). As a result a choice has to be made whether to use measures developed within Africa, or adapt a tool, created in the developed countries, for use in Africa.

The creation of a new culturally sensitive tool, while costly, allows for language differences, socio-emotional functioning, selection materials which children are familiar with and the development of norms for the particular setting. Of note, the Kilifi Development Inventory and Developmental Milestones Checklist created in Kenya (105) and the Malawi Developmental Assessment Tool (MDAT) (39) respectively are examples of tools developed in Africa. In instances where it is not feasible to create a new tool; or the research goal is to compare findings across different cultural groups, a well-developed adapted tool may measure similar developmental constructs in individuals from a cross-cultural context (106).

Types of adaption that can be made depend on the objective of the assessment and are namely: construct, language, culture, theory, and familiarity recognition as reported by Malda and colleagues (107). In test adaptation, it is prudent to adhere to established procedural guidelines in order to conserve the validity of the test (107;108). Appreciation of differences in the cultural definition of construct such as intelligence is important as it guards against measurement difference and the introduction of systemic bias. It is generally agreed that Western communities define intelligence by sophistication in knowledge, reasoning development, and level of skill. In contrast, in much African setting, intelligence is defined by

level of social participation (109). Clearly the measurements are different. The exorbitant copyright fees for assessment tools is another challenge for many practitioners in the developing countries. When there are no appropriate follow up services for participants identified with medical cognitive behavioral or developmental impairment, ethical dilemmas arise. Despite the above constraints, in Africa, the commonly used adapted assessment tools for young children include the Griffiths (110), Bayley Scales of Infant Development (111), Mullen scales of early development (112) and the Denver Developmental Scales (113).

Regardless of the development measure chosen, in order to follow up child development, repeated developmental measurements are necessary. However, this introduces practice effect as a source of bias. Various researchers have used different tests at various ages in the same prospective study to try and minimize the practice effects. Since the scoring system is different for the various instruments, aspects of cognitive function measured are diverse, making it difficult to compare findings.

1.4.1 Rational for a domain specific neurodevelopmental test

It is generally accepted that HIV infection acts on a number of cells in the CNS resulting in cortical and subcortical deficits. Therefore a single test of one cognitive domain such cognitive function may not be sensitive to subtle early changes in cognition. In order to accurately characterize the impact of HIV infection on the developing brain, it is prudent to use a neurodevelopmental test with various domains. The justification for our selection of the neurodevelopment test were informed by clinical studies conducted among children with HIV infection, living in similar resource limited setting, see table 1.

Table 2: Description of the Bayley Infant Neurodevelopmental Screener (BINS)

The 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. 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. The BINS was chosen for its brevity as the screening and scoring takes approximately 10 minutes, making it convenient for use in a busy, low resource setting.

Table 3: Desciption of the McCarthy Scales of Children`s Abilities (MSCA)

The MSCA was designed to measure cognitive and motor development in children aged 2 ½ to 8 ½ years. The original MSCA consists of 18 items, which are summed to generate 5 domains: 1) verbal, which refers to those cognitive abilities related to information processing; 2) quantitative, relates to numerical abilities; 3) memory assesses short-term retention of information (verbal, perceptive or numerical); 4) perceptive–performance, which refers to tasks related to perceptive information processing and 5) motor abilities (114). Items from the verbal, perceptual-performance, and quantitative domains are content oriented and are computed to create the General Cognitive Index (GCI). The mean for the General Cognitive Index (GCI) is set at 100, with a Standard Deviation (SD) of 16 according to the MSCA administration manual. For each of the 5 subsets, the Index scores have a mean of 50 with a SD of 10. Items from the verbal, perceptual-performance, and quantitative domains are content oriented, with no subtests from one domain contributing to the score of another domain. The memory and motor domains are process oriented, with all subtests in the memory domain overlapping with verbal, perceptual-performance, or quantitative domains (114). Cognitive impairment was defined as a score -2SD below the mean for MSCA (100).

The MSCA was selected over other tests for intelligence because of the following factors: It is a tool that has been stood the test of time since it was designed in 1972 and has been used in several studies (11;34;114). It is easier to administer and it is fun for the children compared to extensive tests such as the Stanford-Binet test. It separates acquired factual learned knowledge from ability to solve novel problems (115). The Kaufman Assessment Battery for Children (KABC) is also easy to administer and score, but it relies on verbal responses which might prejudice non English speaking children in their performance. The MSCA also assesses motor ability simultaneously eliminating the need for a separate test. It may be adapted for non-English speaking communities in cohort studies of HIV infected children (13). Furthermore,

the tool has been as been validated for cultural appropriateness in two similar African settings South Africa (34) and Zimbabwe (116).

2. BACKGROUND

2.1 Zimbabwe, country profile

2.1.1 Geography

Figure 2: Map showing the study site, Harare and Chitungwiza city Zimbabwe ©GraphicMaps.com 2008

Zimbabwe, a country with a generalized HIV epidemic, lies in southern Africa sharing borders with Zambia in the north, Mozambique on the east, South Africa on the south and Botswana on the south west. 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 Asians constitute the remaining 2%. The Shona language is spoken by the majority (70%) although there are other indigenous languages. Zimbabwe is divided into 10 administrative provinces, which are further divide into 58 districts. Wards (ten house units in towns) or villages in rural areas form the smallest administrative units.

2.2 Population Demographic Characteristics

In the 2012 census, the population of Zimbabwe was estimated at 13 million with females constituting 51.8 % (85). Over 70% of the population resided in the rural areas and population density was estimated to be 32.3 per square meter.

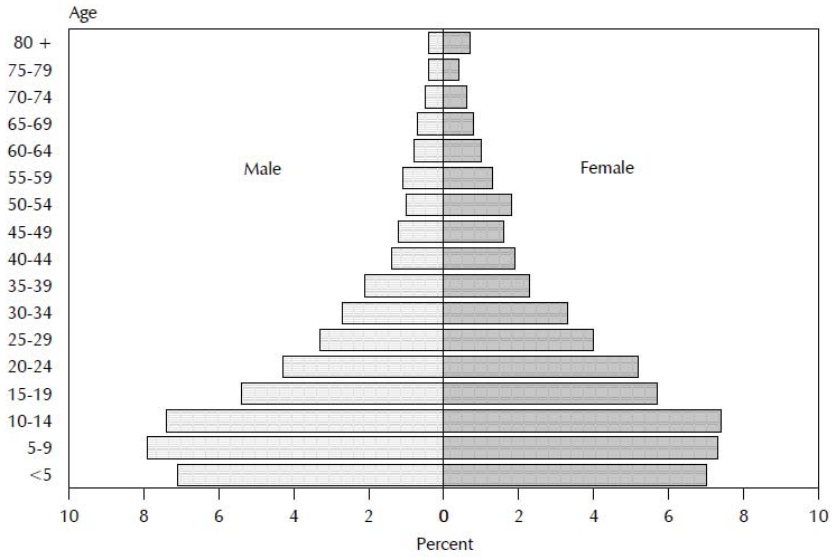

Figure 3: The age-sex structure of the Zimbabwe population as shown by a population pyramid in 2010-2011

The age-sex structure of the population is shown Figure 3.The population pyramid has a broad base and a narrow top, which reflects a youthful population, with a large proportion of children. The number of children under five is less than the number age five to nine years, a finding that is consistent with a recent fertility decline. Children under 15 years of age made up 45 % of the population while that of persons over 65 years of age was about 5 percent. The projected annual growth rate was 1.1% and the average fertility rate is 4.1 per woman (85). The life expectancy at birth was estimated at 58 years, see table 4.

Table 4: The trends in selected demographic indicators of Zimbawe

Indicator	2002 Census	2012 Census
Total population (thousands)	11,632	12,973
Distribution by ethnic group (percent)		
African	99.3	99.7
European	0.2	0.1
Coloured	0.4	0.1
Asian	0.1	0.1
Distribution by age group (percent)		
0-14	41	41
15-64	55	55
65+	4	4
Not stated	0.4	0
Crude birth rate (births per 1000 population)	30	32
Crude death rate (death per 1000 population)	17	10
Number of males per 100 females in the population	94	93
Life expectancy at birth	45	58

2.3 Zimbabwe`s economy

Zimbabwe is classified as a low income country by the world bank and has a wide range of natural resources which makes agriculture, tourism and mining the main pillars of the economy (117). Agriculture and industry account for about 17% and 29% of gross domestic product (GDP), respectively. The country is endowed with rich mineral resources including chromate, coal, methane gas, platinum, asbestos, copper, nickel, gold, iron ore and alluvia diamonds. Large-scale commercial farming has nearly collapsed since 2000 under the government's controversial land reforms. The largest industries which used to produce metal

products, food processing, chemicals, textiles, clothing, furniture and plastic goods have sharply scaled back operations due to the poor operating climate.

Zimbabwe, once the bread basket of Southern Africa has gone through a major economic meltdown. A myriad of factors have been implicated in the economic crisis including a succession of droughts, a land reform, and economic sanctions. The country`s economic problems have had a profound impact on all development indicators. According to the poverty assessment study survey (PASS) of 2003, the proportion of households below the food poverty line (a measure of extreme poverty) increased from 20 % in 1995 to 48% in 2003 (118). The human development index[HDI][2], which is a measure of wellbeing and equity, declined from 0.621 in 1985 to 0.505 in 2003 (119) and inequality, the distribution of family income in a country as measured by the Gini coefficient worsened from 0.53 in 1995 to 0.61 in the same year (119). The Gini coefficient is a number between 0 and 1, where 0 corresponds with perfect equality , where everyone has the same income; and 1 corresponds with perfect inequality , where one person has all the income and everyone else has zero income (119).

Due to speculative market forces, the local currency crashed in November 1999, resulting in unprecedented inflation levels reaching an all-time record high level of 231 million % by July 2008. In response, the government introduced the multi-currency policy (120). As a consequence food security deteriorated both at national level and household levels resulting in the country resorting to food imports for several years. A nutritional sentinel surveillance conducted in 2005 identified that 72% of the districts under study were food insecure. Only a third of the children had access to three meals in the previous 24 hour recall period in that report (121). In a society where wealth is assumed if one owns a herd of cattle; a fine house ; has access to money and a good education, the limited resources available to families has negated on the gains on child survival once enjoyed soon after the country`s independence in 1980. It is therefore anticipated that the levels of under nutrition will continue to soar among the very young children.

2.4 Zimbabwe school education system

Since the country attained independence, education was made free for primary school children. Compared to its neighbours, Zimbabwe has a high adult literacy rate, estimated at 83.6% between 2008-2012 (122). As a result of the economic challenges affecting the country, school attendance has decreased due to school dropout or teachers emigrating to

neighboring countries in search of greener pastures. Primary school education is offered in one of the three systems, government, church or private. The majority of children (65%) reside in the rural areas and is enrolled in the government system. The primary school participation is over 90% (122).

2.5 Health infrastructure

At the time of this study, the health system in Zimbabwe had collapsed due to perennial poor funding, poor communication infrastructure, drug, health personnel shortages and economic sanctions levied against the country. 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 center, 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 center. 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.

Indicators to monitor child health status in the country are on the decline, see table 5. In 2012, according to UNICEF, the infant mortality rate was 57/1000 live births, (12), a small decline from the rate of 64/1000 live births in the pre independence era of 1978-1982 (123). Although there is some improvement in the child health indicators, if the current trend is not changed, the country will not be able to fulfill MDG 4 by year 2015.

Table 5: Child mortality rates in Zimbabwe, 2012

Mortality	Rate
Neonatal mortality	39/1000 live births
Infant mortality	57/ 1000 live births
Under 5 year mortality	84/ 1000 live births

2.5.1 Child follow-up schedules at primary care clinics

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 the following schedules: at birth, 6

weeks,10 weeks,14 weeks, 9 and 18 months (During the study period, a different national infant vaccination schedules was being followed: at 3, 4, 9 and 18 months). In Zimbabwe, children are considered fully vaccinated when they receive altogether one dose of BCG vaccine, three doses each of DPT and polio vaccines, and one dose of measles vaccine, see figure 4. During clinic visits, child neurodevelopmental milestones namely gross motor, fine motor, hearing, vision and social development are assessed by enquiry. Those perceived as developmental delayed are referred to the next referral center for further evaluation.

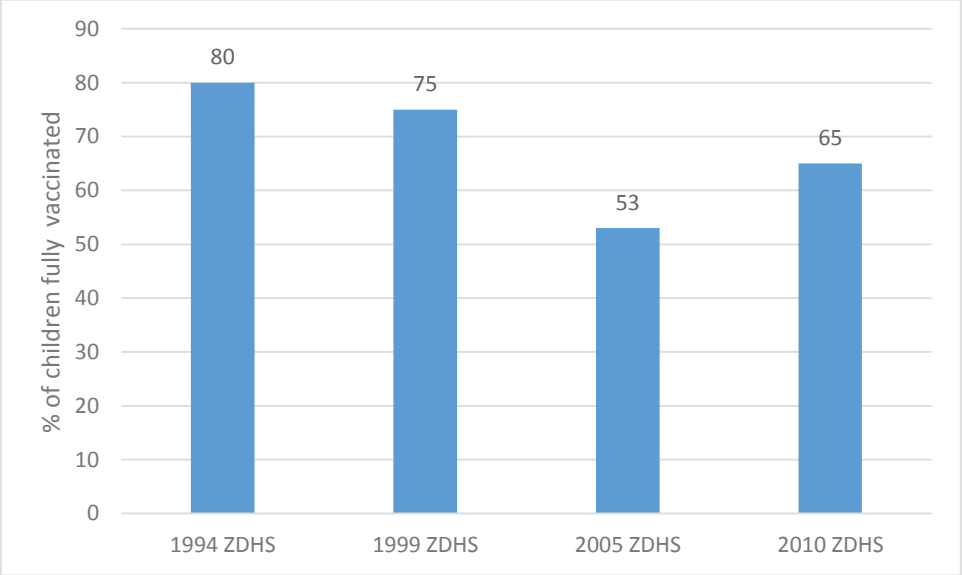

Figure 4: Trends in immunization coverage, percentage of children aged 12-23 months who completed all basic vaccinations (fully vaccinated), according to ZDHS 1994-2010

2.6 Adults HIV/ AIDS prevalence

Globally it is estimated that close to 34 million people are infected with HIV (16). More than half (15.7 million) are women and 2.1 million are children aged below 15 years (17).

The current adult HIV type 1 prevalence rate in Zimbabwe is estimated at 15% (19), down from 26 % in 1999 (124). The main modes of transmission are heterosexual contact and mother to child transmission. In Zimbabwe, subtype C (125-127) is the dominant HIV-1 subtype. The national HIV prevalence data in Zimbabwe is derived from surveillance of pregnant women attending ANC and supplemented by national demographic and health surveys. Pregnant women constitute an easily accessible population which is generally representative of the sexually active population (128). The routine sentinel surveillance of

pregnant women attending ANC commenced in 1999 and has provided the estimated HIV prevalence rates for the adult population.

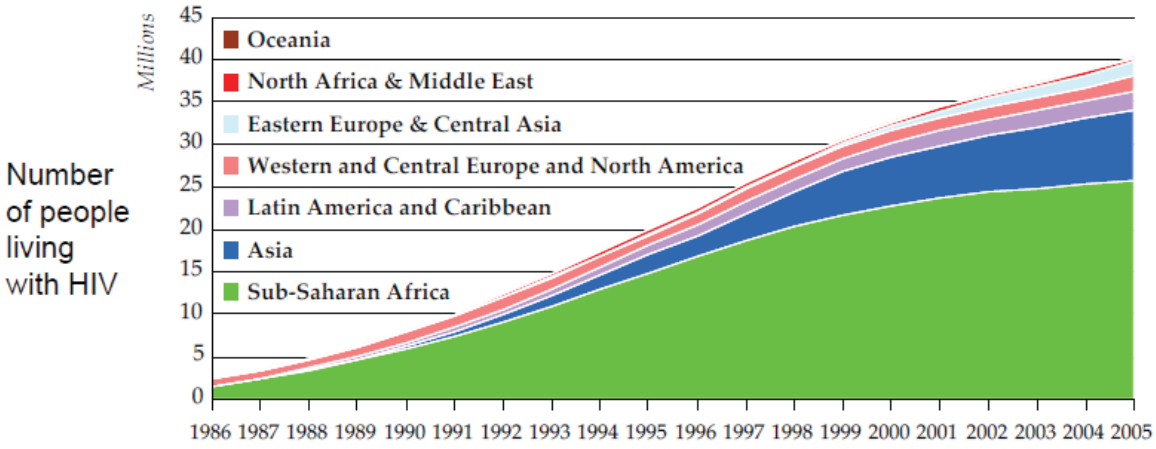

Figure 5: The global HIV prevalence among adults from the year 1986 to 2005

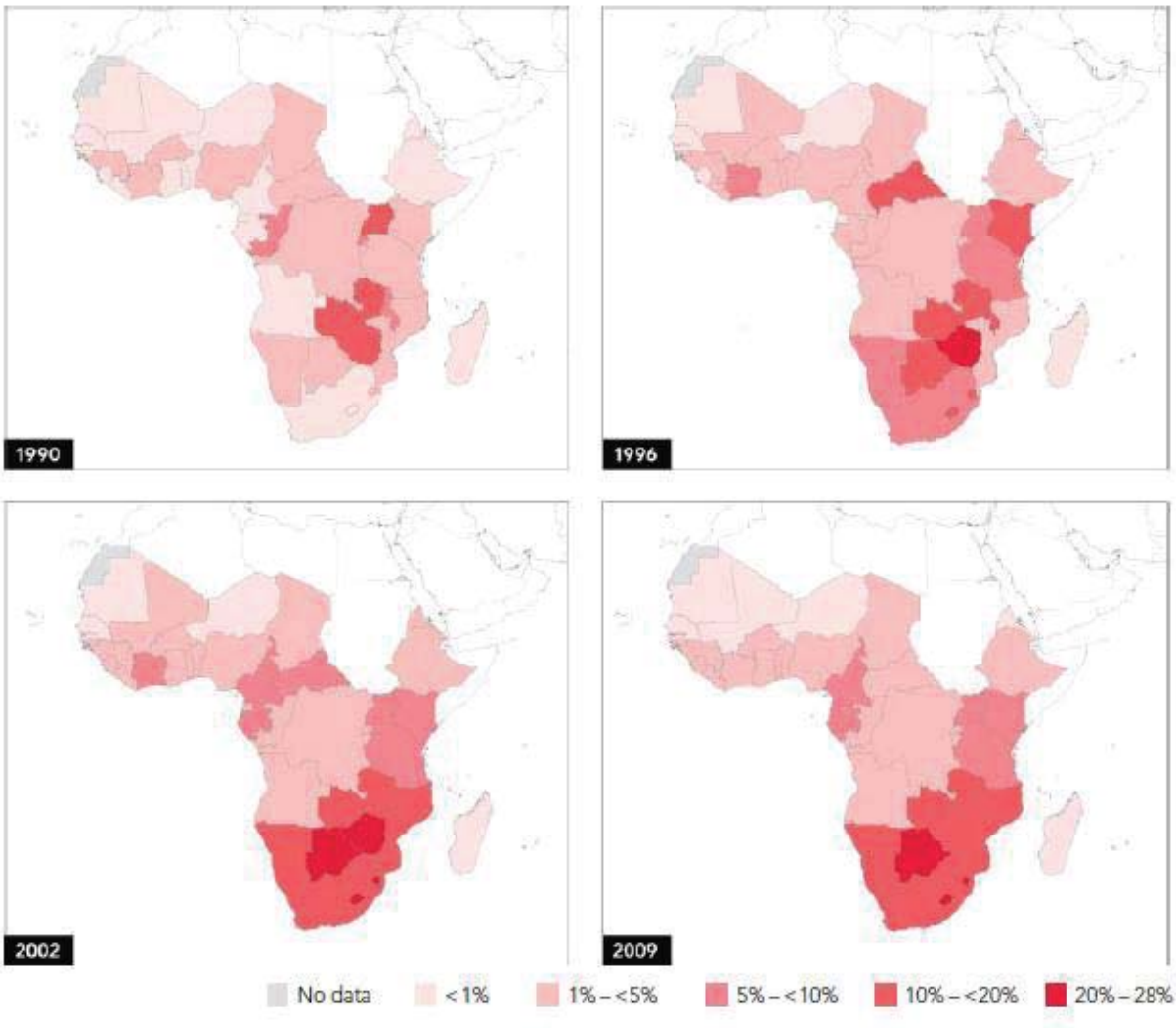

Figure 6: HIV prevalence trends among the 15-49 year olds over the past 10 years in SSA

Although national figures suggests a decline in the HIV prevalence attributed mainly to changes in sexual behavior and to some extent to effective preventive programmes, the rates are still one of the highest in the region (129).

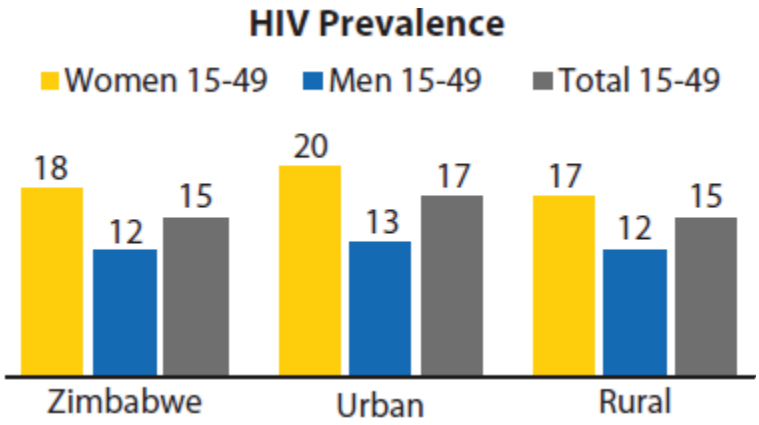

Figure 7: HIV prevalence among 15-14 year old stratified by gender and place of residence

HIV prevalence is higher among women aged 15-49 (18%) than men of the same age (15%), see figure 7. One reason for the discrepancy is the biological differences between men and women where HIV is more easily transmitted from men to women than from women to men. Issues of gender inequality where young women are unable to negotiate for safe sex may also contribute to the higher HIV prevalence in women (130).

Since the first clinical case of AIDS was reported in 1985 (131), the Government of Zimbabwe has introduced policies to try and combat the HIV scourge. A national AIDS trust Fund was set up to fund HIV / STI programmes. The integration of family planning with HIV/STI programmes; the establishment of maternal health services with voluntary counseling and testing (VCT); the rolling out of the prevention of mother-to-child transmission (PMTCT) programme and voluntary male circumcision were some of the programmes adopted with the intention of preventing both horizontal and vertical transmissions (132).

2.7 Epidemiology of Paediatric HIV.

United Nation Children`s Fund estimates that 180 000 Zimbabwe children under the age of 14 years are infected with HIV and that at least one million are orphans whose parents succumbed to HIV infection (12). The majority of children acquired the infection vertically from their mothers (17).

2.7.1 PMTCT guidelines in Zimbabwe

Mother-to-child transmission of HIV occurs in utero, peripartum, and postnatally via breastfeeding. In the absence of interventions, the risk of perinatal HIV-1 transmission is 20

to 45 percent (133). Comprehensive PMTCT services and guidelines have evolved as more evidence for more efficacious antiretroviral regimens, suitable for resource constrained communities, became available. Globally, the target is to initiate antiretroviral treatment for at least 90 % of all pregnant women in need of treatment for themselves by the year 2015 and all HIV exposed infants to have virological testing within 6 weeks of life. WHO recommends the four -pronged- approach to PMTCT: i) primary prevention of HIV infection, ii) prevention of unintended pregnancies in HIV-infected women, iii) prevention of Mother-to-Child transmission, and iv) provision of care and support for HIV-infected women, their infants, and families which aims reducing HIV infection in infants and young children (134).

At the time of this study`s recruitment, the regimen of giving single dose nevirapine (NVP) to the mother at the onset of labour and single dose NVP given to the infant within 72 hours of birth was the standard of care (135), see figure 9. The current WHO 2013 guidelines for antiretroviral drugs for treating pregnant women and preventing HIV infection in infants recommend that countries follow option B+ and in countries and where this is not feasible, option B, see table 6.When other options are not available, Option A (2006 guidelines) is cited as the minimum that should be offered for PMTCT.

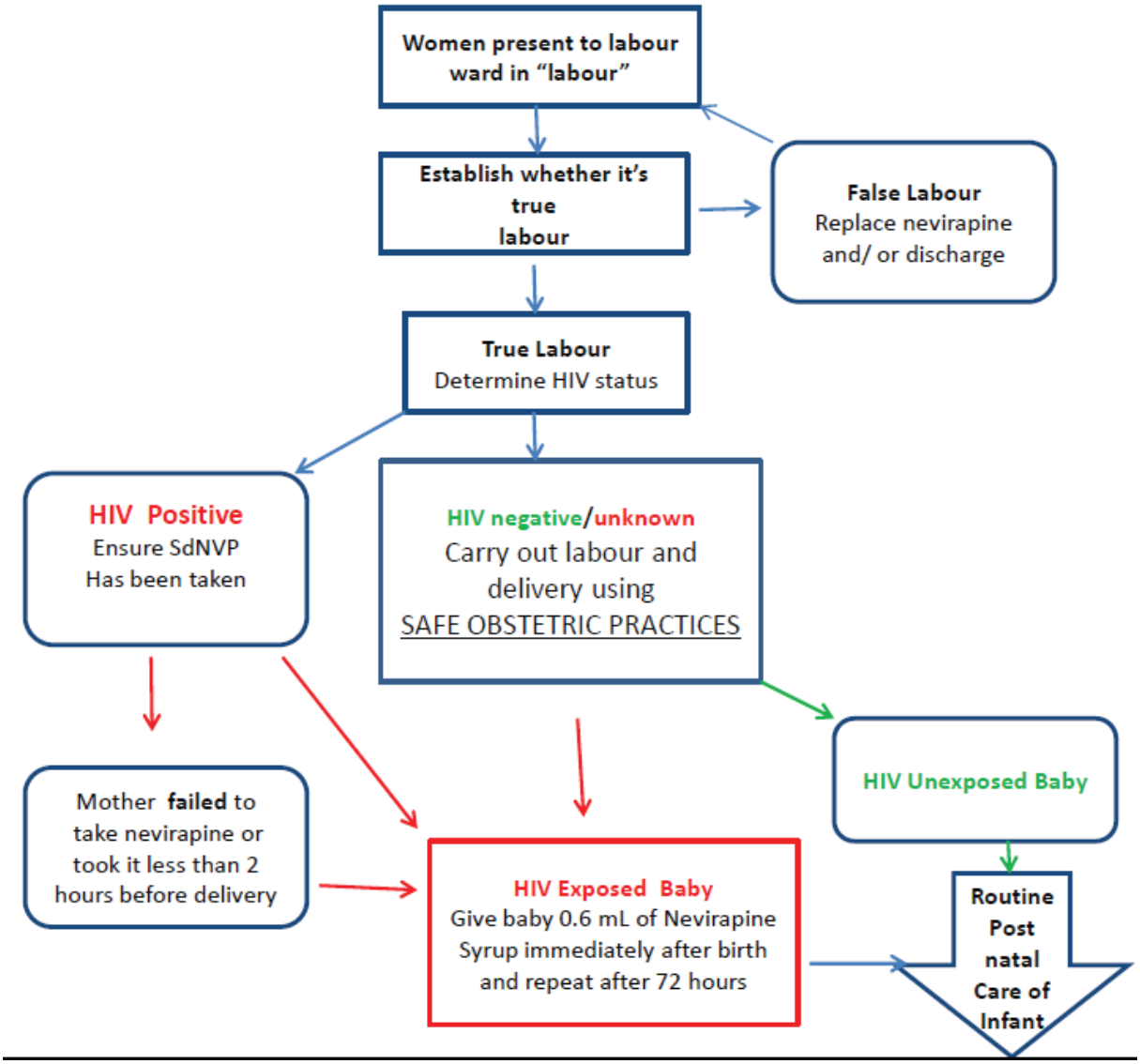

Figure 8: Summary of PMTCT practices during labour, delivery, and postnatal period at the time of the study

Table 6: WHO guidelines for PMTCT in resource limited countries, 2010

<table>
<tr><td></td><td colspan="2">Women receives:</td><td>Infant receives:</td></tr>
<tr><td rowspan="2">Option A</td><td>Treatment

For CD4 count <350cells/mm3</td><td>Prophylaxis

For CD4 count >350cell/mm^3</td><td rowspan="2">Daily NVP from birth through 1 week beyond complete cessation of breast feeding, or if not breast feeding or mother on treatment through age 4-6 weeks.</td></tr>
<tr><td>*Triple ARVs starting as soon as diagnosed, continued for life</td><td>Antepartum: AZT starting at 14 weeks gestation
Intrapartum: at onset of labour sdNVP and first dose of AZT/3TC
Postpartum: daily AZT/3TC through 7 days postpartum</td></tr>
<tr><td rowspan="2">Option B</td><td colspan="2">Same initial ARVs for both</td><td rowspan="2">Daily NVP or AZT from birth through 4-6 weeks regardless of infant feeding option</td></tr>
<tr><td>Triple ARVs starting as soon a diagnosed, continued for life</td><td>Triple ARV starting as early as 14 weeks gestations, continued through intrapartum and child birth if not breast feeding or until 1 week after cessation of all breastfeeding.</td></tr>
<tr><td rowspan="2">Option B+</td><td colspan="2">Same ARVs for treatment and prophylaxis</td><td rowspan="2">Daily NVP or AZT from birth through 4-6 weeks regardless of infant feeding option</td></tr>
<tr><td colspan="2">Regardless of CD4 cell count, triple ARV started as soon as diagnosed, continued for life.</td></tr>
</table>

*Triple ARVs refers to the use of one of the recommended 3 antiretroviral drug combinations for full HIV suppression treatment options

2.7.2 Breast feeding, HIV and Neurodevelopment

The WHO recommends exclusive breast feeding in the first 6 months of life to optimize growth, development and health (136). Studies investigating the relationship between breast feeding duration and cognitive development have reported positively on the benefit of breast feeding to neurodevelopment. A meta-analysis conducted by Anderson et al in 1999 reported consistently higher intelligence quotient (IQs) in breastfed than in formula fed infants (137). Positive associations between breastfeeding and better developmental outcomes as assessed in infancy were reported by Vestergaard et al (138). An Italian study assessing the effect of duration of breast feeding on long term neuropsychological outcome of healthy children aged 10 -12 years, found a significant association between exclusive breastfeeding duration and test scores in the vocabulary (139). Of note is that the definition of exclusive breast feeding varied between the studies and maternal education was a confounder in the European studies.

While breastfeeding carries significant health benefits to infants and young children, HIV can

be transmitted during breastfeeding from an HIV-infected mother to her infant (140). Prior to the isolation of the HIV virus in breast milk, there had been aggressive campaigns to promote BF, see Table 7. However, since the first cases of HIV transmission through breast-feeding were documented, the debate over how to best guide HIV-infected mothers in resource-poor settings on infant feeding has raged on for more than two decades. Breastfeeding (BF), a universal phenomenon with a 98% uptake from 0 to 18 months especially in SSA (141), has proven benefits for child survival. Breast feeding is estimated to prevent 1.3 million children deaths in under five years (142) and associated with better child development outcomes (140).With the advent of HIV infection, globally, breastfeeding is responsible for approximately 300,000 HIV infections per year (140) while not breast feeding or formula feeding with contaminated water accounts for 800,000 deaths in children under five annually according to the Lancet 2013 nutrition series (143). In developing countries, it is difficult to determine when it is safe and feasible to formula feed, therefore recommendations for non-breast feeding mothers remain a major challenge.

Table 7: Guidelines on infant feeding for resource limited settings

Year issued	Author/organization	International Guidelines on infant feeding
1970	Bellagio declaration	Health for all Universal BF uptake in Africa
1985	Ziegler in	CDC in America complete avoidance of breast feeding among all HIV infected women. Replacement feeding for all HIV exposed infants
1991	Inocenti declaration	Protecting, Promoting and Supporting BF
1991	WHO, UNICEF	Baby-friendly Hospital Initiative launched to improve maternity services so that they protect, promote and support breastfeeding.
1992 1996	WHO and UNICEF	"Where infectious diseases and malnutrition are the main cause of infant deaths and the infant mortality rate is high, breastfeeding should be the usual advice given to the pregnant women including those who are HIV infected. This is because their baby's risk of HIV infection through breast milk is likely to be lower than the risk of death from other causes if it is not breastfed"
1997	WHO, UNICEF, UNAIDS	"When children born to HIV infected women can be assured of uninterrupted access to nutritionally adequate breast milk substitutes that are safely prepared and fed to them they are at less risk of illness and death if they are not breastfed. However, when these conditions cannot be met, in particular in environments where infectious diseases and malnutrition are the primary causes of death during infancy, then artificial feeding substantially increases children's risk of illness and death. The policy objective must be to minimize all infant feeding risks and to urgently expand access to adequate alternatives so that HIV-infected women have a range of choices.
2000	WHO	"Formula feeding is recommended for HIV-infected women who find it culturally acceptable and who are able to prepare artificial milks hygienically.

		Where formula feeding is not 'acceptable, feasible, affordable, sustainable and safe', HIV infected women are recommended to breastfeed exclusively for the first few months".
2001	WHO	Antenatal counseling focused on feeding options: either exclusive breastfeeding or rapid weaning around 6 months or exclusive formula feeding from birth.
2006	WHO	Exclusive breastfeeding (EBF) for 6 months unless replacement feeding(formula feeding) is acceptable, feasible, affordable, sustainable and safe(AFASS) "At six months, if replacement feeding is still not AFASS continuation of breastfeeding with additional complementary foods is recommended, while the mother and baby continue to be regularly assessed. All breastfeeding should stop once a nutritionally adequate and safe diet without breast milk can be provided".
2009	WHO	National or sub national health authorities estimate which feeding strategy is likely to provide the greatest chance of HIV-free survival for infants based on several factors, including background levels of infant mortality and the leading causes of infant mortality. Authorities should then decide whether health services should mainly counsel and support HIV-infected mothers to breastfeed and receive ARVs, or instead avoid all breastfeeding.
2009	WHO Rapid advice	**Mother -**Triple ARV therapy should be started irrespective of gestational age, and continued throughout pregnancy and thereafter **Infant-** Breastfeeding infant; Daily NVP from birth up to 6 weeks of age -Non-breastfeeding infant; Daily AZT or NVP from birth up to 6 weeks of age
2010	WHO	Counselling and support to mothers known to be HIV-infected, and health messaging to the general population, should be carefully delivered so as not to undermine optimal breastfeeding practices among the general population
2013	WHO	**Mother -**Triple ARV therapy should be started irrespective of gestational age, and continued throughout pregnancy and thereafter **Infant -**Breastfeeding infant; Daily NVP from birth up to 6 weeks from cessation of breast feeding -Non-breastfeeding infant, Daily AZT or NVP from birth up to 6 weeks of age

ART- antiretroviral therapy; AZT-Zidovudine; NVP-Nevirapine; BF-Breastfeeding

2.7.3 Paediatric HIV treatment challenges

Between 1980 and 2005, among 10 million children born in Zimbabwe, a cumulative 504,000 were vertically infected with HIV (144). As of 2010 it is estimated that about 120000 children under 15 years are living with HIV/AIDS, of which 3.4% of children aged 10 years are long-term survivors of MTCT (145). Despite national commitment from relevant stakeholders, paediatric cART coverage increased from 22 % in 2009 to 37% in 2011 (146) which is still far below the recommended national target (17), see figure 9. Paediatric HIV treatment guidelines, likewise, have evolved as more evidence became available, Table 8. What is not clear is the long term effect of antiretroviral exposure on the developing brains.

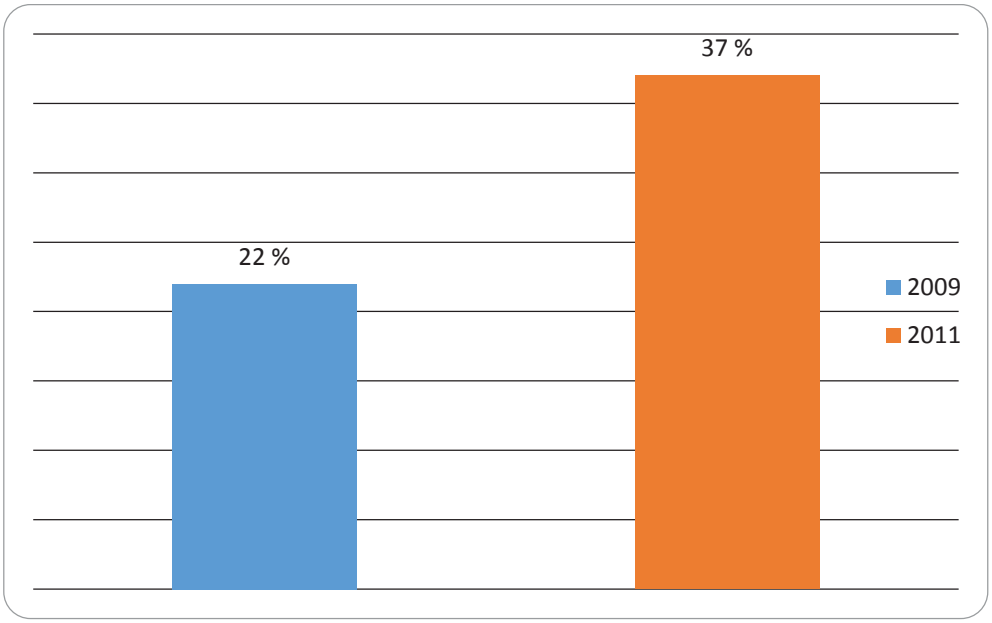

Figure 9: Estimation of cART coveragefor children 0-14 year in 2009 and 2011

Table 8: WHO guidelines for initiation of cART in children according to year

Year			**Age specific recommendations to initiate ART**		
			Infant <12 months	12-59 months	≥5years
2006 (147)	**Immunological marker**	CD4 percentage CD4 count	25% 1500	< 15% 350	Treat as adults(200 cells)
	Clinical stage		All children if stage 3 or 4		
2010 (148)	**Immunological marker**	CD4 percentage CD4 count	Treat all children irrespective of CD4 count or percentage	< 25% 750	Treat as adults(350 cells)
	Clinical stage		All children if stage 3 or 4		
2013 (149)	**Immunological marker**	CD4 percentage CD4 count	Treat all irrespective of CD4 count or percentage	Treat all irrespective of CD4 count or percentage	Treat as adult (500 cells)
	Clinical marker		Treat all irrespective of clinical stage		

2.7.4 Long term survival of antiretroviral naive children from resource limited setting

Early in the HIV epidemic, it was generally thought that children from developing countries with perinatal acquired HIV infection would not survive beyond the first year of life in the absence of highly active antiretroviral infection. However, a pooled cohort analysis estimated that at least 13% of such children will survive to age 10 years (150) and, more recent projections suggest that 17% will survive to age 15 years (151). Despite evidence on the proven benefits of early initiation of cART in children, a gap still exists between those who need and those receiving cART in Zimbabwe due to resource constraints (145). In Southern Africa, cART coverage among adults has increased from 10% to 32% in 2007, while PMTCT coverage was 43% in the same year (152). This has led to the increase in the population of cART naive children with HIV infection surviving into adolescence. Research suggests that about one-third of infected African infants are slow progressors with a median life expectancy of about 16 years (150). It is postulated that children infected postnatally through breast feeding are more likely to be slow progressors than those infected in utero or intrapartum (153). The child survivors in this study may reflect those children with the less aggressive disease.

Other hypothesis put forward to explain the survival selection include maternal host factors, infant host factors, viral phenotype, viral load levels, CD4 counts, timing of transmission and disease stage (154-157). Infants with intrauterine infection were documented to have more rapidly progressive disease than children with intra or postpartum infection (158). Infection by a less virulent HIV type 2 is another possibility, although no studies have documented sole HIV type 2 infections in the Zimbabwean population. On average, between 18 to 25% of HIV infected adults had dual infection with HIV type 1 and HIV type 2 in a survey conducted in Zimbabwe by Stanczuk et al (159).There is lack of data on the association of a dual HIV infection on child cognitive function. Studies conducted in adults seem to suggest that HIV-1 disease progression is inhibited by concomitant HIV-2 infection and that dual infection is associated with slower disease progression (160).

2.7.5 Major challenges facing child development in the wake of HIV / AIDS epidemic

Similar to other developing countries with high burdens of child morbidity and mortality from tropical diseases, interventions that aim to mitigate against neonatal and infant mortality are

prioritised at the expense of child neurodevelopment programmes. Under nutrition was estimated to be 32% among rural under 5 years old children in Zimbabwe in between 2010 and 2011 (85). Yet supplemental school feeding programs have long been abandoned due to government underfunding. Zimbabwe has had fairly good primary immunization coverage rates in the past, which presupposes that children up to the age of 18 months had access to health care institutions where growth and child development could be documented (161). However during the study period, the national immunization coverage for BCG, 3 doses of DPT+Polio and measles, decreased steadily from 80% to 53 % between 1994 to 2005-06 (85). In 2010, only 65 % of the children were fully immunized. Recent data from 2010-11 however indicate that overall immunisation coverage has begun to recover (85).

Zimbabwean`s independence in 1980 coincided with UN's International Year of the Disabled which generated strong donor support towards establishment of a community-based rehabilitation programme. A children`s rehabilitation center was established at the tertiary Harare central hospital in1986 with the aim of providing screening and developmental assessment services for children with identified risk factors for neurodevelopmental impairment. A national register and database was created for children with confirmed neurodevelopmental deficits. After examination and assessment by qualified rehabilitation technicians, children with confirmed diagnosis of neurodevelopmental impairment are recorded on the national registered and issued with red coded "At risk" stickers for easy identification by health workers. Although a program to train community rehabilitation workers was initiated in the 1990s, the numbers of rehabilitation technicians are few and rehabilitation services are restricted to big cities of Harare and Bulawayo (162).The acute shortage of trained staff, appropriate affordable screening materials and child friendly facilities remain important challenges for child neurodevelopment.

2.8 Justification

The magnitude of neurocognitive impairment among children with or without HIV infection remains underestimated despite the burden of known risk factors in resource limited settings. The advent of the HIV epidemic has added an extra risk factor for poor neurodevelopment, in particular for children living in sub Saharan Africa (150;163). Of note is the sad reality that interventions aimed at preventing vertical transmission of HIV or the early infant diagnosis and treatment are not readily available (164). Inevitably, the numbers of children infected or

exposed to HIV are expected to increase, yet there is lack of information on the neurodevelopmental performance of children as they mature from infancy to adolescence.

Previous research has identified gaps in knowledge with respect to potential differences in the prevalence of neurodevelopmental impairment, the neurocognitive domains affected, impact of exposure to maternal and infant antiretroviral therapy, role of breastfeeding and home environment on neurodevelopment function (11;61;102). The few studies conducted in developing communities differed on the prevalence of neurodevelopmental impairment due to study methodological differences in terms of age groups, choice of neurodevelopmental tools and neurodevelopmental outcomes. Different domains of neurodevelopmental function were reported by various researchers making comparison of study findings difficult. Furthermore, research findings were confounded by the presence of other risk factors to neurodevelopmental impairment such as under nutrition, micronutrient deficiency, malaria and poor socioeconomic status which was not controlled for in some cases (4).

Information on the relationship between paediatric HIV and neurodevelopment was predominantly based on studies conducted in developing countries. However, there was confounding effect of maternal and child antiretroviral therapy (11). Although treatment with cART resulted in arrested progression of HIV encephalopathy and decreased incidence of opportunistic infections among children with HIV infection, the long term neurodevelopmental effects of antiretroviral therapy exposure on the developing brain is largely unknown (59). Furthermore, the research findings from developed communities were inconsistent due to small sample sizes of children infected with HIV and the heterogeneity neurodevelopmental study populations and assessment tools (38;47;57).

It was previously thought that children from developing countries with perinatal acquired HIV infection would not survive beyond the first year of life in the absence of cART (145). Zimbabwe has more than 150 000 children living with HIV infection, of which only 43 % of those eligible for treatment were accessing cART in 2012. Despite evidence on the proven benefits of early initiation of cART in children, a gap still exists between those who need and those receiving cART. The poor paediatric uptake of cART has led to the increase in the population of cART naive children with HIV infection who survives into adolescence. There is lack of information on the neurocognitive function of long term surviving cART naïve school age children from resource limited setting.

While Zimbabwe is one of the few countries demonstrating a significant decline in adult HIV prevalence, from 29.3% in 1997 to 15% in 2012, it remains among the countries with a high HIV rate (85). While focus has been on important issues such as PMTCT and treatment of HIV, scant information is available on the impact of HIV and AIDS on neurodevelopment. With the rolling out of more efficacious PMTCT regimens it was anticipated that HIV infection would become a chronic rather than a fatal disease. What is unknown is the relationship between HIV infection and neurodevelopment in children, from a predominantly breast feeding population, living in a resource limited setting. Only a few studies to date have examined neurodevelopment in a large community-based cohort and compared neurodevelopmental outcomes of children without HIV infection, exposed uninfected and infected with HIV from a resource-constrained environment. This study was undertaken to follow up and to assess neurodevelopmental outcomes among HIV uninfected and HIV infected children from the community. It was necessary to study the neurodevelopment of children infected, exposed uninfected or uninfected unexposed so as to characterize the overall neurodevelopmental function and detect any specific neurocognitive deficits.

This information is essential towards efforts to promote early infant diagnosis and treatment of HIV. Furthermore, the characterization of neurodevelopmental deficits regardless of HIV infection, may guide rehabilitation management programs for children in resource limited settings.

3. MAIN OBJECTIVES

a) To document the different levels of the risk of neurodevelopmental impairment (NDI) among infants born to mothers infected with human immunodeficiency virus and uninfected mothers using the Bayley Infant Neurodevelopmental Screener in the BHAMC cohort.
b) To valid the MSCA for cognitive screening in school age Zimbabwean children.

c) To document cognitive function according to MSCA in 6-8 year old children infected, exposed uninfected and unexposed uninfected with HIV.

SECONDARY OBJECTIVES

a) To identify maternal and infant factors associated with neurodevelopmental impairment in infancy.

b) To identify parental and child (sociodemographic, clinical, nutrition, behavioural) factors associated with cognitive impairment at school age.

4. MATERIALS AND METHODS

4.1 Better Health for the African Mother and Child study (BHAMC).

The current study was part of the Better Health for the African Mother and Child cohort study (BHAMC) whose aim was to explore the role of sexually transmitted infections in pregnancy outcomes. From 2002 to 2004, a total of 1050 pregnant women at 36 weeks of gestation with a documented HIV results were enrolled from a national PMTCT programme in Zimbabwe: 479 (46%) HIV infected women and 571 (54%) uninfected. The sample size of the children was derived from calculations for the primary study. The intention was to recruit 300 pregnant women infected with HIV and 600 uninfected pregnant women and follow their infants for neurodevelopmental outcomes. The initial study design was modified mid-way to conveniently enroll more HIV infected pregnant women as their numbers were very few. During the study period, a total of 17528 pregnant women delivered at the study sites whilst the national HIV prevalence rate among pregnant women attending ante natal clinics was estimated at 23 % (165).

The women`s baseline socioeconomic demographics were collected and in the case of mothers infected with HIV, information on the use of prophylactic intrapartum single dose NVP in the mother–infant pair was documented, as was the standard practice as the time of the study. At the time of the study, neither CD4 counts nor cART was routinely available for HIV infected women. The women were reviewed at scheduled visits at 6 weeks, 4 months, and 9 months and 15 months where screening for reproductive tract infections and in the case of HIV uninfected women, blood was drawn for HIV screening. Neither the HIV unexposed uninfected mothers who participated in the neurodevelopmental assessments nor their infants, sero-converted for HIV infection during the study period. Their infants were not tested further for HIV infection. The infants were reviewed at 6 weeks, 3 months, and every 3 months until the age of 24 months, then yearly thereafter for growth, development assessments and clinical care. HIV exposed infants` HIV infection status were determined by HIV DNA PCR (Roche Diagnostics Indianapolis, USA) if the children were aged less than 15 months and rapid HIV antibody tests Determine (Abbot Diagnostics, Indianapolis, USA) and Oraquick (Abbot Diagnostics, Indianapolis, USA) at age 15 months. The proportion of HIV infected infants has been reported (166). Among the 598 infants assessed in infancy, none converted from HIV negative status to HIV positive status.

The study was approved by the Medical research council of Zimbabwe and the Norwegian ethical review committee, reference numbers MRCZ/A/1399 and Regional ethics committee 2011/233a respectively.

Financial support. This study was supported by the Letten foundation, Norway

4.2 Role of the PhD student in the BHAMC Study

The candidate is the paediatrician who joined the BHACM study in 2005. The enrollment of the women had ceased. She continued with the follow up of the children in the study at scheduled visits for six years providing clinical care to both children infected and uninfected with HIV according to national guidelines. She also validated the MSCA tool for cultural appropriateness among 6-8 years old children from the general population. She collected the data, cleaned, entered and analysed the results of the study. She wrote papers in this thesis namely paper 1, 2 and 3 (116;167;168). She has coauthored eight papers (92;166;169-174), where she provided clinical care as a member of the research team, and also reviewed the manuscripts.

4.3 Study design

A prospective cohort of pregnant women, infected and uninfected with HIV, enrolled at 36 weeks of gestation, whose children were followed up from birth to 8 years (175). Neurodevelopmental assessments were conducted cross sectional in infancy and again at school age.

4.4 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 20 kilometer radius. It is administered by a rural administrative board. However, following a Government directive, prior to the study period , families perceived to be living in urban slums of Chitungwiza and Epworth were forcibly evicted to the rural areas in a programme called Murambatsvina (Operation Restore Order) (176). Consequently the follow up of the children was limited by the dispersion of town communities. Some families could not be located due to lack of forwarding addresses.

4.5 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 family health services and are used mainly by the low income population.

4.6. Study population and eligibility

The population in this study comprised of three sub samples.

4.6.1: Paper 1 Kandawasvika GQ, Ogundipe E, Gumbo FZ, Kurewa EN, Mapingure MP, Stray-Pedersen B. Neurodevelopmental impairment among infants born to mothers infected with human immunodeficiency virus and uninfected mothers from three peri-urban primary care clinics in Harare, Zimbabwe. Dev Med Child Neurol. 2011 Nov; 53 (11): 1046-52.

Study Population

Participants in this study were 598 infants born to mothers participating in a national PMTCT program and followed up to 12 months for growth and neurodevelopment assessment. The inclusion criteria were infants infected with HIV, infants exposed uninfected with HIV, and infants unexposed uninfected with HIV whose mothers were participating in the BHAMC study. Also included were infants with at least one BINS assessment. Excluded were infants who had central nervous system (CNS) pathology due to causes other than HIV and in the case of a twin pregnancy, the second twin. Informed written consent was obtained from the mother.

Samples size determination

The null hypothesis was that HIV infection has no effect on the risk for neurodevelopmental impairment in infancy after the introduction of single dose NVP.

The sample size of the children was derived from calculations for the primary study. The intention was to recruit 300 pregnant women infected with HIV and 600 uninfected pregnant women and follow their infants for neurodevelopmental outcomes. The calculated sample size for the pregnant women was based on a 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 two-tailed test with a = 0.05, and allowing for a 25% loss to follow-up. 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 479 HIV infected and 571 HIV uninfected, see figure 11.

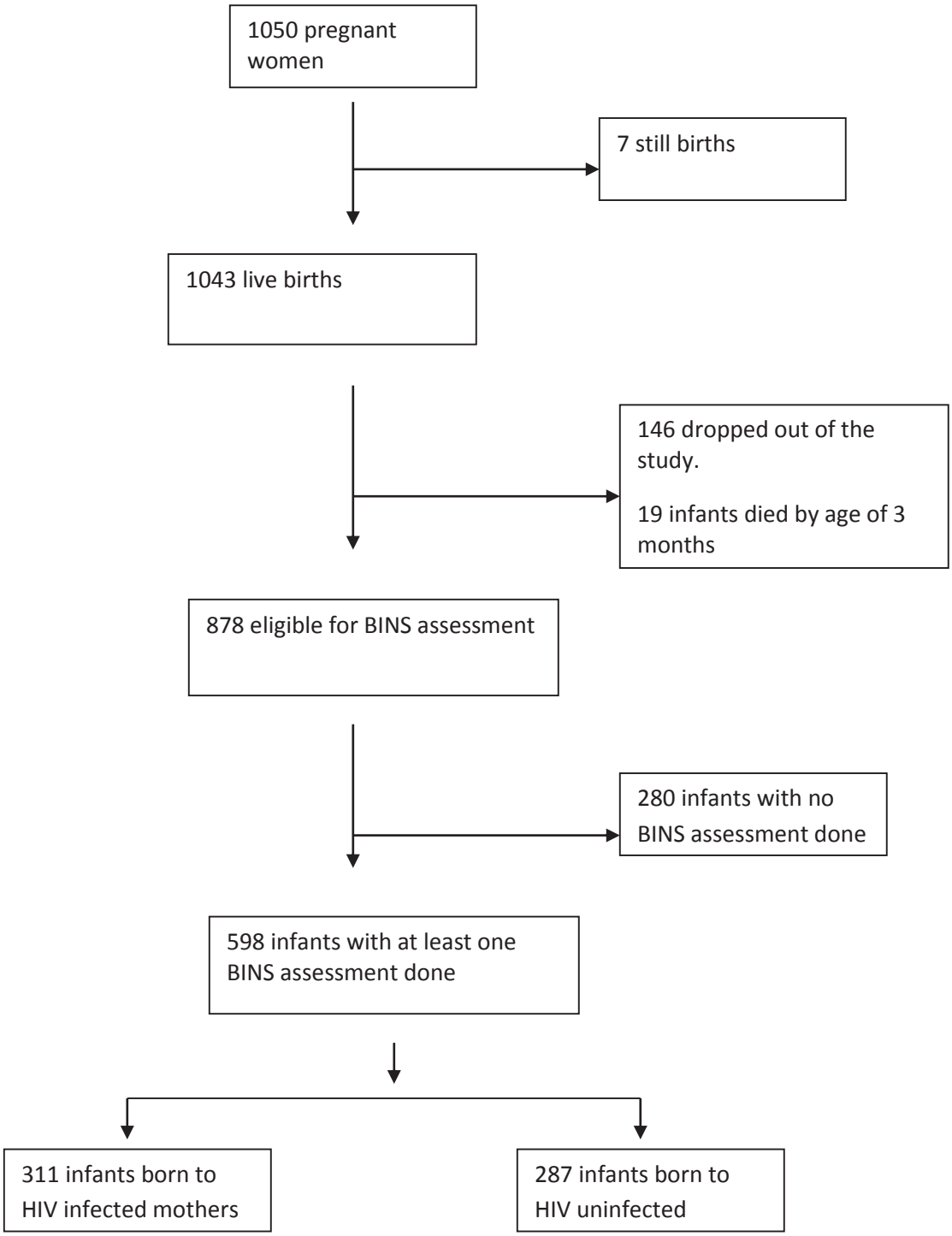

Figure 10: Flow diagram showing paediatric cohort selection at infancy

Neurodevelopmental outcomes in infancy procedures:

The dependent variable was risk for neurodevelopmental impairment (NDI) as measured by the BINS tool. The neurological development of infants was evaluated using the BINS at the ages of 3-4, 5-6, 7-9, and 11-12 months, according to the BINS manual. The BINS is a screening tool designed to identify, in general paediatric practice, infants between the ages of 3 and 24 months who are at risk of developmental delay or neurological impairment. Four global conceptual areas are assessed at 3 month intervals from the ages of 3 to 12 months: neurological functions; expressive functions; receptive functions; and cognitive processes. The scores from the four conceptual areas of ability are totaled to yield a summary score reflective of the infant's ability. The level of risk of NDI is categorized into three risk groups: low (normal), moderate, or high. Four study nurses were trained by a paediatrician licensed to administer the BINS. Test content and format were pre- served when the paediatrician observed all the nurses. Data were reviewed regularly to optimize quality control, and inter-observer reliability was enhanced by strict adherence to the manual's scoring system. Piloting was done on 30 infants not participating in the study. The BINS has not been standardized in Shona-speaking children. Infant assessments were carried out at scheduled visits by trained project nurses who were blinded to the HIV status of the mothers and infants. If infants were sick the visit was rescheduled.

***Socioeconomic status*.** Three proxy socioeconomic measures were used, maternal education employment status and availability of financial subsistence (ability to subsidize income even when not formally employed). Maternal education was operationalized as number of years the mother attended formal education. Maternal age was classified into two groups: < than 20 years versus 20 years and older; marital status was classified into two groups: married/ cohabitating versus single /divorced/ widowed; Maternal HIV status classified into two groups: HIV infected versus HIV uninfected as; Maternal syphilis was defined as a positive serological test by rapid plasma reagent test (RPR).

Infant anthropometric measurements: Weight in kilograms at one decimal place was measured using hanging Salter scale, which was calibrated before use; head circumference in centimeters was measured by a non-stretchable tape measure and vertex to heel recumbent length was measured with the infant in a supine position on a paediatric length-board standiometer. Birth weight of less than 2500grams was defined as low birth weight and head circumference of < -2 standard deviation SD below the mean for age was defined as a small head. For infants, anthropometric indicators of nutrition status were determined from weight

and height data. Infants with a Z score of <–2 were defined as undernourished, with a Z score <–2 for weight for age and height for age defining underweight and stunting, respectively (82). Moderate to severe stunting was defined as the presence height for age of -2 to -3 Z score.

Single dose NVP prophylaxis compliance referred to both the HIV infected mother and her infant each receiving a single dose of NVP (2mg/kg body weight) within 72 hours of delivery. Infant feeding history was obtained from the caregivers and categorized into two groups: those who were exclusively formula fed or those who ever breast fed (which included both infants exclusively breast fed up to 6 months of age and those who were mixed fed infants before 6 months of age). Infant health status was classified according to WHO`s Intergrated Management of Childhood Illness (IMCI) guidelines (177). Infant HIV status in infancy was categorised into 4 groups: HIV infected, HIV exposed but uninfected and HIV unexposed uninfected and child with unknown HIV status (child not screened for HIV). The children with unknown HIV status were born to HIV infected mothers, whose parents or guardians did not give consent for HIV testing.

Laboratory methods: Infant blood samples were processed and tested for HIV with DNA polymerase chain reaction (PCR) 1.5 (Roche Diagnostic, Indianapolis, IN, USA) if the infant was aged less than15 months and with the rapid HIV antibody tests, Determine (Abbott Diagnostics, Abbott Park, IL, USA) and Oraquick (Abbott Diagnostics) if the child was aged 15 months or older. A child was considered to be infected with HIV if HIV DNA PCR test was positive for those aged less than 15 months or HIV antibody test positive for those 15 months or older.

Data collection for neurodevelopment study in infancy

In infancy, information was collected at birth or within 10 days of delivery. A pre-designed data collection tool that had been pre-tested in a pilot study was used to collect data. Follow up visits were scheduled at 6 weeks; 3-4 months; 5-6 months; 7-10 months and 11-12 months, which coincided with the neurodevelopmental assessment schedules according BINS test manual. At each follow-up visit, the infant`s past medical history was obtained from the mother and a physical examination performed. The mother was asked to provide clinical and dietary information. The women signed informed consent.

Data identification

Unique identification numbers and not names were issued against each name and these were used for all client identification purposes (patient files, laboratory forms and follow up appointment cards) throughout the study. The same number was used for the mother and infant pairs.

Data entry

Data was checked for errors at the end of the every working day. After reconciliation, data was then entered and analysed in the Statistical Package for Social Scientists (SPSS version 16.0, Chicago, IL, USA). Data files were kept in a secure cabinet only accessible to members of the research team.

Data analysis

Descriptive statistics were used to summarise demographic, and birth anthropometric measures of infants for whom at least one neurodevelopmental assessment with BINS was available. Proportions of neurodevelopmental impairment were presented stratified by the infant`s HIV infection status. The Pearson Chi-square test was used to test homogeneity of proportions; in the case of small sample sizes, the Fisher's exact test was used. The independent student `s t test was used for continuous data .The outcome variable, i.e. the BINS score, was dichotomized to Low risk, i.e. normal and High risk category (Low risk versus Moderate & High risk). We used the US standardization population norms as the BINS had not been validated in Zimbabwe. Odds ratio (OR) was calculated at 95% confidence interval to measure the strength of association between various risk factors and NDI. We examined the following maternal and infant factors: maternal age in years, maternal education (up to primary level/ secondary level or beyond), employment (unemployed/employed), marital status (married, cohabitating/single, divorce, widowed), financial subsistence available (ability to supplement family income yes / no), infant birth weight (< 2500 grams/$\leq$ 2500 grams), birth length for age (normal/ small), birth head circumference for age (normal/small), infant feeding option (ever breast fed (exclusively or predominantly breast fed)/ exclusively formula fed), infant HIV status (infected / exposed uninfected / unexposed uninfected / unknown status (i.e. untested infant of born to a HIV infected mother). Multiple regression analysis was performed to identify independent risk factors for the NDI. A cut of p value <0.20 in the univariate analysis was used as the criterion to include variables in the

multivariate models, using the stepwise backward likelihood ration procedure. The level of significant was set at p value <0.05.

4.6.2: Paper 2: Kandawasvika GQ, Mapingure PM; Nhembe M, Mtereredzi R, Stray-Pedersen B.Validation of a culturally modified short form of the McCarthy Scales of Children's Abilities in 6 to 8 year old Zimbabwean school children: a cross section study. BMC Neurol 2011; 12: 147

Study population

Participants in this study were a separate 101 children aged 6 to 8 years from the community who lived in and around Harare, the capital city. These were school children attending main stream kindergarten. Three types of primary schools are currently available in Zimbabwe: government, church or private. All registered schools adhere to the same curriculum and the language of instruction in schools is predominantly English. A limited number of schools, mostly privately owned, offer special education classes for children with developmental impairment. Due to the lack of primary school teachers trained in special needs education in most government schools, children with special educational needs are taught together with mainstream pupils. The validation sample was therefore conveniently selected from a representative sample of the children per area of residence were enrolled from among those attending primary school in an urban middle income district (North Park; n=24), urban low income district (Mbare; n=39) and in a rural district (Goromonzi; n=43).

The inclusion criteria were children aged 6-8 years attending mainstream kindergarten, from urban and rural schools, willing to participate and had given their assent. Excluded were children with cognitive impairment, as a sequel of malaria, head injury, meningitis or genetic conditions such as Down`s syndrome.

Sample size determination

This was an analytical study with the following null hypothesis: There is no difference in sensitivity and specificity between the MSCA and the gold standard in the diagnosis of cognitive impairment in school age children.

Measurements*:* Cognitive impairment was defined as academic performance of below 2 chronological years for age according to the educational psychologist's assessment. The psychologist assessed basic arithmetic skills with the British abilities scale (BAS) (178) and

word building skills with Daniels and Diack's graded spelling test (179). The British abilities scale (BAS), assesses general cognitive abilities based on verbal, non-verbal reasoning and spatial ability and demonstrates the child`s current cognitive perfomance (178). These were the gold standard tests that were compared to the MSCA. The BAS and MSCA have similar developmental constructs (i.e. verbal component) but were standardized against different populations (98). The BAS and Daniels and Diack`s graded spelling test are both Western tools, which have not been validated for Shona speaking Zimbabwean children. Academic competence was computed from a table of norms representative of British children standardized norms. However, the tests performance of these tools was supplemented by the clinical assessments by the educationist.

The performance of the MSCA was compared against the educational psychologist assessment. The MSCA measures the ability to solve problems and process information. The general cognitive index is computed from the verbal, quantitative and perceptual performance domains. Cognitive impairment according to MSCA was then assessed at 3 selected cut of points:-2SD, -1.5SD and -1SD below mean GCI score of 100, according to South African children standardization norms (34). Two categories of children were identified; those with normal development or children with developmental delay. The paediatrician had received training in neurodevelopmental assessment at established neurodevelopment centers in Harare, Zimbabwe and Oslo, Norway,whilst the educational pyschologist held a degree in pychology and a post graduated diploma in educational pyschology.

The independent variables were as follows: child `s area of residence (rural/urban), gender (male / female), prior preschool attendance (yes/ no), current school grade, underweight (-2SD Z score for weight for age), wasting (-2 SD Z score for weight for height), stunting (-2SD Z score for height for age).

Data collection

Information was collected on a pre-designed data collection tool that had been pre-tested in a pilot study.

Data collected included demographics, school grade, past medical history and cognitive function test scores.

***Cognitive assessment*:** Each child's cognitive performance was assessed independently by two examiners: the researcher and the educational psychologist within a 24 hour period. The

children were counter balanced between the two examiners with the first half examined by the researcher first while the other was examined by the educationist first. A swop over was made the next day where the first half was examined by the educationist and visa versus.

Data identification

Unique identification numbers were issued against each name and were used for all client identification purposes (patient files and follow up appointment cards) throughout the study.

Data entry

Data was checked at the study site at the end of the every working day. Data errors and omissions were corrected within twenty four hours of data collection in consultation with the school authorities. After reconciliation, the data was then entered analysed in the Statistical Package for Social Scientists (SPSS version 16.0, Chicago, IL, USA). Data files were in a secure cabinet and were only accessible to members of the research team.

Data analysis

Descriptive statistics were used to summarise the socio demographic profiles of the children. The sensitivity (probability that a test result will be positive when the disease is present) and specificity (probability that a test result will be negative when the disease is not present) was calculated. The positive predictive value (probability that the disease is present when the test is positive) and the negative predictive value (probability that the disease is not present when the test) were calculated at -1SD, -1.5SD and -2 SD cut of points. Raw agreement between the 2 observers was calculated using the kappa coefficient were the value of 0.81-1.00 was defined as almost perfect agreement, 0.61-0.80 as substantial, 0.41-0.60 as moderate, 0.21-0.40 as fair, 0.00-0.20 as slight and values below 0.00 as poor agreement(180). Proportions of cognitive impairment were presented by area of residence. The Pearson Chi-square test was used to test homogeneity of proportions; in the case of small sample sizes, the Fisher's exact test was used. The independent student`s t test was used for continuous data. The outcome variable, i.e., GCI score, was dichotomized to normal cognitive function and impaired cognitive function. A score of 68 and below (-2 SD below the mean) was selected as the cut-off point for cognitive impairment. Odds ratio (OR) was calculated at 95% confidence interval to measure the strength of association between risk factors and cognitive impairment.

4.6.3: Paper 3: Kandawasvika GQ, Kuona P, Chandiwana P, Masanganise M, Gumbo FZ, Mapingure MP, Nathoo K, Stray-Pedersen B .The burden and predictors of cognitive impairment among 6-8 year old children infected and uninfected with HIV from Harare, Zimbabwe: A cross sectional study: Dev. Med. Child. Neurol 2015; 53 (11): 1046-1052. Epub 2014 Jan 13.

Study population

The eligible study population (children with known addresses) consisted of 389 children aged 6 to 8 years identified from the cohort who had participated in the BHAMC study (181). The inclusion criteria were HIV infected, HIV exposed uninfected and unexposed uninfected children aged 6 to 8 years enrolled in the initial cohort, willing to participate and had given assent, see figure 11. Excluded were children with cognitive impairment as a sequel of other conditions such as malaria, head injury, meningitis, and congenital infections. In cases of twins, only the first twin was enrolled.

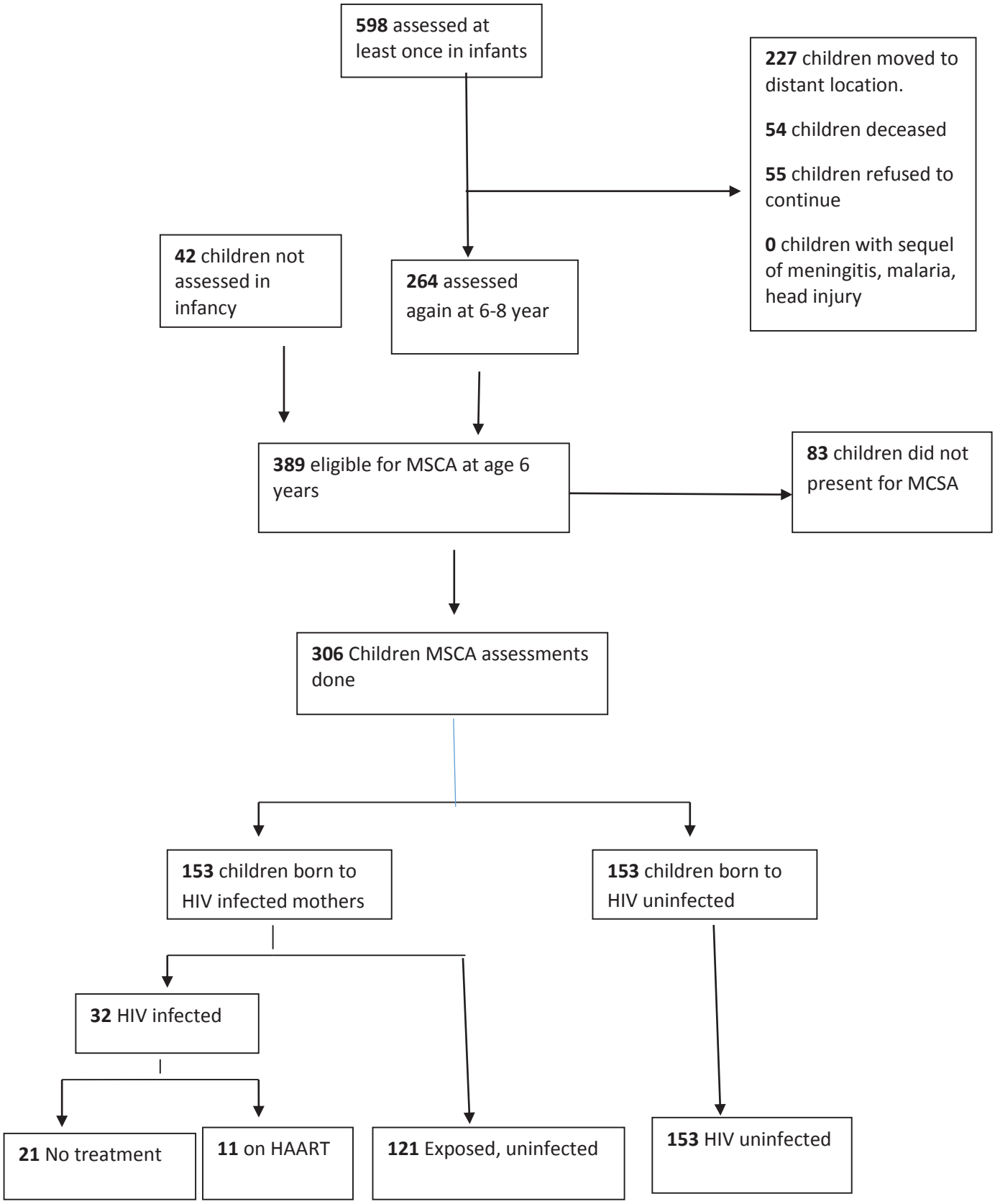

Figure 11: Flow diagram showing paediatric cohort at age 6-8 years

At school age, a total of 306 out of the 389 eligible children (children with known addresses) were available and agreed to participate in this study see figure 11. Of the 306 children; 32 were HIV infected, 121 HIV exposed uninfected and 153 HIV unexposed uninfected. Their median age (range) was 95 (75-109) months and 179(58%) were female. Eighty three children did not return for follow up despite repeated home visits and cellular phone calls. The main reason was the lack of time as the caregivers were busy working and therefore unable to attend the clinic. In some cases there had been a change in child`s primary caregiver due to death of a parent and consent was not available from the guardians. Significantly more children infected with HIV died 4.6% vs 29%, p value < 0.01.

Of the total sample, 32 (10%) children were infected with HIV, eleven of whom were on cART and 21 were clinically asymptomatic of HIV infection and were not on antiretroviral therapy. Reported mean duration of cART prior to study enrolment was 5 years and all the children on cART were classified as WHO clinical case definition stage 3 at the time of assessment during the study period. In the HIV infected group, CD4 counts tested within three months of study enrollment were known for 18 children. Comparison of the mean CD4 counts between the cART experienced and cART naïve children were similar: 535 and 680 cells/mm^3 respectively.

Sample size determination

The null hypothesis was that HIV infection has no effect on the cognitive performance at the age of 6-8 years.

The study power determination was calculated using the Power and Sample Size Calculation program (PS program), version 3.1.2, 2014, WD Dupont &WD Plummer, Nashville, USA. Based on estimated prevalence of cognitive impairment among normal school children aged 6-8 years of 3% from previous studied (116), and anticipated level of cognitive impairment in HIV infected children of 16%, this gave the current study a power of 72%. For a study power of 80% the required sample size for HIV infected children was 40.

Cognitive assessment

Intelligence, as measured by MSCA, the child`s ability to solve problems and process information was the dependent variable. Each child`s cognitive function was assessed once. The culturally modified McCarthy Scales of Children `s Abilities (MSCA) was administered individually in the presence of the parent or guardian in the local Shona language by a

paediatrician blinded to the children`s HIV sero-status (182). The MSCA consists of 18 items, which are summed to generate 5 domains: 1) verbal, which refers to those cognitive abilities related to information processing; 2) quantitative, which relates to numerical abilities; 3) memory assesses short term retention of information (verbal, perceptive or numerical); 4) perceptive–performance, which refers to tasks related to perceptive information processing and 5) motor abilities. Items from the verbal, perceptual-performance, and quantitative domains are content oriented are computed to generate the General Cognitive Index (GCI). The mean for the General Cognitive Index (GCI) is set at 100, with a Standard Deviation (SD) of 16 according to the MSCA administration manual. For each of the 5 subsets the Index scores have a mean of 50 with a SD of 10. Items from the verbal, perceptual-performance, and quantitative domains are content oriented, with no subtests from one domain contributing to the score of another domain. The memory and motor domains are process oriented, with all subtests in the memory domain overlapping with verbal, perceptual-performance, or quantitative domains(114). Cognitive impairment was defined as a score -2SD below the mean for MSCA (100).

Measurements:

Socioeconomic status. Three proxy socioeconomic measures were used, maternal education employment status and financial subsistence. Maternal education was operationalized as number of years the mother attended formal education. Orphan hood was defined as double orphan if both parents were deceased, single orphan if one parent was deceased, maternal orphan if mother decease or paternal orphan if father deceased. Health status was classified according to IMCI guidelines (183):History of diarrhea (yes / no), History of pneumonia (yes./.no), history of fever (yes / no), History of ear pain (yes./ no) (183). Child HIV status was categorized into 3 groups: HIV infected group, HIV exposed but uninfected and HIV unexposed uninfected. For children infected with HIV, the paediatric HIV clinical staging was assessed according to WHO clinical case definition algorithm(stage 1= asymptomatic/ stage 2 = mild symptoms/ stage 3 = advance symptoms / stage 4 = advanced symptoms)(147). Anthropometric indicators of nutrition status were determined from weight and height data. Children with a Z score of <–2 were defined as undernourished, with a Z score <–2 for weight for age and height for age defining underweight and stunting, respectively (82) .Chronic malnutrition was defined as the presence of moderate-to-severe stunting. The neurological assessment included evaluation of mental status by the Glasglow coma scale, examination of cranial nerves, sensation, muscle tone, power, upper and lower extremity reflexes, and balance.

Analytical Procedures: Haemoglobin (hb) levels were determined in the clinics for all children using HEMOCUE® Hb 201, microcuvette, hemoglobin System, Quest Diagnostics, SE-262 71 Ängelhom, Sweden. Anaemia was classified according to WHO recommendations as mild if hb level was >8-11 g/l, moderate if hb was 5-8 g/l and severe if hb was <5 g/L(184). Children had 4 mls of blood collected for full blood count and micronutrients levels. CD4 counts which were documented within three months of study participation were obtained from children infected with HIV`s clinic notes files. Laboratory forms and blood tubes had case numbers with no names to maintain confidentiality.

The Pediatric Symptomatic Checklist (PSC), was used to screen for behavioral problems. The PSC is a Western tool PSC which not been validated among the Shona in Zimbabwe. However, the validated Setswana culturally adapted PSC was reported to have high sensitivity when used as a screening test for psychological problems among children with HIV infection in Botswana, a country with similar HIV prevalence rates to Zimbabwe (185). The PSC was chosen for simplicity in test adminstration in a busy clinical setting. The The tool consists of 35 items reflecting caregiver impression of the child's psychosocial function. A score at or above the cut-off score of 28 indicates the need for further evaluation for behavioral problems (186) .

Data collection

The children were invited the outpatient clinic on a designated date for physical, neurological and psychometric examination. Neurocognitive testing was deferred in children with an acute illness. Information about the children's health complaints and home environment was obtained from the primary caregivers. A pre-designed data collection tool that had been pre-tested in a pilot study was used to collect data.

Data identification

Unique identification numbers were issued against each name and were used for all client identification purposes (patient files, laboratory forms and follow up appointment cards) throughout the study. The same number was used for the mother child pairs.

Data entry

Data was checked for errors at the end of the every working day. After reconciliation, the data was then entered and analysed in the Statistical Package for Social Scientists (SPSS version 16.0, Chicago, IL, USA). Data files were kept in a secure cabinet only accessible to members of the research team.

Data analysis

Descriptive statistics were used to summarise socio-demographic characteristics of the primary caregivers and children. The mean index scores in verbal, perceptive performance, quantitative and memory were compared by child HIV status using One-Way analysis of variance (ANOVA), and Bonferroni post- test to show which groups had differences if any. Three groups of children were compared: HIV infected; HIV exposed but uninfected and HIV unexposed uninfected who were the controls. Cognitive impairment was defined as a score -2SD below the mean for MSCA (100). The Pearson Chi-square test was used to compare categorical variables between impaired and normal children; in the case of small sample sizes, the Fisher' s exact test was used. Student's t-test was used to compare continuous variables. Odds ratio (OR) was calculated at 95% confidence interval to measure the strength of association between various risk factors and cognitive impairment. We examined the following caregiver and child factors: primary care giver (parent /other relative), caregiver educational level (up to primary level/ secondary level or beyond), caregiver employment status (unemployed/employed), care giver financial subsistence available (ability to supplement family income yes / no), child orphan hood (yes /no), current school grade, child health status (normal /abnormal), child HIV status (infected/ exposed uninfected /unexposed uninfected), WHO clinical stage (stage 1/ stage 2/ stage 3 / stage 4), child on combinatin antiretroviaral therapy (yes or no), underweight (yes/no) ,stunting (yes/ no), anaemia (yes /no), Head size (normal > -2SD for age/ small $\leq$ 2SD for age), risk for behavioral problems (no risk, score < 28/ risk present, score $\geq$28).Multiple regression analysis was performed to identify independent risk factors for the cognitive impairment. A cut of p value <020 in the univariate analysis was used as the criterion to include the variable in the multivariate models, using the stepwise backward likelihood ration procedure. The level of significant was set at p value <0.05.

4.7 Ethical consideration

Application for ethical clearance was sought from the Medicine Research Council of Zimbabwe and the Norwegian Research Committee reference numbers MRCZ/A/1399 and 2011/233a respectively. Ethical concerns in this study included the involvement of children in research, informed consent from minors, confidentiality and beneficence and standard of care. Children in research are a vulnerable group and issues that deal with child development are sensitive to both the child and family. It is of great importance to present research results in a

way that does not promote the stigmatization of children with developmental impairment. The care givers were informed that through participation in the study their child could be identified to have neurodevelopmental impairment which might result in stigmatization in the community. Children identified with neurodevelopmental impairment were referred for rehabilitation at tertiary centers offering such services. The counseling of caregivers and children was provided by the research team counselors. The guardians and children were reimbursed any transport costs they incurred when they came to the study clinic.

5. RESULTS

5.1 Paper 1:Kandawasvika GQ, Ogundipe E, Gumbo FZ, Kurewa EN, Mapingure MP, Stray-Pedersen B.Neurodevelopmental impairment among infants born to mothers infected with human immunodeficiency virus and uninfected mothers from three peri-urban primary care clinics in Harare, Zimbabwe.Dev Med Child Neurol. 2011 Nov;53 (11):1046-52.

The paediatric cohort selection from the primary study is presented in figure 10. Non-compliance with follow-up in infancy was significantly higher in uninfected mothers compared to infected mothers; 50% versus 35%, p value = 0.001. Of the 598 infants assessed, 305 (51%) were female and 293 (49%) were male. Sixty-five infants (11%) were infected with HIV, 188 (31%) were exposed but uninfected, 287 (48%) were unexposed, and 58 (10%) were of unknown status (infants born to mother infected with HIV who had not been tested). HIV DNA PCR testing was not routinely offered at the time of the study in 2002. Infants with unknown HIV status were similar to their peers with known HIV status in terms of maternal baseline demographics, infant birth arthropometric measurement and infant feeding options.

Baseline mother and infant characteristics are summarized in table 9. HIV infected mothers were older, single and had no financial subsistence compared to HIV uninfected mothers. More infants born to HIV infected mothers were smaller at birth and formula fed compared to those born to HIV uninfected mothers.

Table 9: Baseline maternal and infant characteristics compared by maternal HIV infection status

Maternal factor	Maternal HIV infected n(%)	Maternal HIV uninfected n(%)	P value*
Maternal age			
≤20 years	30 (10)	62 (22)	0.00
Maternal education			
Primary	68 (22)	46 (16)	0.07
Marital status			
Single, divorced, widowed	36 (12)	14 (5)	0.00
History of alcohol use			
Yes	28 (6)	19 (3)	0.18
Financial subsistence available			
No	79 (27)	52 (19)	0.05
Infant factors			
Birth weight			
<2500	22(8)	10 (4)	0.04
Head circumference at birth			
Small	42 (16)	28 (12)	0.2
Length at birth			
Small	43(17)	25 (11)	0.2
Multiple pregnancy			
Yes	3 (100)	0	0.3
Ever Breast fed			
Yes	275 (89)	276 (99)	0.00

*To detect group differences on categorical and continuous variables, χ^2 and independent-samples *t* tests, 2-tailed, were used, as appropriate.

Overall neurodevelopmental outcomes in infancy

Cross-sectional assessment were conducted at the ages of 3-4, 5-6, 7-10 and 11-12 months. Total of 409 infants were assessed at ages 3-4 months; 80 at 5-6 months; 370 at 7-10 months and 102 at 11-12 months respsctively. The majority of infants fell in the low risk category group for NDI (542⁄598), The prevalence of high risk for NDI at any time among the infants screened between 3 and12 months was 9.4% (95% CI 7.1–1.1%): 9.2% in males versus 9.6 % in females.Two infants who were categorized as high risk, one at 3 months and one at

6months, continued to be in the high risk group at the 9-month visit. The BINS score at 3 months was predictive of high risk for NDI at 9 months in (2/8) 25% (95% CI 5-55%) of the comparisons.

Table 10: Maternal and infant risk factors for neurodevelopmental impairment for 598 infants

	Unadjusted Odds ratio OR (95% CI) *	**AdjustedOdds ratio OR (95% CI)***
Maternal Factors		
Maternal Education		
(Secondary vs Primary)	0.96 (0.47 -1.91)	0.51 (0.22-1.21)
Marital Status		
(Married,cohabitating vs Single, divorced,widowed)	0.74 (0.30-1.83)	0.65 (0.12-3.91)
Financial subsistance available		
(Yes vs no)	2.62 (1.44 - 4.76)	2.55 (1.02 - 6.36)
Maternal HIV infection		
(No vs yes)	0.86 (0.49 -1.49)	0.51 (0.22 -1.21)
Maternal syphilis infection		
(No vs yes)	0.16 (0.02 - 1.00)	0.21 (0.03 - 1.57)
Infant Factors		
Birth Weight		
(>2500g vs < 2500g)	2.36 (0.92 - 6.10)	1.82 (0.61 - 5.39)
Head circumference at birth		
(Normal vs small)	2.6 (1.29 - 5.22)	2.22 (1.04 - 4.82)
Nevirapine prophylaxis		
(Yes vs no)	0.99 (0.99 -1.0)	0.9 (0.99 -1.00)
Multiple pregnancy		
(Yes vs no)	4.91 (0.44 - 55.0)	7.86 (0.43 - 1.40)
Child HIV status		
(unifected vs infected)	2.1(1.0 - 4.32)	1.7 (0.69 - 4.2)

***Odds ratio (OR) , calculated at 95% confidence interval to measure the strength of association between maternal and infant factors and risk for NDI.*

Of the 56 (9.4%) children identified as high risk for NDI, 11 (20%) were HIV infected, 17 (30%) were exposed uninfected, 25 (45%) unexposed uninfected and 3 (5%) were of unknown HIV status. Infants infected with HIV demonstrated a higher risk for NDI than their non-infected peers by the age of 3 months; see Paper1, table 111. Small head circumference and lack of family subsistence, a proxy for low socioeconomic status, were risk factors for increased risk of NDI, see table 10. Infant birth weight, gender, exposure to single dose nevirapine or being breast fed, did not influence risk for neurodevelopmental impairment in

first 12 months of life. Exposure to single dose NVP did not influence HIV vertical transmission rates.

5.2 Paper 2: Kandawasvika, GQ; Mapingure, PM; Nhembe, M; Mtereredzi, R; Stray-Pedersen, B.Validation of a culturally modified short form of the McCarthy Scales of Children's Abilities in 6 to 8 year old Zimbabwean school children: a cross section study. BMC Neurol 2011; 12: 147

Of the 101 children from the community assessed, their median (range) age was 97 (77-102) months and 60 were female. Distribution of participants by area of residence was 40 (40%) rural, 37(37%) urban low income and 24 (24%) urban high income. All the children had attended preschool.

Table 11: Comparison of demographic data and nutritional status for the validation population and the Zimbabwe demographic health survey (ZDHS) 2005

Characteristic	Validation study population N = 101, n (%)	ZDHS population N = 8907, n (%)
Gender		
Male	41 (41)	7175 (45)
Female	60 (60)	8902 (55)
Area of residence		
Urban	40 (40)	3500 (39)
Rural	61 (60)	5405 (61)
Nutritonal status		
Height for age		
Height for age below -2SD (stunting)	21 (21)	2492 (28)
Height for age > -2SD (normal range)	75 (75)	6610 (72)
Missing data/ unknown	4 (4)	-
Weight for age		
Weight for age below -2SD (underweight)	14 (14)	1513 (17)
Weight for age > -2SD	83 (83)	7389 (83)
Missing data/unknown	4 (3)	-
Weight for height		
-2SD (wasted)	7 (7)	623 (7)
Weight for height >-2SD	91 (91)	8283 (93)
Missing data/ unknown	4 (4)	-

The demographic data (table 11) demonstrate the validation sample is similar to the national average in terms of nutritional status, area of residence and gender.
In paper 2, tables 1, 2 and 3 show the comparison between MSCA and the local gold standard (in this case, the educational psychologist`s independent assessment on the presence of

cognitive impairment according to BAS and Daniels and Diack's test scores). The sensitivity rates were low, ranging from 17 to 50 % with lower sensitivity at cut-off -2SD. Specificity rates had less variation ranging from 95% to 100 %. The positive predictive values ranged from 69 to 100 % whilst the negative predictive values had less variation and ranged from 84 to 89%. The total agreement between the local gold standard and the MSCA at cut off point -2SD,-1.5 SD and -1 SD below the mean 86%, 89% and 87% respectively indicating moderate agreement whilst the kappa coefficient at the same cut off points was 0.3, 0.5 and 0.5 respectively, indicating fair to moderate agreement.

The number of children identified with cognitive impairment using -2SD, -1.5SD and -1SD below the mean for MSCA as a cut-off point were 3 (3%), 7 (7%) and 13 (13%) respectively while the psychologist identified 18 (18%) children overall. The rural children tended to score significantly lower marks compared to their peers from urban areas, mean (SD) 98 (15) and 107 (15) respectively, p=0.01. There was no difference in the mean (SD) scores between boys and girls, 103 (17) and 103 (15) respectively, p value = 1.

5.3 Paper 3: Kandawasvika GQ**,** Kuona P, Chandiwana P, Masanganise M, Gumbo FZ, Mapingure MP, Nathoo K, Stray-Pedersen B .The burden and predictors of cognitive impairment among 6-8 year old children infected and uninfected with HIV from Harare, Zimbabwe: A cross sectional study: Child Neuropsychol 2015; 21(1): 106-120.

The paediatric cohort selection at 6-8 years of age is presented in figure 11. Table 12 presents a comparison of the children included in the study cohort at age 6-8 years stratified according to HIV status group with respect to a number of demographic variables. No differences in proportions were found among the three groups with respect to maternal age, education, marital status and income. The 306 children were evenly divided by gender. Children in the HIV infected group were more likely to be in the first school grade (P value = 0.03) and to have smaller head size for age, p value = 0.03 compared to the HIV unexposed uninfected. The children in the exposed uninfected group were more likely to be orphans, (p value < 0.01).

There were no significant differences in baseline characteristics of the children lost to follow-up at age 6-8 years compared to those that completed the study follow-up period except that children born to HIV uninfected mother were more likely to be non-compliant with the follow up visit 54 (26%) vs 29 (16%) p value < 0.01.

Table 12: Baseline characteristics for the HIV infected (n=32), exposed uninfected (n=32), unexposed uninfected (n=153) 6 to 8 year old children.

Variable	HIV Infected n (%)	HIV uninfected exposed n n (%)	HIV uninfected unexposed n n (%)	p-value
Gender				
Male	15 (47)	53 (44)	59 (39)	**0.5**
Current school grade				
Median (Range)	1 (0-3)	2 (0-3)	2 (0-3)	**0.001***
Did child attend preschool				
Yes	22 (69)	94 (78)	116 (76)	0.5
Primary care giver				
Parent	26 (81)	83 (69)	126 (82)	**0.04***
Is child Orphan				
Yes	14 (44)	57 (47)	17 (11)	**0.00***
History of fever in past 3 months				
Yes	17(59)	50 (52)	67 (49)	0.6
Haemoglobin level in g/ dl				
<11	4 (13)	13 (11)	12 (8)	0.5
Weight/age				
Weight < -2 Z score	6 (19)	13 (11)	23 (15)	0.4
Height/age				
Height < -2Z score	7 (24)	25 (21)	31 (20)	0.9
Head size				
Head size < -2 SD	4 (13)	3 (2)	4 (4)	**0.03***

*P value from an exact χ^2 test comparing distributions of proportions among the three groups.

Nutritional profiles

Out of 306 children, 42 (14%) children were underweight whilst 63 (21%) had moderate to severe stunting. Nutritional status was similar across the three groups, table 1, Paper 3. Haemoglobin levels were determined in 301 children. The majority of children had normal haemoglobin (90%) whilst 27 (9%) had mild anaemia and two (1%) had moderate anaemia. There was no difference in mean haemoglobin (SD) among the three groups: HIV infected 12.5g/dl (10.8-16.8); HIV exposed uninfected 12.6g/dl (8.5-15.6) and HIV unexposed uninfected 12.7 (7.9-16.6).

Neurological characteristics

Cranial nerve deficits were clinically identified in two children with HIV infection: one had third cranial nerve palsy and the other had eighth cranial nerve palsy. None of the children demonstrated abnormalities in tone, power or upper and lower extremity reflexes.

Positive screens for behavioral problems was reported in 71 (23 %) of the children and was equally divided among the three groups.

Neurocognitive profile across the three groups: children with HIV infection, exposed uninfected with HIV and Unexposed uninfected

The mean (SD) GCI for the whole study group was 82 (15). Children with HIV infection scored significantly lower than the HIV unexposed uninfected children in perceptual performance domain, p value = 0.03, Paper 3, table 2. However, they did not differ significantly with the other groups in the verbal, quantitative and memory domains. Children already on cART had the lowest scores on all domains, although not statistically significant.

The comparison of risk for cognitive impairment across the three groups: children with HIV infection, exposed uninfected with HIV and Unexposed uninfected

Of the 306 children, 49 (16%) (95% CI 12-20 %) had cognitive function of -2SD below the mean for MSCA (the standardization population means were used). There was no difference in the prevalence of cognitive impairment by child HIV status; 14% in HIV uninfected unexposed; 18% in HIV exposed uninfected and 16% in HIV infected group. Among the HIV infected group, there was no difference in cognitive function between those on cART and those without: three (18%) and two (14. %) respectively. Unemployed caregivers were more likely to have cognitive impaired children than their employed counterparts, p value = 0.01. Cognitive impairment was significantly associated with parental loss, a history of fever three months prior to the study, and presence of moderate to severe under nutrition in univariate analysis, table 3, Paper 3 Children with maternal compared to paternal loss tended to have the lower scores. In the multivariate logistic regression model, caregiver unemployment status remained a risk factor for cognitive impairment after adjusting for other factors, with an odd ratio of 2.1 (95% CI 1.03-3.4) for all children, see table 13.

Table 13: Factors associated with cognitive impairment in the 6 to 8 year old HIV infected, exposed uninfected, unexposed uninfected children.

Factor	Cognitive Impaired n (%)	Normal Cognitive function n (%)	Unadjusted Odds Ratio (95% CI)	P value*
Median (range) age in years	35 (18-70)	35 (23-70)	1.01(0.98-1.04)	0.7
Sex Male	0	13 (5)	incalculable	0.1
Main care giver sibling/grandparent/other	14 (29)	56 (22)	1.43 (0.72-2.84)	0.3
Education Primary	19 (39)	76 (30)	1.5 (0.8-2.8)	0.2
Maternal HIV status Infected	22 (45)	131 (51)	1.19 (0. 6-2.2)	0.5
Occupation Unemployed	30 (61)	105 (41)	2.29 (1.2-4.8)	**0.008**
Reported Monthly income in US$ (mean/SD)	127 (100)	138 (102)	0.99 (0.99-1.00)	0.5
Sex Male	22 (45)	105 (41)	1.2 (0.64-2.18)	0.6
Is child Orphan Yes	19 (39)	69 (27)	2.13 (1.13-4.00)	**0.02**
Did child attend preschool No	15 (31)	58 (23)	1.48 (0.76-2.91)	0.3
History of fever in past 3 months Yes	27 (66)	111 (48)	2.07 (1.03-4.14)	**0.04**
Child HIV status Uninfected, exposed Infected Unexposed, uninfected	22 (50) 5 (19)	99 (43) 27 (17)	1.32 (0.69-2.52) 1.10 (0.38-3.17) 1	04 0.9
Haemoglobin level in g/ dl <11	4 (9)	25 (10)	0.85 (0.28-2.56)	0.8
Weight/age Weight <-2 Z Score	12 (25)	30 (12)	2.40 (1.13-5.10)	**0.02**
Height/age Height <-2Z score	18 (38)	45 (18)	2.73 (1.40-5.33)	**0.002**
Head size Head size < -2 SD	5 (10)	8 (3)	3.42 (1.07-10.95)	0.03
Behavioral problem screen Positive	9 (23)	62 (27)	1.031 (0.09-1.15)	0.7

**P value from an exact x^2 test comparing distributions among the three groups.*
-Odds ratio (OR), calculated at 95% confidence interval measuring the strength of association between caregiver and child factors and risk for NDI.

The predictive utility of BINS high risk status in infancy for cognitive impairment at 6-8 years in 264 children.

Of the 306 children aged 6-8 years, only 264 had come for BINS assessments in infancy. Overall cognitive impairment was present in 40 (15%) of these children There was no significant difference in cognitive function when stratified by gender, HIV infection status or level of risk of neurodevelopmental impairment in infancy. Thirty nine children with low risk for NDI in infancy fell in the cognitive impaired group at school age. Of the 10 children with high risk for NDI in infancy, nine (90%) improved and had normal cognitive function whilst one did not improve. The positive predictive value (those who were high risk and then had cognitive impairment at 6- 8 years was 10% (95% CI 9-29%). The negative predictive value (those with no risk for NDI who did not develop cognitive impairment) was 85% (95% CI 80-89%), see table 14. An early high risk classification for NDI was not associated with increased probability of cognitive impairment at school age.

Table 14: Calculation table for predictive value of BINS (NDI in infancy) compared to MSCA (cognitive impairment) at 6 to 8 years old

Cognitive impairment at 6-8 years			
High risk for NDI	Yes	No	Total
Yes	1 *a*	9 *b*	10 *a+b*
No	39 *c*	215 *d*	254 *c+d*
Total	40 *a+c*	224 *b+d*	264

Positive Predictive Value= a/a+b

Negative Predictive Value= d/c+d

6. DISCUSSION

This PHD thesis is based on a cohort study that has followed up children from birth to 8 years, whose mothers participated in a HIV prevention program in Zimbabwe. Only a few prospective cohort studies conducted in both developed and developing countries have evaluated the course of neurocognitive and motor development in infants infected with HIV from birth due to various reasons (13;31;33;37;65). In developing countries, there is the lack of infrastructure and the expertise necessary to develop or validate screening tools. Furthermore, the conduction of prospective studies on HIV usually involves laboratory diagnosis and follow up, which is costly for most resource constrained communities.

6.1 Main findings

The frequency of high risk for NDI at any time among the infants screened during the period between 3 and 12 months was 9.4% with no difference between the sexes. Infants infected with HIV demonstrated a higher risk for NDI than their non-infected peers by the age of 3 months. A small head circumference for age at birth and the lack of family financial subsistence were factors associated with high risk for NDI. Infant`s birth weight, exposure to single dose prophylactic nevirapine or being breast fed, did not influence risk for neurodevelopmental impairment in first 12 months of life. Exposure to single dose NVP did not influence HIV vertical transmission rates.

In the validation study, the culturally modified MSCA showed high specificity but low sensitivity among the 6-8 year old children attending main stream school. The positive predictive values and the negative predictive values were high ranging from 86 to 100 % and 84 to 89% respectively. The children from the rural areas tended to score significantly lower marks compared to their peers from urban areas.

At school age, the overall prevalence of cognitive impairment was 16% among the 306 children in the BHAMC cohort, with no difference in prevalence of cognitive impairment by child HIV status. Parental loss, a history of fever three months prior to the study, a small head circumference for age and presence of moderate to severe under nutrition, were significantly associated with impaired cognitive performance in the univariate analysis. After adjusting for other factors, caregiver unemployment status remained a risk factor for cognitive impairment. Children with HIV infection however scored significantly lower than the HIV unexposed uninfected children in perceptual performance domain.

6.1.1 Risk for neurodevelopmental impairment (NDI) in infancy

Previous studies have reported that NDI is more frequent in infants infected with HIV than in infants uninfected with HIV, which is similar to our findings (31;33;42). The higher risk of NDI among the infants infected with HIV reported in the study may reflect the early effect of HIV infection on the immature central nervous system. Exposure to perinatal HIV infection has been suggested to be associated with reduced brain growth and neurological decline in children infected with HIV (187). The progressive HIV encephalopathy has been described in infants as young as 3 months of age (188). This critical period provides a window of opportunity to screen HIV-exposed infants early for subclinical NDI and institute affordable neuro-protective interventions such as initiation of cART and consistent cognitive stimulation of the child by the caregivers. Although the relationship between of timing of infant HIV transmission to NDI was not explored in this study owing to a small sample size of children with HIV infection, the timing of infant vertical HIV infection influenced the rate of neurodevelopmental decline in a study conducted among American infants vertically infected with HIV (38). However, the following HIV transmission rates were reported elsewhere, in a BHAMC cohort study investigating mother to child HIV transmission rates from delivery time to 15 months period: 4.3 % intrauterine transmission rate; 1.5 % intrapartum transmission rate and 21.8% overall HIV transmission rate (166). A separate study conducted in Zimbabwe assessing the risks of the timing of mother to child transmission of HIV to infant mortality in the first 6 months of life reported the following transmission rates: 9.4% intra-uterine, 16% early post-partum and 5.4% late post-partum (158).

Breastfeeding was not associated with a low risk for neurodevelopmental impairment in this study where 88% of the infants were ever breast fed. The high rate of breast feeding observed in this study is similar to the practice in many low income and middle income countries (189). Breast feeding, either exclusive or partial confers health benefits for infants and mothers, such as bonding. It is generally agreed that breast fed children are more intelligent compared to their formula fed peers (190). The benefits of breastfeeding are postulated to be mediated by long-chain polyunsaturated fatty acids (PUFA) which are present in human milk, but not in cow`s milk or most infant formulas(191). However, the relationship between breast feeding and child neurodevelopment is confounded by a myriad of factors such as maternal

socioeconomic status, age, level of education, duration of breast feeding , the type of neurodevelopmental tool used and infant`s age (192). A meta-analysis reviewing the effect of breastfeeding on child neurodevelopment in developed and developing Asian communities was inconclusive due to the presence of confounders and methodological differences in the studies reviewed (192). In the African setting where mothers predominantly breastfeed (189), there is paucity of information on the long term neurodevelopmental outcome related to breastfeeding (193).

The relatively high prevalence of NDI according to BINS classification among the unexposed uninfected infants at the age of 9 months might have been confounded by the presence of other risk factors for NDI for such as low socioeconomic status, nutritional factors, or suboptimal home environment. Lack of evidence of a difference in the risk factors for NDI at 9 months according to the infant`s HIV status might be due to the few numbers in the infected group as cART naive infants with HIV infection probably died due to poor survival. Paediatric HIV infection is estimated to increase child mortality by four fold by the age of two years compared to HIV unexposed infants (194). Non-compliance with study follow up was higher among the HIV uninfected than among the HIV infected mothers and this could have introduced bias as it is more likely that HIV uninfected mothers with unhealthy or sick children were the ones who come for follow up. The translated BINS might have underestimated the strength of the relationship between BINS score and HIV infection at 9 months of age. It is possible that some cultural bias still remained in the translated BINS test since it was developed and validated in the United States, with no normative data for BINS in other societies. Furthermore the BINS scores do not allow differentiation between delay in achieving new milestones and losing previously acquired milestones.

The BINS high risk category in infancy tool showed low positive predictive value for cognitive impairment at 6-8 years. The Positive and negative predictive values are influenced by the prevalence of disease in the population that is being tested (166). In a test conducted in a high prevalence setting, is more likely that persons who test positive truly have disease than if the test is performed in a population with low prevalence (195).

The study had the following limitations and should be interpreted cautiously: Almost 10% of the infants were of unknown HIV status (had not been tested for HIV in infancy).This decreased the number of infants with a definitive status, limiting the HIV infected sample

size. The timing of HIV infection could not be established in this study owing to the cost of HIV DNA polymerase chain reaction testing,which was not available routinely at the time of the study.This might have assisted in comparison of neurodevelopmental outcomes in infants infected with HIV at an early or later stage. Clinical markers of HIV infection progression in the infants, such as viral loads and CD4 count, were not routinely available during the study period owing to cost. We used an adapted tool with American norms and cut off scores to determine high risk status for NDI. However, the norms for a Zimbabwean infants might be different, therefore influencing the prevalence of high risk for neurodevelopment in this setting. The BINS, as with other infant screening tools,does not predict long-term outcome, but alerts the examiner to the need for further,more comprehensive diagnostic assessment. Parental report on the developmental progress of the infant and the effect of the home environment, were not explored in this study, where the parents were generally of similar low income status. Lack of infant stimulation at home, presence of a sick caregiver, and poor socio economic status have been associated with poorer neurodevelopmental outcomes in other settings.

6.1. 2 Experience in the validation of neurodevelopmental assessment tool.

The magnitude of cognitive impairment among school children in developing countries is inadequately documented due to lack of appropriate neurodevelopment tools. We validated the MSCA for cultural appropriateness among 6-8 year old school Shona speaking children from different socioeconomic backgrounds. From our experience in this study, we learnt that it was possible to adapt components of an established psychometric tool such as MSCA to suit local culture and practice and conduct a community based study among normal 6- 8 year old rural and urban children.

Sensitivity rates for the culturally modified MSCA were low at -2SD, compared to the specificity rates which were highest (95 to 100 %) when using the more stringent cut-off for the standardized assessment of -2SD. It is plausible that the short MCSA does not contain enough items to capture the diverse cognitive problems with equivalent precision. A low sensitivity in a developmental screening tool may provide a false assertion to parents and guardians who would otherwise benefit from referral for remedial at tertiary centers. In our context of a developing community, screening children with MSCA would identify 3/18 and 9/18 using 2SD and 1 SD respectively of children with mild to severe impairment who might

not have been identified and would serve as an entry point towards a comprehensive primary prevention strategy that seeks to promote early childhood development.

The positive predictive values were high ranging from 86 to 100 % whilst the negative predictive values had less variation and ranged from 84 to 89%. The positive predictive values (the probability that a child who screens positive actually has a cognitive impairment) and the negative predictive value (the probability that a child who screens negative actually does not have cognitive impairment) reported in this paper support the ability of the tool to discriminate normal children from those with impairment. Since both positive and negative predictive values are impacted by the prevalence of cognitive impairment in the population under study, this may suggests high prevalence of developmental impairment in the sample studied.

The overall prevalence of cognitive impairment among the 101 school aged children was 3 % which was comparable to the 6.1% reported prevalence of mild mental retardation in a community based study among 6-10 year old Pakistan children (196). The prevalence of cognitive impairment among school children in Zimbabwe is not well defined. A national community based survey conducted in Zimbabwe in 1997 reported a 1.2 % prevalence rate of delayed development among the 70 under five years old children surveyed (197). Of note, cognitive impairment was not evaluated separately in that survey. The rates of developmental delay were lower in that survey compared to other regions probably due to lack of routine documentation of children with developmental delays in the community (198;199).
The study had the following limitations and should be interpreted cautiously: A single criterion measure (general cognitive index) was used. We did not evaluate motor, emotional development, or activities of daily living. We did not administer a supplemental parental or guardian completed screening tool which might have provide more information on the child neurodevelopmental function. We used an adapted tool with American norms and cut off scores to determine cognitive function at 6-8 years. However, the norms for a Zimbabwean children might be different, therefore influencing the prevalence of cognitive impairment in this setting. The adaptation we made to the MSCA might have influenced the reliability of the test score as some cultural bias might have still remained in the tool. We chose to compare the perfomance of the MSCA test to an assessment by an education psychologist (using a combination of UK based tools), as is the local standard practice, since there is no gold

standard culturally appropriate developmental instrument. However, the tests performance of these tools was supplemented by the clinical assessments by the educationist.

6.1.3 Cognitive function at 6-8 years age

In comparing children with HIV infection to those uninfected, significant deficits in perceptive performance were noted. This supports similar findings reported among 117 preschool American children with perinatal HIV infection, participating in a multicenter, natural history, longitudinal study (13). Perceptive performance assesses visual-motor coordination and nonverbal reasoning. A large network of neurons is involved in visuomotor coordination including the frontal cortex, the parietal cortex and the basal ganglia (200). It is likely that CNS HIV infection in children results in frontostriatal dysfunction (200). Consistent with other studies , children with HIV infection in our study tended to score lowest in verbal, memory and quantitative scales compared to their uninfected peers, though not statistically significant (10;11;45;201;202). Two studies (57;66) reported executive function deficits as the most sensitive cognitive measure in relation to HIV disease progression. A study by Koekkoek et al among 22 school-age children with HIV infection found impaired executive function despite normal global estimate of cognitive function. These findings suggest the need for follow up even in asymptomatic children with HIV infection as global measures of cognitive function may mask subtle neurocognitive deficits.

We identified a 16% prevalence of cognitive impairment in children with HIV infection, which is much lower than 56% as reported by Boyede in a study among Nigerian(6) and 71% reported by Puthanakit among Thai school aged children (72) with HIV infection (72). In both studies the children were symptomatic of HIV infection and were on cART: 71% and 87% in Nigerian and Thai children respectively. In contrast, the low prevalence of cognitive impairment among children with HIV infection in our study is possibly due to survival bias since the severely HIV infected and untreated children were likely to have died in the first 2 years of life (153). Since we used an adopted Western tool, it is possible that bias still remained in the modified MSCA, underestimating the prevalence of cognitive impairment in particular among the HIV infected children. In a household survey documenting health conditions primarily responsible for disability in a low income suburb in Harare, the estimated prevalence of all paediatric disability (cerebral palsy, cognitive impairment, deafness,

behavioral problems combined) among children under 15 years was 2.3% in 1997 (203). However, cognitive impairment was not assessed separately that survey.

At school age, factors associated with cognitive impairment were lower socioeconomic status, child orphan hood and under nutrition. A study by Coscia et al among 43 American children infected with HIV aged from 2-12 years, found that the quality of the home environment mediated the relationship between socioeconomic status and child cognitive function (7) 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 (100). We identified lower socioeconomic status as an independent risk factor for cognitive impairment in this study, a finding supported by previous research from resource constrained settings (6;32;72;204). Poverty in the home has adverse effects on child development since it results in increased maternal stress or depression and inadequate child stimulation in the home(204). The quality of the home environment is postulated to compromise the cognitive development of children even in the absence of HIV infection (28). The present study found a relatively high prevalence of cognitive impairment of 18% among children exposed uninfected with HIV infection possibly due to the harsh home environment defined by having close family members, particularly the mother succumb to HIV related illness. Whereas our findings suggest that poverty predicts child cognitive function, a causal relationship is not inferred. Eighty eight children (25%) were orphans and had significant lower scores on the psychometric test. It is generally accepted that orphans and vulnerable children from resource constrained settings have poor health outcome (205-208). The family unit is important as it forms the first immediate environment in which a child is raised. Child headed households are a new reality for countries in sub-Saharan Africa due to the HIV epidemic. Although extended families usually provide social support, the unavailability of sufficient resources to provide for basic needs and lack of stimulation might have impacted negatively on cognitive function orphans in this study. It is critical that access to cART is made available to families with HIV infection for their health and their children`s neurocognitive development. To our knowledge no study has documented the effect of orphan hood on cognitive function among school age children in the context of high HIV prevalence.

Under nutrition was another factor associated with cognitive impairment at school age. Two studies conducted in developing countries identified poor anthropometric indices such as underweight, stunting and small head size as risk factors for cognitive impairment (209;210), which is similar to our findings. The prevalence of underweight was 14% whilst moderate to severe stunting was 16%. These figures are higher than the estimated national figure for children below the age of five (85), possibly due to the country's deteriorating economic situation which has resulted in lower family resources being allocated to nutritional needs.

We did not identify any relationship between the behavioral problem screening score and cognitive impairment, in contrast to findings by Noyzce et al, from a multicenter randomized clinical trial, that assessed the behavioral and cognitive outcome of asymptomatic antiretroviral experienced 274 American children with HIV infection, aged 2-17 years (37). The behavioral screen results must be interpreted with caution since a Western behavioral screening tool was used that had not been validated for the local setting. Translation alone does not address for local customs, hence it is possible some cultural bias remained in the translated PSC version. There is need for a larger study in order to validate and standardize the PSC for use in Zimbabwe.

The BINS showed poor positive predictive value (10%) for cognitive impairment at 6-8 years. This supports earlier reports where measures of cognitive function during infancy were poor predictors of later intelligence quotient (211-213). Possible explaination for the poor prediction of cognitive function is due to the difficulties inherent in infant testing, measurement error, change in function of the child, change in the content of tests with increasing age and environmental influences that become more evident after 2 years of age (35;214). Furthermore, we used of American norms in a Zimbabwean population and therefore the prevalence cognitive impairment may be different depending on what the actual norms might be for Zimbabwean children.

The study had the following limitations and should be interpreted cautiously: The follow-up of children in the original BHAMC study children was limited by the dispersion of town communities that took place prior to this study. There was a high loss to follow-up among the study participants that might have introduced selection bias. Furthermore, the lopsidedness in the study groups, in particular the small sample size of children with HIV infection, resulted in decreased study statistical power. Children's biomedical profiles such as viral loads for disease monitoring or clinical progress were not assessed due to cost and were not routinely

available at the time of the study. Further investigation into other promoters of cognitive function such as measure of the home environment or the quality of interaction between caregiver and the child were not made in this study, although we used proxy measures such as family income and child orphan hood.

We used an adapted tool with American norms and cut off scores to determine cognitive function at 6-8 years. However, the norms for a Zimbabwean children might be different, therefore influencing the prevalence of cognitive impairment in this setting. The adaptation we made to the MSCA might have influenced the reliability of the test score as some cultural bias might have still remained in the tool. However, the tests performance of these tools was supplemented by the clinical assessments by clinician.

Methodological considerations

It is important to consider whether the findings in this thesis can be generalized to represent the neurodevelopment outcomes of children born in PMTCT programmes in Zimbabwe.

The main study was a birth cohort where by children were assessed cross sectionally at two different time points. Cohort studies have been used in both developed and developing countries to evaluate the course of cognitive and motor development in infants infected with HIV from birth (31;33;37;38;65). The advantages include establishing causal relationship and the ability to document the various temporal developmental stages in children as the nervous system matures. The method is not efficient in documenting rare diseases and is weakened if there are high losses to follow up in the cohort (215). Selection bias in cohort studies limits the extent to which research findings can be generalized to the other settings.

6.2.1 Study validity

It is possible that selection bias was introduced in the initial study design as mid-way through the study more HIV infected pregnant women were conveniently enrolled as their numbers were very few. Furthermore, our cohort represents children with HIV infection who survived to school age. 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 died early and were documented to have more rapid progressive disease than children with intra or post-

partum infection (38;158). Therefore the child survivors in this study may reflect those children with the less aggressive disease.

As inherent in cohort studies, loss to follow-up was a challenge. A child was considered as lost to follow up if he or she did not come for the stipulated visits and was not declared as deceased by either the parents of caregiver. The overall dropout rate for the cohort was 19% at 9 months follow up (175). The high drop out within the first year, is similar to observations reported in a Malawian PMTCT program (216). Factors associated with lost to follow up in the Malawian study included difficulties accessing care and treatment, and lack of support from husbands, negative community reactions and stigma associate with home visits. Later in this study, the follow up of the children was further worsened by the dispersion of town communities that took place in response to a Government of Zimbabwe directive. 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. The unavoidable population mobility in our study as participants moved to distant locations introduced selection bias. The children`s attrition rate at the 6-8 years old study time had risen to 56.2% among the children born to HIV infected mothers and 58.1% among the children born to HIV uninfected mother (217). Attrition is the loss of participants during a follow programme due to participants drop out or death. More uninfected mothers failed to comply with the study follow-up schedule to 5years and beyond. The high loss to follow-up among the study participants probably introduced selection bias.

The sample sizes for the 3 groups of children at school age were lopsided: 32 Children with HIV infection; 121 children with exposed uninfected with HIV; and 153 children unexposed uninfected with HIV, probably due to the high mortality among the children with HIV infection. This resulted in a small sample size of children with HIV infection which decreased the study`s statistical power.

Although we used participant identification numbers, standardised questionnaires, structured interviews, physical examination and the laboratory in the data collection methods to minimize inter –observer variability; it was not possible to completely blind the clinician on clinical signs of HIV infection which might have introduced bias in cognitive assessment scoring.

6.2.2 Study reliability

In order to minimize bias, trained qualified staff administered the MSCA in strict adherence to instructions and scoring procedures described in the test manual. Inter-tester reliability among study examiners was maintained by centralized training of all the project examiners, periodic reviews with clarification of the scoring criteria and also selected review of videotapes that discuss demonstrated item administration. However since the MSCA test instructions were translated from English into the local language, it is possible that misinformation bias might arise as a result of translation and back translation even with the use of professional linguists.

6.3 Limitations

The study findings are specific to Zimbabwean children. The selection of mothers occurred at peripheral clinics, which is generalisable to urban clinics in Zimbabwe.

The study had a high attrition rate at 6-8 years follow up. Only 264 (44%) out of the 598 children assessed in infancy came back for re-assessment at the age of 6-8 years. Of the 598 children assessed at least once in infancy, 54 (9%) had died by age 6-8years, 55 (9.1%) refused to continue participating in the study and 227 (33.8%) had dispensed to distant regions. However, the study provided an opportunity to document longitudinally from birth information on nutritional status, health status, neurodevelopmental outcomes and mortality rates of children born within a PMTCT program before cART became routinely available. Children`s biomedical profiles such as HIV viral load was not assessed as it was not routinely available at the time of the study. For the HIV infected children these provide an indication on the disease stage and can be used in the monitoring of clinical progress. The relationship between NDI and the timing of the child`s HIV infection (in utero, intrapatum or post natal) was not examined in this study due to the few numbers of children with document HIV transmission. This might have provided answers to the variation in the pattern of cognitive function at school age.

Investigations of other components of neurodevelopmental function such as adaptive living skills not possible due to lack of local expertise. However, we screened the children for risk of child behavioral disorders. The documentation of a measure for the home environment, observation of interaction between caregiver, assessment for social and emotional intelligence would have strengthened the study findings.

The BINS and MSCA were both developed and validated in the United States and there is no normative data for these tools in others societies. There is no gold standard cognitive assessment tool standardized for Shona speaking Zimbabwean children. Adaptation we made to the MSCA might have influenced the reliability of the test score which might have underestimated the strength of the relationship between GCI and HIV infection at school age. It is possible that some cultural bias in the MSCA still remained. The computed GCI from the subtests of MSCA may not be the most sensitive and specific test to identify subtle differences in the global cognitive performance school children. Furthermore MSCA`s the index scores do not allow differentiation between delay in achieving new milestones and losing previously acquired milestones.

6.4 Strength of the study

The strengths of this study are its large sample size of children followed up in a national PMTCT program and 3 comparison groups of children: children with HIV infection, children exposed uninfected with HIV infection and children unexposed uninfected. A validated psychometric tool was used to assess neurocognitive function at school age. This study therefore provides important information on the neurocognitive function of children in resource-constrained setting, where most children with HIV infection live.

7. CONCLUSION

The current study has demonstrated that it is possible to follow up children in a resource constrained setting, from birth to adolescence and assess neurodevelopment function by utilizing adopted tools such as BINS and MSCA, despite the observed attrition rates. In infancy, children with HIV infection showed greater risk for NDI by age 3 months. As the children grew older, among those who survived to school age, children infected with HIV had major deficits in perceptive performance. However, there was no evidence of significant difference in general cognitive function among the children by HIV infection status: infected, exposed uninfected or unexposed uninfected. Lower socioeconomic status, under nutrition and child orphan hood, was associated with cognitive impairment. In resource-constrained settings, strategies aimed at poverty alleviation and good nutritional management should complement early infant diagnosis and treatment of all children under 5 years old regardless of CD4 counts in order to optimize neurocognitive potential.

8. RECOMMENDATIONS

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

1. Strengthen early HIV infant diagnosis and continuum of care for the HIV infected children.
2. Incorporate growth and neurodevelopmental monitoring of children using age appropriate simple standardized instruments into the expanded program of prevention of parent to child transmission of HIV. Children who falter on growth or developmental milestones can then be identified early and referred for intervention and treatment to tertiary levels offering rehabilitation services.

3. Develop a health education policy 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.

4. Emphasize the counseling of pregnant mothers who participate for PMTCT services on the importance of knowing the HIV status of the child so that all children with HIV infection , aged less than 5 years , can be initiated on cART treatment regardless of the CD4 counts .

9. FUTURE STUDIES:

1. Develop an extensive cultural appropriate neurodevelopment assessment tool that measures motor, language, cognition and socio-emotional development and also includes parental report on the child`s developmental progress.

2. Validate the Pediatric symptom checklist in Zimbabwe for the diagnosis of behavioral problems in children.

3. Conduct follow up research on the impact of neurocognitive intervention, use of cART, quality of life and behaviour outcomes as the children reach adolescence.

4. Further studies are need to assess the neurodevelopmental outcomes of children born to women with HIV infection since Zimbabwe the adoption of the 2013 WHO PMTCT guidelines, which recommend cART for all pregnant women and treatment of HIV infected children below 5 years regardless of the CD4cell counts.

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APPENDIX

Appendix 1

Consent form

Parental / guardian consent form

STUDY ID NO: ☐

Title of Research: Neurodevelopment and growth among peri-urban Zimbabwean school age children from a high prevalence HIV community.

Investigator: Gwendoline Q Kandawasvika

Phone number: 0772235643

Supervisors: Prof B Stray Pedersen (Consultant Obstetrician)

Prof Nathoo (Consultant Paeditrician)

What you should know about this study:

- We give you this consent so that you may read about the purpose, risk and benefits of this study.
- Routine care is based upon the best known treatment and is provided with the main goal of helping the individual patient .the main goal of research is to gain knowledge that will improve the care of future patients.
- We cannot promise that this research will benefit your child .similar to regular care this research may have unforeseen side effects that can be serious or minor.

Please note that:

- Your participation in this research is entirely free
- 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.
- Please review this form carefully. Ask any questions before you make a decision.

Purpose

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, school age, of children born to HIV infected and uninfected mothers and identifies factors that may predict delay development .In order to track development comparison will be made with earlier performance as screened by the BINS. Your child is being selected as a possible participant because he/ she has previously been followed up for developmental out comes since birth in the same study. We are going to select 295 children for the purpose of the study. The study will run for 9 months from 1 March 2010 to 31 December 2010. You may be asked to complete a questionnaire asking about the child`s behavior and their perception of quality of life.

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 using the MSCA. I will perform a lancet prick on the pulp of the middle finger to draw a drop of blood to assess haemoglobin levels by haemocule method. Blood results for CD4 counts will be recorded from the child health book for the HIV infected children. **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.

RISK AND BENEFITS

Risks and discomforts

There is potential for some physical pain on lancet prick but it is short lived. The child might be uneasy or shy and so the caregiver will be requested to be present at all times.

You and your child might discover for the first time the child`s intellectual problem during the course of this evaluation and this might cause psychological trauma to the family as a whole. In such an event you and your family will be referred for professional counseling on how to deal with the stressful information.

Through this study your child may be identified to have cognitive impairment which may result in stigmatization in the community. The risk is low as the information gathered during the examination will be treated with strict confidentiality within the members of the research team. Counseling sessions will be provided to you and your family by the study.

Benefits to participants

We do not guarantee that your child will benefit directly from the study. If a participant is found to have an abnormal result he / she will be referred for further appropriate management by paediatricians or clinical psychologists. The study will help document neurodevelopment performance of HIV children followed up from birth to at early school age which may improve the care of HIV infected children. By conducting this study we hope to raise awareness on developmental issues among health providers and child caregivers. This might sensitize the community on early referral for rehabilitative measures in order to improve the neurocognitive outcomes in children. The study will provide an opportunity to train health workers on administration developmental tool.

COST AND COMPENSATION

You will be given a cash reimbursement to cover the transport expenses to and from the study site. You or your child will not pay for any clinical examinations, laboratory tests or treatment of opportunist infections identified in the study. If the child needs further assessment or treatment, referrals to public tertiary health centers will be paid for in full by the study.

Confidentiality

Due to the sensitive nature of some of the questions asked, strict confidentiality will be maintained throughout the study. Each child already has a unique study identification number. All data will be collected and analysed according to these numbers. The coded numbers identifying study participants and all records will be locked in a cabinet file. Any links linking participants' identification numbers to other identifying information will be stored separately in a locked cabinet with limited access. Only members of the research team will have access to data.

Voluntary participation

Your participation in this study is voluntary.If you decide not to participate in the study this will not affect the way you will be treated at the clinic at all times. If you have got questions about this study you can phone and talk to Dr Gwendoline Kandawasvika on 0912235643.

Discontinuation

If you decide to discontinue from the study you are free to withdraw your consent at any time without penalty and without giving reasons. This will not affect your regular care.

Dissemination of results

Individual results will be given to participants during the course of the study. The final results will be disseminated to the study and will be presented as part of the part of the PhD for Dr Dr GQ Kandawasvika**.**

Authorisation

Before you sign this form please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think it over.

YOU ARE MAKING A DECISION WHETHER OR NOT TO ALLOW YOUR CHILD TO PARTICIPATE IN THIS STUDY .YOUR SIGNATURE INDICATE THAT YOU HAVE READ AND UNDERSTOOD THE INFORMATION ABOVE ,HAVE HAD ALL YOUR QUESTIONS ANSWERED ,AND HAVE DECIDED TO ALLOW YOUR CHILD TO PARTICIPATE.

The date you sign this document to enroll your child in this study is today `s date MUST fall within the dates on the approval stamp affixed to each page .The dates indicate that this form is still valid when you enroll your child into the study but do not reflect how long your child will participate in the study. Each page of this consent form is stamped to indicate the form `s validity as approved by MRCZ.

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.

Name of parent/ guardian (print)..... date.....

Signature of parent/guardian.....

Relation to child……..

Signature of investigator……..

If you have any questions concerning this study beyond those answered by the investigator, questions about the research, your rights as a research participant or research related injury or you feel you have been treated unfairly and you would like to talk to someone other than the research team you are free to contact the medical Research council of Zimbabwe on telephone 00263 4 791 792 or 00 263 4 791 193

Appendix 11

Fomu remubereki / muchengeti rekubvumidza mwana kupinda muongororo .

Ongororo yekukura nekuvhurika pfungwa muvana vechikoro vane makoro matanhatu kusvika masere vanobva munzvimbo dzakaotenderedza gutaguru reHarare muZimbabwe

Muongorori: Gwendoline Q.Kandawasvika

Nhamba dzenhare :0912235643

Vakuru vemuongorori: Prof B Stray Pedersen (Chiremba mukuru)
Prof Nathoo(chiremba mukuru)

Zvamunofanirwa kuziva nezveongororo ino

- Tinokupai gwaro rino kuti muzive chinangwa ,zvichaitika ,nekusagadzikana uye zvatichawana kubva muongororo iyi.
- Kubatsirwa kunoitwa vanhu kunobva muruzivo rwezvekurapa kunobva mukuongororrwa kwevamwe vanhu.chinangwa chikuru che ongororo ndechekuwana ruzivo runobatsira varwere vemangwana
- Hativimbisi kuti ongororo iyo ichabatsira mwana weny.sezvinowanikwa mukurapa .ongoror iyi inogona kuita zvimhingaidzo zvakakura kana zviduku
- Zvamunenge amsarudaz kuita hazvikanganisi kurapwa kwemwana wenyu .nyatsonzwisisai gwaro iri .Bvunzai mibvunzo munzwisisie musati maisa runyoro rwenyu.
- Kupinda kwemwana muongororo kunobva mukuzvisarudzira kwenyu

Chinangwa chechirongwa

Muri kukumbirwa kupinda muongororo yakarongwa ne University of Oslo Norway yakabatana pamwechete ne University Of Zimbabwe College Of Health Sciences. Chinangwa

ndechekutarisa kuti zvirwere zvepabonde zvinowedzera zvakadini mikana yekutapurirana kwehutachiona hunokodzera mukondombera kuvana uya kuti hutachiona hunodzikisira makuriro epfungwa dzevana zvakadini .Tsvakurudzo dzakaitwa munyika dzakabudirira ne kumabvazuva kwe africa dzintaridza kuti hwutachiwana hudzikisira uchenjeri hwevana.Ongororo yevana vanengenvari pedyo nekutapurirwa urwere uye kukurumidza kuonekwa kwekusakura kwpfungwa dzavo zvichashandiswa pakutsvak nzira dzakafanira dzekurapa zvichiendarana noudzamu hwehweurwere.Tsvakurudzo ino icharatidza kukwanisa kuziva zvinnhu,muvana vachiri kutanga chikoro.Kukura kwepfungwa kuchaongororwa kuchishandiswamagwaro e Mccarthy Scale of Children Abilities.

Kana masarudza kuva muongoror muchakumbirwa kunyora zita renyu kana kuisa mudhindwa wechimunwe chikuru chorudyi,pamber pechapupu.

Rangarirai kuti:

Hamubhadharo kuti mupinde muongororoino

Makasununguka kurega kana kuzorega pavavaya kuva muchirongwa chino pasina kuzoshaiwa rubatsiropachipatara.

Zvichaitwa

Masarudza kuva muongoror iyi ,muchabvunzwa mibvunzo maerereno neupenyu hwenyu nehwemwana .Chiremba achaongorora makuriro emwana wenyu achishandisa magwaro e MSCA.Mwana achabayiwa pachigunwe chiduku zvichitirwa kutora donhwe returopa .Ropa iri richashandiswa kuongorora huwandu hweeropa muviri wemwana.Ma CD4 achakoponorwa kubva mugwaro rehutano rigara nemwana.

Kurwadzikana nekusagadzikana

Pakitorwa ropa zvicharwadza asi kurwadza kwachohakuendereri mberi . Mungangovhundutswa nekuudzwa kuti mwana akavhiringidzika pfungwa imomuongororo ino. Chirongwa chichakunyorerai gwaro rekuti imi ne mhuri yenyu muende kuno nyaradzwa navana mazvikokota.

Masarudziro(selection criterio)

Kunyangwe manga muine chido chekuva muurongwa hwuno,chiremba anogona kurambira mwana wenyu kana anga asina kumboongororwa makuriroepfungwa achiri muduku.

Zvamunowana kubva muchirongwa

Hativimbisi kuti ongororo iyi ichabatsira mwana ipapo.Vana vatinenge tawana vaine zvakakanganisika tichaita kuti vaonekwe namazvikokota vevena vabatsirwe .Zvichabuda muongororo iyi zvichabatsira kuti tizive kuvhurika pfungwa kunoita vana nanenge wazvarwa vaine utachiona wemukondombera .Mubereki kana mwana haabhadharikuongororwa nekurapwa muongororoino.Kana mwana achida kuzoongororwa nachiremba kana kurapwa ongororo inopuhwa pachena.Hapana muripo pakupinda muchirongwa .Mari dzekufambisa munobhadharirwa.

Zvakavanzika

Zvose zvatichataurirana kana kuita pamwana zvinoramba zviripakati pedu neavo vane chokuita neongororoiyichete nokudaro makasununguka kupindura mibvunzo zvizere.Tinoshandisa nhamba kwete zita pamapepa atiri kunyorere nezveutano hwemwana uye achachengetedzwa nemuongorori.Hapana anokwanisa kushandisa mapepa aya kuti aone kuti nderani.

Kuzvisarudzira kupinda muongororo

Munozvisarudzira kupinda muongororo .Kana musina kusununguka kuti mwana apinde muchirongwa ichi munokwanisa kuramba.Izvi hazvikanganisi kubatsirwa kwenyu kana kwemwana kwemazuva ose.Kana mune mibvunzo pamusoro peongororo iyi munogona kutaura na Dr Gwendoline Kandawasvika panhamba dzinoti 0912235643.

Kubuda muongororo

Muchinge masarudza kupinda muongororo mukazofunga kuchinja makasununguka kubuda musingapi tasnangudzo.Izvi hazvikanganisi marapirwo eny emazuva ose**.**

Kuziviswa nezvichabuda muongororo

Zvichabuda muongoror iyi zvichaudzwa avo vanenge vapinda muongororo uye ku University uko kudzidzira muongororri chiremba G . Kandawasvika**.**

Zvichabuda muongororo

Kunyorwa kwemapepa anorondedzera nezvekukura kwepfungwa muvana**.**Zvichatipa mukana wekuzivisa veruzhinji nezve nyaya yekuvhurika pfungwa yevana uye kukurumidza kuendesa vana vane pfungwa dzisina kuvhurika kuchipatara .Vane mukoti vachadziziswa kushandisa gwaro rezvekuvhurika pfungwa.

Kubvuma kupinda muongororo

Musati masina runyoro rwenyu pagwaro rino bvunzai mibvunzo kana pane pamusina kunzwisisa.torai nguva yakakwana kunyatsofunga nezvazvo.Ndaverengerwa zviri muongororo ino ndikanzwisisisa chinangwachacho.Mukunyora zita rangu /kuisa mudhindwa wechigunwe chikuru cherudyi papepa rino ndinotaridza kubvuma kuva muongororo iyi pachangu.

Zita remubereki/muchengeti……..

Runnyoro rwemubereki/muchengeti…….
Zuva…….

Runyoro rwemuongorori……

Kana paine zvimwe zvamungade kuziva nezveongoror iyi zvisana kukwanisa kupindurwa zvizere nemuongorori,kodzero yenyu semunhu ari kupinda muongoror kana kumwe kusagutsikana musingakwanise kutaura nemuongorororori makasununguka kubata ve Medical research Council of Zimbabwe panhare 002634791792 kana 002634791193

Appendix 111

Assent Form

Title of Research: Neurodevelopment and growth among peri-urban Zimbabwean school age children from a high prevalence HIV community

Investigator: Gwendoline Q. Kandawasvika

The purpose of this from is to explain to you the purpose of the study,what is going to be done and and the benefits and discomfort that may occur.the aim of the study is to find out if Children infected with HIV at birth perform any differently on intelligent tests from children without HIV infection. The study is going to recruit 295 children over a period of 9 months from March 2010 to December 2010. You are asked to participate because you are already a participant in the Better Health for Mother and child study. Your participation is voluntary. If you agree to participate I am going to ask you to perform a few tasks to check your level of intelligence. I will also draw blood from your finger using a small needle. There will be some pain on pricking, but it will be short lived .Your parent or guardian will be present at all times. If there are any abnormalities in the test you will be referred for further evaluation by psychologists. All the information about the study participants will be recorded using a study number and the information will not be linked to you. Only the investigator and the supervisors will have access to the files. You are free to withdraw your assent at any given time without giving reason. This will not affect your routine care.

I have read and understood the information and that explained to me. I am willing to participate.

Name……..

Signature ……..Date……

Signature of researcher……..

Appendix 1V

Ongororo yekukura nekuvhurika pfungwa muvana vechikoro vane makoro matanhatu kusvika masere vanobva munzvimbo dzakaotenderedza gutaguru reHarare muZimbabwe.

Fomu remwana rekubvuma kupinda muongororo

Muongorori GQ Kandawasvika

Gwaro rino rinotsanangura chinangwa cheongoror ino,zvichaitwa uye zvinogona kuwanikwa kubva muonmuongororo ino .Chinangwa cheongororo ndechekutarisa kukura pamwe kuvhurika pfungwa zvichienzaniswa vana neutachiwana hwe mukondombera nevana wasina utachiona.Ongororo iyi iiri kutarisa vana mazana matatu uye ichaitwa pamwedzi mina kubvira muan Kuvumbi to Zvita 2010.Urikukumbirwa mvumo yako kuti uongororrwe kukura kurikuita pfungwa dzako.Pauchakokwa kuchipatara,uchaitiswa bvunzo sekunyora kwakaitwa mugwaro re MSCA.Ndichakubaya ndotoraropa rako pachigunwe.Ucharwadziwapakubayiwa asi kurwadza kwacho hakuendereri mberi. Kana pawanika zvakakanganisika pakukura pamwe ne kuvhurika pfungwa uchaonekwa navanamazvikokota ezvepfungwa chichipata.Zvose zvichataurwa kana kuitwa zvinenge zvakavanzika tinoshandisa manhamha kwete mazita nokudaro munhu hakwanisi kuziva izvi zvabva kwauri.Muongorori nevakuru vake vane chikuita neongororo ndivo chete vanokwanisa kuona mapepa ako.Unozvisarudzira kupinda muongororo.wakasununguka kubuda muongororo panguva ipi zvayo usingapi tsananguro.Izvi hazvikanganisi marapiro ako emazuva ose.

Ndanzwisisa zvandaverenga uye zvandatsangurirwa maererano neongororo iye. Ndinobvuma kupinda muongororro iyi.

Zita rangu……

Runyoro rwangu……..Zuva……..

Runyoro rwemuongorori……

APPENDIX V Child interview guide

AGE AT VISIT (months) / Zera munwedzi……

Date/zuva_____ Study Identification number/Nhamba muongororo: ____

1. Child s date of birth / zuva rekuberwkwa / __ /_ /
2. Sex / Munhuyi 1.boy / mukomana 2. Girl/musikana
2. How are you related to this child/muneukama upi nemwana uyu……
3. a)Who does the main care for this child/muchengeti we mwana ……..

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

b)Has there been changes in care givers/ Asi muchengeta akachinja here? 0 No 1 Yes

4. Care taker's age in years/ Makore emuchengeti……

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

6. Care taker`s level of education/Muchengeti akadzidza zvakadii ……. .

0.No formal education 1. Primary education 2. Secondary education 3. Tertiary education

7a. Care taker`s Occupation/ basa remuchengeti 0.Not employed 1.Formally employed 2. Self employed

7b. What is the family income per month?/Muhoro wemhuri.....

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

9. Is MotherAmai vapenyu here 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 / Mwana akarwara zvirwere zvinotverera here No Yes

11-Diarrhoea /manyoka 0 1

12-Vomiting /kurutsa 0 1

13-Fever /kupisa muviro 0 1

14-cough /kukosora 0 1

15 Ear discharge /kuputika nzeve 0 1

16.Any other problems, specify/ pane zvimwe here ……

17. How many times did you feed the child in the last 24 hrs /Mwana akadya kangani nezuri …….

18 Did child attend preschool /mwan akaenda ku creche here? 0 N0 1 yes

19. Is child attending school Now/ Mwana ari kuchikoro here iyezvino 0 No 1 yes

20 Which grade ?/ Gwaro ripi .....

PHYSICAL EXAMINATION

21 Height in cm ---

22. Weight in kg……

23. Weights/ Height-----

24. Head circumference------

No yes

25. Underweight 0 1

26 . Stunted 0 1

27. General condition 0 Normal 1 Abnormal 26. Lymphadenopathy 0 1

28. Skin disorder 0 1

29 If abnormal specify…….. ……

30. Mouth condition 0 1

31 If abnormal specify……..

32. Cardio vascular System 0 Normal 1.Abnormal

If abnormal specify findings……..

33. Respiratory system 0 Normal 1.Abnormal

If abnormal specify findings……

34. Gastro-intestinal Tract 0 Normal 1.Abnormal

If abnormal specify findings……

35. Neurological Status 0 Normal 1.Abnormal

36 abnormal specify findings……..

37 Mental status 0 1

38 Cranial nerves 0 1

39 Sensation 0 1

40 Muscle tone 0 1

41Reflexes 0 1

42Coordination 0 1

43. WHO Paediatric Clinical stage : 0 1 .2. 3. 4.

44

a) If HIV infected CD4 profile(%)…….

b) Is child on HAART……..

c) Has disclousure been done to child …….

45 MSCA assessment Mean GCI score…….

46 Paediatric symptom check list score------

McCARTHY SCALES OF CHILDREN'S ABILITIES

Record Form

NAME _____ AGE _____ SEX _____

HOME ADDRESS _____

NAMES OF PARENTS OR GUARDIAN _____

SCHOOL _____ GRADE _____

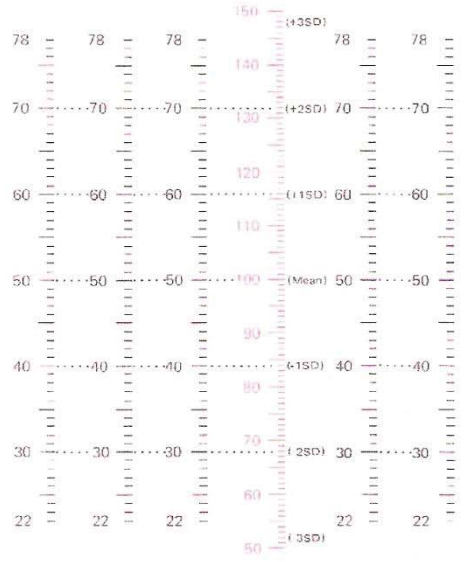
PLACE OF TESTING _____ TESTED BY _____

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.

SCALE INDEX	Verbal	Perceptual-Performance	Quantitative	General Cognitive	Memory	Motor



	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 161 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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Paediatric symptom check list

Please mark under the heading that best suit your child

	Never	Sometimes	Often
1.Complains of ache and pains musoro			
2.Spends more time alone Mwana anowanzo kutambaega kana kuti ega?			
3.Tires easily Anokurumidza kuneta zvisina kufanira			
4. Fidgety ,unable to sit still Asingagadzikani			
5.Has trouble with teacher **Mudzidzisi akamboona dambudziko pamwana**			
6. Less interested in school **Anofarira chikoro here**			
7. Act as if driven by motor Kushereketa here			

8.Daydreams too much Anovarirwa zvakanyanya here			
9. Distracted easily Anokwanisa kuisa pfungwa panzvimbo imwe chete here kwenguva yakareba			
10.Is afraid of new situations Anotya kusanga nezinhu zvitsva,vanhu zvakanyanyisa			
11.Feels sad ,unhappy Kusuruwara			
12. Is irritable ,angry Mwana ane hasha dzakanyayisa			
13. Feeels hopeless Mwana wenyu anoratidza kushaya tariro here			
14.Has trouble concentrating Kuisa pfungwa pamwe chete			
15. Less interest in friends Anofarira kutamba nevamwe			
16. Fights with other children Anorwa nevamwe			
17.Absent from school			

Anorovha			
18 School grades are dropping **arikudzikira**			
19. Is down on him or herself Anozitarisira pasi kudzikisira			
20 .Visits doctor with doctor finding nothing wrong Anonyepera urwere			
21 .Has trouble sleeping Ane dambudziko here pakurara Kushaya hope,kurarisa			
22.Worries a lot Anoshushikana zvakanyanya			
23. Wants to be with you more than before Anogara pamuri zvakanyaya,zvasiyana nekare			
24.Feels he or she is bad anozvishora			
25.Take unnecessary risks Anotamba zvinenjodzi here			
26.Gets hurt frequently Anogarokuva kuva here			

27. Seems to be having less fun Maonere enyu ,ari kuratidza kusanyanyo nakidza zvaisaita kare			
28 .Acts younger than children his or her age Anoita zvito zvezera rake here			
29.Does not listen to rules Anoterera mitemo here			
30. Does not show feelings Ano budisa zvaari kufungwa			
31. Does not understand other peoples`s feelings Haanzwiri vamwe tsitsi			
32. Teases others Kugaro svotesa vamwe			
33.Blames others for his or her troubles Anopomera vamwe here mhoswa dzake dzese			
34 .Take things that do not belong to him or her Anotora here zvinhu zvisiri zvake			
35. Refuses to share			

Anogovana nevamwe here			