THE NEURODEVELOPMENTAL STATUS OF KENYAN CHILDREN INFECTED WITH THE HUMAN IMMUNODEFFICIENCY VIRUS.

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Study site: Kenyatta National Hospital Nairobi, Kenya 2007

DECLARATION

I, Dr Mary Mupa Madumadu Kigira declare that this research report is my own work. It is being submitted for the degree of Master of Science Child Health (Neurodevelopment Option) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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…….. Day of…….. 2008.

DEDICATION

This work is dedicated to the important people in my life. Wambugu Kigira my husband thank you for being around. Mum Victoria and dad Glynn thank you for your support. George, Jane, Chiku, Madu, Kip, the Kaches and Chebby, thank you for coloring my world.

PUBLICATIONS AND PRESENTATIONS

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ABSTRACT

Background: Sub Saharan Africa hosts 90% of the world's Human Immunodeficiency Virus infected children, and in 2007 an estimated 150,000 of these were Kenyan (UNAIDS, 2007). Baseline neuropsychological performance is a strong predictor of their disease's progression (Van Rie et al, 2006). There is no data on the baseline neurodevelopment (ND) status of Human Immunodeficiency Virus infected children in Kenya. Interventions to minimise morbidity and improve quality of life are routinely not instituted in Kenya.

Aim: The aim was to determine the prevalence, spectrum and severity of ND delay among a cohort of HIV infected Kenyan eligible for HAART initiation but had not received HAART previously children at Kenyatta National Hospital Comprehensive Care Center.

Methods: This was a prospective observational cohort study carried out at the Kenyatta National Hospital, comprehensive care center, in Nairobi, Kenya. Bayley Scales of Infant Development third edition (BSID III) was carried out on 36 highly active anti-retroviral therapy (HAART) naïve HIV infected children aged between two weeks and 36 months, about to start HAART. These had met all eligibility criteria for HAART according to the KNH CCC protocols and were due to start the therapy. Study subjects were scheduled to have monthly bailey scales assessments to a maximum of at least six months post HAART. This was to enhance follow – up as only the initial and sixth month assessment was crucial for data analysis. The children

underwent laboratory tests and other clinical services in accordance to the hospital's standard of care for HIV children.

Results: Thirty two - out of thirty - six children with HIV had neurodevelopment delay in at least one of the five constructs assessed by the BSID III at baseline. In descending order of frequency ND was most common in motor, language, cognitive and adaptive BSID III constructs respectively. The child aged 18 months and older demonstrated more frequent ND delay in all constructs measured except motor while secondary and above maternal education level was associated with worse cognitive performance of this cohort.

Cognitive, language and social emotional scores improved in the 12 children who completed follow up for at least six months of HAART. The clinical significance of this data is the fact that even after 6 months of HAART patients still fell in the ND delayed category. This shows HAART alone is not sufficient to address ND problems. This data is of clinical significance but further research needs to be done to validate its statistical significance. HAART had no effect in improving motor delay in these twelve children.

Conclusion: Neurodevelopment delay in this cohort of Kenyan children with HIV is prevalent; 83.3% motor delay, 66.6% language delay, 61.2% cognitive delay, 60.6% adaptive delay and 36.4% socio-emotional delay. All facets of ND delay as measured by the BSID III are affected. The magnitude of delay falls in the range that would benefit from early interventional rehabilitation. Data of the effect of highly active antiretroviral provision in this cohort is minimal but it shows that these drugs alone are not enough to manage the delay. Further research needs to be done to validate this point.

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* SES: Socio emotional status

* GAD: General Adaptive Behaviour

LIST OF ABBREVIATIONS

AAMR	American Association of Mental Retardation
APA	American Psychiatric Association
BD	Borderline
BSID III	Bayley Scales of Infant Development third edition
CCC	Comprehensive HIV Care Center
CNS	Central nervous system
ELISA	Enzyme Linked Immuno Sorbent Assay
EL	Extremely low
GAD	General Adaptive behaviour
HAART	Highly active anti – retroviral therapy
Hb	Hemoglobin
HIV	Human Immunodefficiency Virus
KNH	Kenyatta National Hospital
MTCT	Mother to child transmission
ND	Neurodevelopment
PCR	Polymerase Chain Reaction
PMTCT	Prevention of mother to child transmission
SES	Socio emotional status
TAT	Trans Activator Protein
WHO	World Health Organization

LIST OF DEFINITIONS.

Neurodevelopment Delay	:	Below normal or impaired neurodevelopment functioning
Neurodevelopment Construct:		Neurodevelopment parameter
Neuroaids	:	Neurodevelopment results of HIV AIDS.

CHAPTER 1

1.1 INTRODUCTION

1.1.1 HIV IN KENYA

The Human Immunodeficiency Virus (HIV) has caused a big pandemic, infecting 33.2 million people globally (UNAIDS 2007). Of these 2.1 million are children. Worldwide this virus caused the death of 290,000 children in 2007 (UNAIDS, 2007). The sub Saharan African belt in which Kenya lies hosts 90% of the children living with HIV worldwide (UNAIDS, 2007).

Figure 1.0-1: Map of Kenya in Africa

Kenya is an East African country with a provisional population of 28.9 million people (1999 census). She has a fertility rate of 4.9 per woman according to the Kenya Demographic Health Survey (KDHS) 2003 version. Her current adult HIV prevalence is 6.1% (UNAIDS, 2007). The first case of HIV in Kenya was reported in 1984 and by 1995

the number had risen to 63,179 (Ministry of Health National Aids Control Council, 2001). UNAIDS reported 1.3 million Kenyans were living with HIV in 2007.

1.1.2 HIV AND CHILDHOOD OUTCOMES

The HIV scourge has eroded the gains made on the health of children (Luzuriaga et al, 2002). In Kenya the under five mortality rate deteriorated from 65 per 1000 live births in 1998 to 114 per 1000 live births in 2003 (KDHS, 2003). In Kenyan children infected with HIV, Mbori Ngacha et al found two year mortality rates of 40.2% and 46.0% in formula and breast fed babies respectively (Mbori Ngacha et al, 2001). Obimbo et al observed deaths in 52% by two years of age in those infected with HIV during their first year of life (Obimbo et al, 2004). These results are in keeping with a meta analysis of 3468 children from east, west and south Africa reported 378 (99/1000 child years) deaths between the age of one day and 32 months; 35.2% died within the first 12 months (Newel et al, 2004).

1.1.3 PREDICTORS OF RAPID PROGRESSION OF HIV IN CHILDREN

To prevent mortality, HIV disease progression indicators are useful, allowing timely interventions. Studies have been done to identify predictors of rapid disease progression in resource poor settings. Obimbo et al investigating a cohort of 62 Kenyan children identified both maternal and childhood indicators of rapid disease progression. The childhood factors include early growth faltering, formula feeding, and low CD4 counts (Obimbo et al, 2004). A cohort of 80 HIV infected from Abidjan reported that independently higher maternal delivery viral loads and higher pediatric viral loads lead to

faster HIV disease progression (Rouet et al, 2003). Loannidis et al, 2004 came to a similar conclusion. Viral loads are hardly used by most African countries because of their prohibitive costs. Children with higher viral loads have been known to progress faster to death (Rouet et al, 2003).

1.1.4: HIV AND NEURODEVELOPMENT DELAY IN CHILDREN

HIV – related neurodevelopment delay has been strongly associated with higher pediatric viral loads (Chiriboga et al, 2005; Jeremy et al, 2005). Baseline neuropsychological performance is a strong predictor of HIV disease progression (Van Rie et al, 2006). There is no data on the baseline ND status of Kenyan HIV infected children. Interventions that can prevent morbidity and improve quality of life of HIV infected children have not been instituted into routine care. A data gap also exists on the effect of ART on the neuroaids of sub Saharan African children (Van Rie et al, 2006).

This paper is looking at the prevalence, spectrum and severity of neurodevelopment delay among HIV infected Kenyan children. Factors affecting ND delay in these children are also studied.

1.2 RESEARCH QUESTION

What is the prevalence, spectrum and severity of neurodevelopment delay among a cohort of HIV infected Kenyan children eligible for HAART initiation but had not received HAART previously with specific attention to BSID assessment scores.

1.3 AIMS

To determine the prevalence, spectrum and severity of neurodevelopment delay among a cohort of HIV infected Kenyan children eligible for HAART initiation but had not received HAART previously with specific attention to BSID assessment scores.

1.4 OBJECTIVES

1.4.1 PRIMARY OBJECTIVES

To measure using the Bayley Scales of Infant Development the **prevalence** of neurodevelopment delay of a cohort of HIV positive Kenyan children aged between 2 weeks and 36 months eligible for HAART initiation but had not received HAART previously with specific attention to BSID assessment scores.

1. To measure using the Bayley Scales of Infant Development the **spectrum** of neurodevelopment delay of a cohort of HIV positive Kenyan children aged between 2 weeks and 36 months eligible for HAART initiation but had not received HAART previously with specific attention to BSID assessment scores.

2. To measure using the Bayley Scales of Infant Development the **severity** of neurodevelopment delay of a cohort of HIV positive Kenyan children aged between 2 weeks and 36 months eligible for HAART initiation but had not received HAART previously with specific attention to BSID assessment scores.

1.4.2 SECONDARY OBJECTIVES

1. To determine factors associated with ND delay among a cohort of HIV infected Kenyan children eligible for HAART initiation but had not received HAART previously with specific attention to BSID assessment scores. Factors are:
    - Maternal factors; PMTC prevention, delivery mode, mother's education
    - Child factors; baseline age, sex, WHO staging, immunosuppression by CD4%, breastfeeding, HAART.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

Literature Search

The literature search was conducted using both manual and internet resources. Manual search was done by the principal investigator with assistance from the Witwatersrand university medical school library staff. Websites and search engines used included; HINARI, PUBMED and UNAIDS. Keywords included HIV, neurodevelopment, cognitive, language, motor, socio-emotional status.

2.1 EPIDEMIOLOGY: HIV AND PMTCT IN KENYA

The Human Immunodeficiency Virus (HIV) has caused has caused a big pandemic in our times. UNAIDS estimated that in 2008 alone, the number of Kenyan children under 15 years of age living with HIV, could be 170,000 (UNAIDS, 2008). The main routes of HIV infection in children is Mother to child transmission (MTCT) (ANECA, 2008). Infrequent infection modes include direct blood inoculations and sexual contact through abuse. Direct inoculation is now a rare infection route, due to improved HIV screening of blood products initiated during the nineteen eighties (Willen, 2006).

MTCT is the main infection mode (ANECA, 2006; Luzuriaga et al, 2002) accounting for to 90 – 95% of pediatric HIV infections (ANECA, 2006; Van Rie et al, 2006). It takes

place in utero, perinatally and through breast-feeding (ANECA, 2006; Luzuriaga et al, 2002; Van Rie et al, 2006; Willen, 2006).

Kenyan data shows that a cumulative 37% of breast feeding mothers infect their babies by 24 months if no preventive measures are taken (Nduati et al, 2000; Mbori Ngacha et al, 2001). Seventy five percent of MTCT rates in breastfed babies take place within the first months of life and account for 15 - 20 % of HIV infections in this population (Nduati et al. 2000; Luzuriaga et al, 2002).

MTCT makes the Kenyan pediatric HIV epidemic follow closely that of women. The higher the epidemic in Kenyan women of reproductive age the greater the MTCT rates. There are up to 1.1 million Kenyan women aged over 15 years living with AIDS in 2008 (UNAIDS, 2008). The average 2003 figures of those sure of their HIV status stood at 14% for males and 13% for females (KDHS, 2003) despite the fact that 97 % - 98 % of Kenyans had heard about HIV as early as 1994 (National Situational Survey, 1994). There is still significant MTCT with most Kenyan mothers breastfeeding their children for a mean of 20 months (KDHS, 2003). Nduati et al, found cumulative MTCT rates of 36.7% at 24 months in a RCT in which mothers were randomized to breast-feed or formula feed their infants in the former group (Nduati et al, 2000). In 1994 only one third of women and one fifth of men in Kenya knew about MTCT of HIV (KDHS, 2003). One can then deduce that most children born then did not benefit from PMTCT measures.

Prevention of mother to child transmission (PMTCT) programs including anti-retroviral therapy (ART) during pregnancy, elective caesarean sections and infant formula feeding

have decimated the pediatric HIV epidemic in the developed world (Van Rie et al, 2006; Willen, 2006). African countries like Kenya are yet to realize these results.

Since 2004 the Kenyan government has scaled up programs increasing the availability of PMTCT services to 60% in 2007. However in 2007 the percentage of pregnant women who received treatment to reduce MTCT care was only 9.3% (UNAIDS, 2007). These figures support the less than 10% PMTCT global coverage resulting in an increasing pediatric epidemic (Van Rie et al, 2006). Many mothers have given birth and breastfed their babies without knowing their HIV status contributing to a sizable cohort of Kenyan children infected with HIV. These children are part of the 90% of those infected with HIV living in the developing world of which little is known of their neurological signs and symptomatology (Van Rie et al, 2006).

Infant HIV has been associated with brain function impairment (Van Rie et al, 2006; Willen, 2006) especially in those with in utero infection (Van Rie et al, 2006).
This knowledge can help timely Highly Active Anti-retroviral Therapy (HAART) initiation as in up to 18% of infants; it is the first proof of the disease progression to AIDS (Van Rie et al, 2006). Before widespread HAART incidence of progressive HIV encephalopathy was 13-35% and 35-50% in children diagnosed with the disease and AIDS respectively (Van Rie et al, 2006).

2.2 PATHOPHSIOLOGY OF NEURODEVELOPMENT DELAY IN IN HIV INFECTED

2.2.1 THE HUMAN IMMUNODEFFICIENCY VIRUS

This is a single stranded ribonucleic acid (RNA) virus of the retroviridae family and lentiviridae genus. Each virus has two copies of the genome which has two end portions and a mid portion. The end portions have long terminal repeats which code for protein regulatory genes which include tat one of the key players in HIV neuropathophysiology as will be shown later. Mid portion genes are gag coding for core proteins; pol for enzymes and Env whose product GP 120 is another important component of the virus leading to neuroaids causing events.

2.2.2 PATHOPHYSIOLOGY OF NEURODEVELOPMENT DELAY

The human brain is complicated and intolerable to any compromise. Minimal injury may disrupt basic activities like movement, communication and decision making (Olesen et al, 2006). HIV affects the Central nervous system (CNS) both directly and indirectly (Willen, 2006). Direct CNS HIV infection occurs early in the disease process (Epstein et al, 1999; Van Rie et al, 2006; Raskino et al, 1999; Woods et al, 2007; Foster CJ et al, 2006; Lindsey et al, 2008). The earlier the infection the higher the risk on CNS damage (Foster CJ et al, 2006). The virus is easily recovered in perivascular macrophages and microglia (Woods et al, 2007; Van Rie et al, 2006; Willen, 2006).

The systemic circulation is a source of infected CD 4 lymphocytes, macrophages and microglial cells into the brain (Epstein et al, 1999; Van Rie et al, 2006). Vascular macrophages get into the CNS because HIV damages the blood - brain barrier (Rickado-Dukelow et al, 2007; Willen, 2006). Viral proteins including tat, gp 120 and pro inflammatory cytokines, tumor necrosis factor α (TNF α) and interleukin 6 (IL 6) are thought to disrupt tight junctions of the endothelium (Rickado-Dukelow et al, 2007) a fact emphasized by the pallor of white matter being mainly edema rather than myelin damage (Epstein et al, 1999). Tat viral protein also affects the barrier's monocyte migration by exerting oxidative stress on it (Rickado-Dukelow et al, 2007). Infected macrophages secrete cytokines like IL 6, monocyte chemoattractant protein 1 (MCP 1), platelet activating factor (PAF) and TNF α, all which are implicated in neuroaids pathogenesis (Li et al, 2007; Kaul, 2008). These neurotoxic cytokines trigger inflammatory cascades responsible for most of the CNS damage (Epstein et al, 1999; Van Rie et al, 2006; Woods et al, 2007; Li et al, 2007; Kaul, 2008).

Astrocytes are another major source of inflammatory cytokines in the HIV infected brain. Astrocytic population in the brain is large and it's interaction with HIV is postulated to be a major factor in neuroaids (Li et al, 2007; Van Rie et al, 2006). These cells do not have CD4 receptors but express HIV co receptors namely CCR3, CXCR4 and CCR5 (Li et al, 2006). Their infection by HIV is low when compared to CD4 lymphocytes and they rarely die in neuroaids brain pathology (Li et al, 2007). When exposed to tat or gp 120, astrocytes release the same pro inflammatory cytokines as macrophages leading to the same neurotoxic cascades (Li et al, 2007; Willen, 2006). Tat and TNF α cause impaired glutamate intake while gp 120 leads to a calcium dependent glutamate secretion by astrocytes (Li et al, 2007). An infants brain is very plastic and has an over expression of

excitatory amino acid receptors the main one of which is glutamate (Epstein et al, 1999; Robinson, 2005). The final common pathway for neuronal loss in cytokine triggered inflammatory cascades is glutamate mediated excitotoxicity (Epstein et al, 1999; Robinson, 2005). This process may be the main reason behind HIV encephalopathy because the developing brain is highly sensitive to changes in astrocytic function (Van Rie et al, 2006). CNS HIV pathology is therefore a chronic inflammatory state of microglial cells (Epstein et al, 1999; Woods et al, 2007) with reactive astrogliosis leading to impaired brain growth in seropositive infants (Epstein et al, 1999).

The glutamate mediated excitotoxicity results in oxidative stress leading to the main mechanisms of neuronal and glial injury, apoptosis and axonal degeneration (Epstein et al, 1999; Robinson, 2005; Woods et al, 2007). These are present in the whole CNS but especially in connections between the basal ganglia and frontal cortex explaining the neuropsychological HIV profile of cognitive compromise, motor slowing, executive dysfunction and poor encoding and retrieval of memory (Woods et al, 2007). Epstein et al, 1999 and Willen 2006 also noted involvement of the basal ganglia and cerebral white matter while the radiologic diagnostic signs include calcification of the former and cortical atrophy on CT scan (Van Rie et al, 2006; Foster CJ et al, 2006). MRI pathology shows white matter abnormality and central atrophy (Van Rie et al, 2006).

Though there is some data on primary HIV damage to neurons, this is not the main stay of neuroaids pathophysiology (Epstein et al, 1999; Van Rie et al, 2006; Li et al, 2007).

Viral proteins as noted previously also play a significant role in HIV neuropathogenesis (Li et al, 2007; Epstein et al, 1999). One of them, trans activator protein (tat) is a major

neurotoxin and works by triggering mitochondrial injury, oxidative stress, inflammatory cascades and binding to integrin receptors (Rumbaugh et al, 2006).

HIV can also affect pediatric neurodevelopment in an indirect fashion. Mechanisms involved include opportunistic infections, cerebral vascular disease (Van Rie et al, 2006; Willen, 2006) and lymphomas (Van Rie et al, 2006). The interaction of one's genetic make up and the environment also determines one's brain function (Fenoglio et al, 2006). Enviromental factors shown to cause ND delay include use of drugs or alcohol by the mother, poverty, sub standard home environ and low maternal education (Van Rie et al, 2006; Willen, 2006). Children born to HIV parents are under a lot of stress both from the effect of the disease on their bodies and poor environmental support. This is because many have socio-economically disadvantaged and infected parents. The late gestation and early infancy is a critical period of vulnerability where chronic stress levels lead to irreversible damage to the brain including the hippocampus which is involved in learning, memory storage, retrieval and general cognitive functions (Fenoglio et al, 2006).

2.2.3 CLINICAL PRESENTATION

Neuroaids in infants occurs before significant immunosuppression and is the initial AIDS defining illness in up to 18% of children living with HIV (Van Rie et al, 2006; Van Rie et al, 2008; Willen , 2006; Forster CJ et al, 2006). It's presentation is affected by factors like viral load, advanced maternal disease (Willen, 2006; Van Rie et al, 2006) age at assessment and primary infection, interval between the above temporal measures and HAART (Willen, 2006).

2.2.3.1 SPECTRUM OF NEURODEVELOPMENT DELAY

Neural signs and symptoms observed in HIV infected children are many (Willen, 2006). It has been noted that HIV pathology is most evident in neural connections between the basal ganglia and frontal cortex (Woods et al, 2007). This explains the prototype neuropsychological profiling of HIV namely poor executive and memory functioning (Woods et al, 2007), slowing of cognitive and motor functions (Willen, 2006; Woods et al, 2007; Lindsey et al, 2008). A Brazilian cohort reported encephalitis, progressive multifocal leukoencephalopathy, focal signs (hemiparesis and paraparesis), altered tonus, cognitive disturbances, intractable headache, seizures and coma (Fragoso et al, 1999). Jeremy et al when performing baseline neuropsychological tests on 473 children reported microcephaly, hypertonic diplegia/diparesis and hyperactivity disorder (Jeremy et al, 2005). Neurodevelopmental disruption thus presents with cognitive, behavioural abnormalities (Willen, 2006; Epstein et al, 1999) and motor dysfunction (Epstein et al, 1999).

2.2.3.2 SEVERITY OF NEURODEVELOPMENT DELAY

HIV neurological presentations have been summarized into 3 syndromes, HIV related encephalopathy, CNS compromise and apparently normal (Pizzo and Wilfert, 1994). HIV encephalopathy is defined as (1) failure to attain or loss of developmental milestones or loss of intellectual ability; (2) impaired brain growth or acquired microcephaly; (3) acquired symmetrical motor deficit, in the absence of a concurrent infection other than HIV-1, and persisting for at least 2 months (CDC, 1994). HIV related encephalopathy can be static, plateau or sub acute with a rapid relentless course and is the result of the virus

working on an immature brain (Van Rie et al, 2006; Willen, 2006). Children infected through MTCT are at a higher risk of CNS disease with those infected in utero more likely to get the worst of the paediatric HIV encephalopathy syndromes (Van Rie et al, 2006).

Static encephalopathy patients can gain new skills but have a below average score on neural developmental (ND) tools. In the *plateau* type, patients do not loose acquired skills but cannot gain any new ones. The worst prognosis is the *sub-acute* variety where previously acquired skills are lost in addition to behavioural abnormality (Pizzo & Wilfert, 1994; Willen, 2006). The following diagram summarizes the three known disease courses of HIV encephalopathy

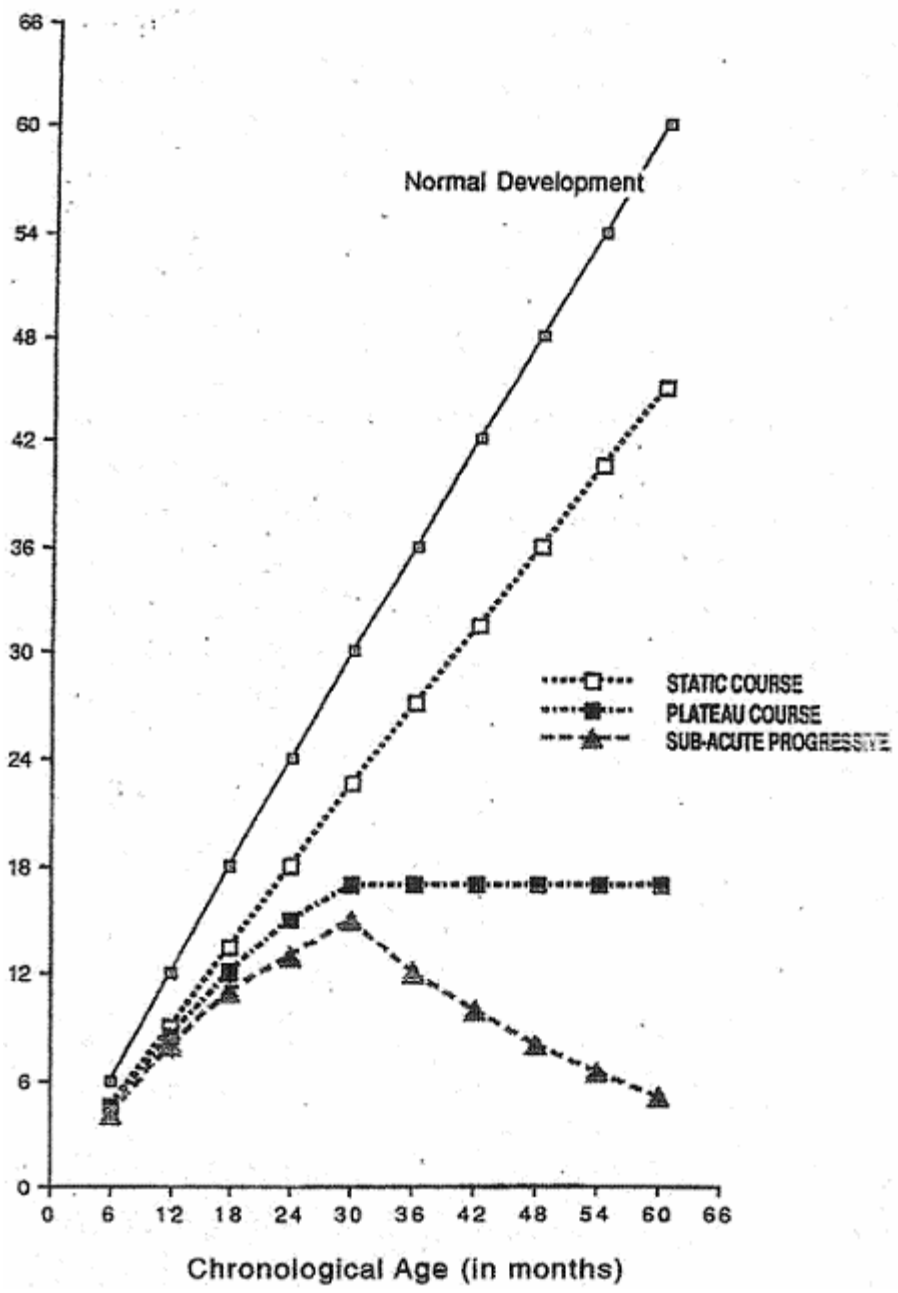


Figure 2.0-1: Schematic representation of the different encephalopathic courses.

(Pizzo & Wilfert, 1994).

From the European collaborative study of 5209 visits of 161 infected children, encephalopathy was associated with HIV disease progression after one year of age

(European collaborative study, 2004). This has been corroborated by the fact that low cognitive and psychomotor scores are predictors of rapid HIV disease progression (Willen, 2006). Severe cognitive and motor delay scores by four months of age is an ominous predictor of early death (Van Rie et al, 2006).

2.2.3.3 PREVALENCE OF NEURODEVELOPMENT DELAY

Prevalence of motor, cognition, speech and language delay in HIV infected children has been reported to range from eight percent to over 60% (Van Rie et al, 2006).

Rumbaugh et al noted an incidence of cognitive impairments in up to 30% of infected persons (Rumbaugh et al, 2006). As noted above, the frontal cortex - which is one of the main cognition lobes of the brain - is one of the hardest hit in HIV infection (Woods et al, 2007). Cognitive delay occurs later in infancy and it's presentation is global rather than specific (Van Rie et al, 2006). Cognitive tasks performed poorly by HIV infected children include sequential processing, spatial memory, auditory and visual immediate recall (Willen, 2006). Learning disabilities are also frequent (Willen, 2006).

Motor lesion symptomatology include loss of developmental milestones, symmetric pyramidal and extrapyramidal dysfunction (Epstein et al, 1999). In infants motor delay especially gross, differentiates between those exposed and infected with HIV (Van Rie et al, 2006). Gross motor abnormalities include hypertonic diplegia (Foster CJ et al, 2006). Motor malfunction namely reduced bulk, strength and abnormal tone are indicative of HIV disease progression (Van Rie et al, 2006; Willen 2006).

Language delay has been reported as part of ND abnormality in HIV (Willen, 2006; Van Rie et al, 2006; Lindsey et al, 2008). It is mainly expressive (Van Rie et al, 2006; Foster CJ et al, 2006). This fact was corroborated by Wolters et al who realized expressive language was more compromised than receptive and more so in encephalopathic children with HIV (Wolters et al, 1996). Van Rie et al realised language delay rates of expression, 84.6%, and comprehension, 76.7%. Language delay occurs before other ND and radiological signs, making its assessment useful for early ART initiation and monitoring (Van Rie et al, 2008).

Significant behavioural and personality change in pediatric neuoroaids has been identified (Wolters et al, 1996; Lindsey et al, 2007). Aetiology is varied and include direct HIV neuropathology like toxin release and structural changes such as basal ganglia calcification (Wolters et al, 1996). Indirect effects like genetic or environmental are also very influential (Lindsey et al, 2007). Behavioural assessments in HIV have been equivocal according to a systemic review by Van Rie et al, 2006. Wolters et al however showed reduced social and emotional responsiveness in infants (mean age 1.8 years) with HIV encephalopathy (Wolters et al, 1996). These children are challenged in 'purposeful, expressive, social emotional and goal directed behavior compounded by and leading to poor interpersonal skills and loss or arrest of verbal or motor skills' (Wolters et al, 1995).

2.3 NEURODEVELOPMENT ASSESSMENT IN CHILDREN

Baseline neuropsychological performance is a strong predictor of HIV disease progression and it is directly related to the severity of HIV encephalopathy (Pearson et al,

2000). It is important to know each child's ND performance, for as noted previously, it may be the first AIDS defining illness before significant immunosuppression in infants (Van Rie et al, 2006; Lindsey et al, 2007). Various standardized ND tools have been developed to obtain this data. These include the Bailey Scales and Griffiths scales among others.

One such tool which has been standardized to capture development information is the Bayley Scales of Infant Development third edition (BSID III). It is an upgrade of the second edition and 'maintains the original nature and purpose of the Bayley scales' (Bayley N, 2006). This is important because extensive work has been done to standardize the second edition for HIV research. BSID III data can then easily compare with results of other HIV neurodevelopment studies and can participate in systematic reviews once published. This is the reason why the BSID III was chosen for this study as it is without any modifications. This assessment tool should be administered by one trained to adminster ND assessments.

The mental development index of the second edition formed the backbone of the cognitive and language assessment of the latter issue, leading to a correlation of $r = 0.60$ and 0.71 respectively. Correlation between the motor composite of the third edition and the psychomotor development index of the second is $r = 0.60$ (Bayley N, 2006).

The BSID III is a development rather than intelligence assessment test. While the division between the two concepts is unclear, BSID III activities are from 'theoretical models of development and empirically validated data at different ages' (Bayley N, 2006). Intelligence data is normalized and results do not change as one gets older.

Interpreting both groups of data however involves getting a development or intelligence quotient and getting a medical biological or genetic cause of it, if abnormal (Walker et al, 2006).

Abnormal quotient or development delay, has been defined as two standard deviations (SD) or more below mean score in one parameter or two one and half SD's below the mean in at least two parameters (Bayley N, 2006). Another definition includes functioning of less than 25% below same aged peers (Bayley N, 2006). The mean in development or intelligence tools both of which have been used to asses ND delay in children is usually a score of 100 with a SD of about 15. This helps correlate the various tools of assessment. The correlation of BSID III and Weischlers III, the main intelligence test, is r = 0.79 and 0.82 between the full scale IQ of the former and cognitive and language composites of the latter respectively (Bayley N, 2006). American Psychiatric Association Diagnostic Statistical Manual – IV – TR (APA DSM – IV – TR) has a development or intelligence quotient cut off, of mental retardation or global developmental delay, of 70 while the American Association of Mental Retardation (AAMR) puts it at 75 (Walker et al, 2006). The latter is useful in planning for rehabilitation and is more in line with the Bayley classification of ND function (See table 3.1 in the case definitions chapter).

BSID III provides information on the cognition, motor, language, social emotional and general adaptation of the child tested. Data on the above constructs is presented as either raw scores or derived scores. Whereas raw scores are the actual tally of an assessment, derived scores are adaptations of the former, allowing for useful statistically backed interpretation of the data as described above. This adaptation is based on statistical data

realized during tool development. Derived scores include, scaled, composite, percentile, developmental age equivalent and growth scores. The latter three scores are useful in explaining results to parents as they are easily understood. Scaled are useful in comparing development within an individual child while composite are useful in comparing results with other measures of ND and are hence the most reported. For the sake of this discussion we will deal with only composite scores which can be interpreted as described above.

Composite scores range from 40 to 160 with a mean of 100 and SD of 15. These are useful in ascertaining how far one's score is from the mean and has a qualitative description per range easily understood by parents as shown in table below.

Table 2.0-1: Qualitative Bayley Composite Score Classifications

Qualitative description	**Composite score**
Very superior	130 and above
Superior	120 – 129
High average	110 – 119
Average	90 – 109
Low average	80 – 89
Borderline	70 -79
Extremely low	69 and below

Using the table above one can classify neurodevelopment delay as those falling in the extremely low category only (APA – DSM IV – TR) or those falling in the borderline and extremely low category (AAMR classification). The result section while clearly taking

into consideration both schools of thought put more emphasis on the latter classification so as not to leave out children who can benefit from rehabilitation intervention. This has direct implication on the later morbidity and quality of life of the child.

Cognition, language and motor development are objectively measured by the Bayley kit. BSID III uses parent filled questionnaires to assess social emotional status and general adaptation of the child.

Cognition scale

The BSID III cognition scale is based on the role of play, information processing, number concepts and counting on a child's higher functional capabilities. Counting, number constancy and cardinality are other aspects tested in BSID III cognition scale.

Language scale

BSID III tests receptive and expressive language. Receptive language includes auditory acuity especially when younger. Older children's understanding and proper response to words and requests is also tested.

Motor scale

BSID III motor scales are based on the motor milestones of a typically developing child. The motor assessment is divided into both fine and gross motor scales.

Social Emotional Status scale

The social - emotional development of infant and young children is identified by milestones typically achieved by certain ages. These are based on the six social emotional milestone levels by Greenspan.

Adaptive behavior Scale

Parents or legal guardians answer questions that check their child's ability to adapt to different aspects of typical daily life.

(Bayley Scale of Infant Development 3rd edition Technical Manual Chapter 1: pages 1 - 10)

2.4 HIGHLY ACTIVE ANTIRETROVIRAL TREATMENT AND NEURODEVELOPMENT IN HIV INFECTED CHILDREN

2.4.1 ANTIRETROVIRAL (ART) DRUGS

Antiretroviral drugs have been developed to help in the management of the HIV infection. Their classification is based on their mechanisms of action. Below is a diagram of the HIV life cycle and points of action of different classes of ART.

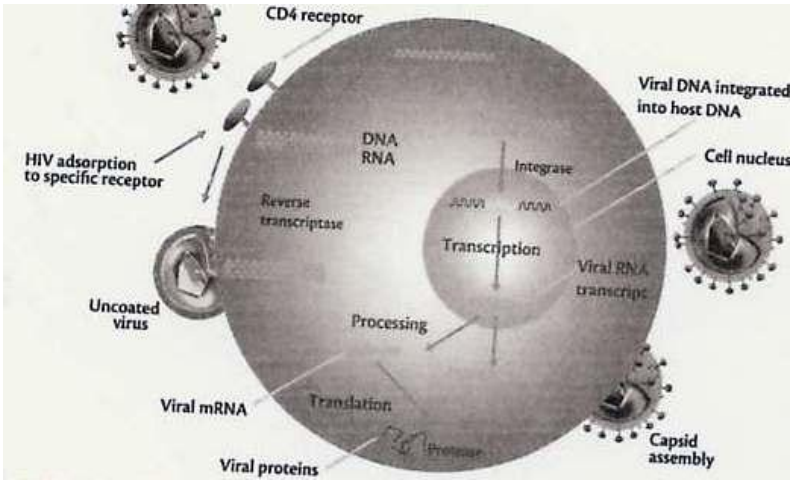


Figure 2.0-2: HIV life cycle (ANECA, 2006)

From above figure one easily identifies various classes of ART namely; reverse transcriptase inhibitors (RTI), protease inhibitors, integrase inhibitors, fusion inhibitors. Only the first two classes have been used comprehensively in HIV treatment. Reverse transcriptase inhibitors are sub classified into nucleoside reverse transcriptase inhibitors (NTRI) including zidovudine, stavudine and non nucleoside reverse transcriptase inhibitors (NNRTI) like nevirapine and efavarence. Protease inhibitors include lopinavir and ritonavir.

Monotherapy is discouraged as the virus mutates rapidly causing growth of resistant populations. HIV is treated through a combination of more than one of the above classes of drugs. Highly Active antiretroviral therapy (HAART) is defined as a combination of at least three ART drugs usually two NRTI's plus either a protease inhibitor or a NNRTI.

2.4.2 KENYAN HAART: PROVISION AND PRACTISE

In the past several years the cost of HAART has dropped considerably in Kenya from a monthly figure of 100 - 200 USD in 2002, it's currently free for patient and the health facility. This was made possible when the government of Kenya got support from the Global AIDS program. By June 2004 only 11,000 Kenyans (15 to 49 years) were on ART (UNAIDS, 2004).

Most children were unable to access ART until the United States Government Presidential Emergency Fund for AIDS Relief (PEPFAR) initiative in 2004. A grant for provision of branded ART to patients of Kenyatta National Hospital (KNH) including pediatric formulations was awarded to University of Nairobi in October 2004 and from January 2005 children were able to access HAART at a cost of USD 1.3 per month at the university teaching hospital. HAART provision to children and the health facility is currently free. HIV care is dispensed using the comprehensive care clinic (CCC) concept, which offers clinical counseling, HAART, and laboratory services to patients.

There are national paediatric HAART guidelines. First line drug combinations include Zidovudine or stavudine with lamivudine and nevirapine. In the second line drug combination the two NNRT's are replaced by didanosine and abacavir while nevirapine is replaced by ritonavir boosted lopinavir (Ministry of Health, 2004).

KNH uses immunological staging using WHO 2006 classification, in initiating and following up pediatric ART. This is the same classification used in the demography of this study (appendix III).

Goals of treatment are to restore or preserve immunological function and to improve clinical parameters, leading to a reduction in morbidity and mortality. All these occur as a result of viral suppression. HIV pathology on the neurodevelopment of children has been strongly associated with higher viral loads (Chiriboga et al, 2005; Jeremy et al, 2005). HAART significantly reduces viral loads but many studies have shown that ND functioning is not as dramatically affected (Chiriboga et al, 2005; Jeremy et al, 2005; Van Rie et al, 2006; Lindsey et al, 2007).

2.4.3 HAART AND NEUROAIDS

HAART is known to keep the cognitive function intact in high risk HIV patients (Deutsch et al, 2001). It is also known to reverse CNS manifestations and reduce risk and severity of HIV encephalopathy (Van Rie et al, 2006). Raskino et al, 1999 using various ND tests, to cater for age, one of which is the BSID II noted that combination ZDV and DDI treatment improved performance in neurocognitive, head circumference and motor assessments than either drug as a monotherapy. Since then many studies have proven HAART improves ND delay. Chiriboga et al, 2005 reported progressive HIV encephalopathy as an infrequent and reversible outcome of HIV that responds to HAART. They however realized that residual motor and cognitive damage persisted necessitating the need for special education. Van Rie et al, 2006 reports high rates of residual behavioral neurologic, cognitive and scholastic abnormalities. She also noted a high risk of relapse. Residual is lingering CNS abnormality after being on HAART. Relapse is recurrence of a CNS abnormality that had improved or disappeared after starting HAART. Lindsey et al, 2007 using the Bayley scales concludes that ‘limited ND

improvements exist despite viral suppression and positive outcomes in immunological and survival status'. Jeremy et al, 2005 seem to agree with the above point in her conclusion that while the efficacy of current anti retroviral therapy (ART) in reducing viral load is good they do not optimally remedy neuropsychological damage at least within one year's follow up. This paragraph is not contradictory but points to the fact that there must be more to HIV CNS manifestations than viral load reduction only.

Efficacy of ART in the CNS is affected by the blood brain barrier (BBB) which creates compartmentalization and hence emergence of distinct viral populations (Van Rie et al, 2006; Shanbhag et al, 2005). These CNS viral populations can cause neurocognitive abnormalities despite successful antiviral performance in other body tissues (Deutsch et al, 2001; Lindsey et al, 2007). Variability in the ability of ART drugs to cross the BBB is the main explanation to the above with protease inhibitors having the poorest CNS penetration (Van Rie et al, 2006; Lindsey et al, 2007). Sub optimal ART CSF penetration then occurs (Shanbhag et al, 2005).

The HIV also benefits from the relatively long lifespan of infected microglia, macrophages and astrocytes as compared to CD4 lymphocytes. This frustrates the speed of clearing this virus from the CNS (Van Rie et al, 2006).

Viral proteins like tat play a role in neuroaids pathogenesis in triggering the inflammatory cascades. Their synthesis by HIV infected cells is not affected by current ART regimes (Rumbaugh et al, 2006). BBB damage by HIV leading to entry of infected macrophages into the CNS is another neuropathological process not affected by HAART (Ricardo-Dukelow et al, 2007).

2.5 CONCLUSION

There is no data on the baseline ND status of Kenyan children infected with HIV. Interventions that prevent morbidity and improve quality of life are then not included in routine care. A data gap also exists on the effect of ART on the neuroaids of sub Saharan African children. Neurobehavioural assessments can provide information on HIV disease progression beyond traditional markers like CD4 count and RNA levels (Van Rie et al, 2006) optimizing on the timing of HAART initiation reducing morbidity and mortality especially in resource poor settings (Willen, 2006). Risk factor evaluation for neurocognitive delay in HIV infected children is also warranted (Shanbhag et al, 2005).

CHAPTER 3: METHODOLOGY

3.1 STUDY DESIGN

This was a prospective observational cohort study

3.2 STUDY POPULATION

The study population was drawn from the Comprehensive HIV Care Clinic (CCC) of Kenyatta National Hospital (KNH). KNH is the biggest public hospital in eastern and central Africa. It is the national referral hospital for Kenya and the University of Nairobi teaching hospital. The Bayley Scales of Infant Development 3^{rd} edition (BSID III) caters for development assessment of children between two weeks and 42 months of age. Since the follow up was for at least six months, HIV infected children aged between two weeks and 36 months were eligible for the study. All children underwent HIV antibody testing and those under 18 months had their diagnosis confirmed using HIV DNA Polymerase chain reaction (PCR).

3.2.1 INCLUSION CRITERIA

- Presence of legal guardian
- Aged between two weeks and 36 months
- Confirmed positive HIV infection by PCR if <18 months or positive HIV ELISA if >18 months.

- HAART naive at enrolment. Patients exposed to short course antiretrovirals for PMTCT but not HAART were included.
- World Health Organization (WHO) clinical stage two, three or four.
- From treatment records should have shown good compliance to two immediate previous clinical appointments.
- Informed consent from parent/guardian to participate in study

3.2.2 EXCLUSION CRITERIA

- HAART experienced.
- Other CNS disease e.g. cerebral palsy, post meningitic neurological disease
- Below two weeks of age or over 36 months of age.

3.3 MATERIALS AND MEASUREMENTS

3.3.1 MAIN RESEARCH TOOL; BAYLEY SCALES OF INFANT DEVELOPMENT 3RD EDITION

This is a standardized tool used to measure the following neurodevelopmental constructs;

1. Cognition
2. Language both receptive and expressive
3. Motor both fine and gross
4. Social emotional status

5. Adaptive behavior Scale. Abilities measured here fall under following tittles; - communication, community use, functional pre-academics, home living, health and safety, leisure, self care, self direction, social and motor.

The BSID III came with a scoring computer program which was used to convert the raw scores into derived scores used for statistical analysis.

3.3.2 ROUTINE CLINICAL MEASUREMENTS FOR HIV INFECTED CHILDREN

3.3.2.1 ANTHROPOMETRIC TOOLS

Ruler; measure recumbent length in those < 24 months

Stadiometer; measure height in those > 24 months.

Weighing scales; measure weight

3.3.2.2 LABARATORY TESTS

The following tests are carried out prior to HAART initiation, and for monitoring response to and for adverse effects of HAART.

CD4 counts; at baseline and after 6 months of followup, measure immune status.
Full hemogram , alanine transaminase; at baseline month one and every three months thereafter. Serum creatinine; at baseline and every six months.

3.4 CASE DEFINITIONS

ND delay is defined as those children falling in the borderline and extremely low Bayley composite qualitative definition (See table 2.1) This is supported by the Bayley classification of Neurodevelopment function as shown in the table below.

Table 3.0-1: Bayley Classification of ND function.

ND Functional classification	Development Quotient
Accellerated	> 115
Normal	85 – 115
Mild Delay	70 – 84
Severe Delay	< 70

(Bayley N,1993)

3.5 PROCEDURE

3.5.1 SCREENING VISIT

The primary investigating doctor, identified potential eligible study subjects by studying patient's records, interviewing their parents and or legal guardians. Once eligibility was established the study was explained to the parents or legal guardians and a request for consent put in. Once a written consent was granted, a demography form and data

extraction sheet was filled through parental or legal guardian interview and study of the hospital file. Routine clinical and initial screening tests were then ordered, which included a confirmatory HIV ELISA if the patient's file had no data on this. HIV PCR was done on samples from children less than 18 months with a positive HIV antibody test. Other routine blood tests requested were full hemogram, alanine transferase, serum creatine and CD4 count and percentage. The child was then led to a phlebotomist who withdrew a total of five milliliters of blood in three tubes from the child. For children less than 18 months with no positive ELISA report the laboratory was requested to store cells for one week for PCR testing. The patient is then given one to two weeks return appointment. This is part of the Study site, KNH CCC, procedure for starting HAART. This is because for patients under 18 months it took one week to get PCR results hence the one to two weeks appointment.

3.5.2 SECOND VISIT AFTER ONE WEEK

Labaratory test results are discussed with the parents and or legal guardians. Those eligible (HIV infected confirmed by ELISA if over 18 months and PCR if under 18 months and WHO stage two to four) were enrolled into the study.

Neuropsychological assessment using the Bayley scales was carried out by Dr Madumadu Kigira the study doctor. She is the only one who did the BSID assessment. This standardised tool comes with a kit which helps one collect raw data. The kit being standardised helped deal with intra observer bias as results were based on rules of the scales rather than subjectivity of the assessor. The kit also came with a computer program that converts raw scores into derived scores and stores them. All data is currently in the

computer. It also prints reports and graphs. Data was coded to identify each study patient with a code rather than name and this was what was analysed with the help of a statistician. Each patient had a code that had MSC for degree, ND for neurodevelopment and registration number for example MSCND001 for the first study subject. The BSID III was carried out on the child early in the clinical visit to optimize co-operation from the child before he or she got stressed by painful and uncomfortable procedures.

Baseline anthropometric measurements were carried out and recorded by the nursing staff as part of their triaging process in keeping with the CCC HAART management protocols. A HAART initiation appointment was then scheduled to those eligible. Monthly follow up visits scheduled as standard CCC protocol for new HAART patients were set up to enhance adherence to the study. The BSID III does allow for monthly growth score charting and monitoring. The growth score charts were then explained and given to the parents at the end of the study period. One week to the monthly appointment a reminder telephone call was made if parents or legal guardians owned a phone.

3.5.3 ANTIRETROVIRAL THERAPY INITIATION APPOINTMENT

The patient followed the Kenyatta National Hospital comprehensive care clinic procedure of being absorbed into the HAART program. This involves two to three counseling appointments by professional counselors. Once the counselor is comfortable with the parents' or guardian's understanding of HAART, the patient was sent to the CCC doctor who prescribed an appropriate HAART regime after studying the laboratory test results. The CCC pharmacy dispensed the drugs and reinforced adherence counseling.

3.5.4 MONTHLY APPOINTMENT PROCEDURE

At each monthly visit anthropometric tests (height or length, and weight) were taken. Adheherence to HAART issues was evaluated. Any clinical problems were treated. A BSID III assessment was also done to get growth chart monitoring results for the parents. The patient then proceeded to the KNH CCC procedure of HAART follow up. This included a full haemogram and alanine transaminase test at month one and three. Since the main aim of these monthly visits was to minimize loss to follow up cases, one week to the monthly appointment a reminder telephone call by study doctor was made if possible.

3.5.5 MONTH SIX VISIT PROCEDURES

This was the last study appointment and it's procedure was similar to the monthly appointment without the reminder telephone call for following month. A cognitive growth chart was filled in for each child who completed the study and it's meaning explained to the mother as part of the benefit of participation.

3.6 STATISTICAL ANALYSIS

3.6.1 SAMPLE SIZE CALCULATION

Sample size calculation was based on the first primary objective. Using MS Excel Sample size V4 draft and taking into consideration the standard deviation of BSID III

composite score which is 15 with a mean of 100, and assuming a drop out rate of 20% and a level of confidence of 95%; the minimal sample size calculated was 33 children. There was no randomization. All children attending the CCC who met the inclusion criteria were eligible.

3.6.2 DATA ANALYSIS

BSID III has a computer program that automatically converts raw scores to

- scaled scores with a mean of 10 and a SD of 3
- composite scores with a mean of 100 and a SD of 15

The program also calculates significant differences between the neurodevelopmental contructs. Fischer's exact and pearson's chi square analysis statistics were calculated using the SPSS software.

3.7 FUNDING.

1. Nestle Nutrition covered the cost of the BSID III tools.
2. The children who participated in this study received their comprehensive HIV care at KNH CCC which is supported by the Government of Kenya and the United States government PEPFAR initiative.

3.8 ETHICS

This research was carried out in Kenya. Ethical committees' clearances were obtained from the Committee for Research on Human subjects University of Witwatersrand South Africa and the Kenyatta National Hospital (KNH) ethical committee, Kenya (See appendix one and two respectively).

The study was fully explained to the parents and legal guardians of the child and written consent obtained before enrollment. All study participants were offered HAART according to the KNH CCC protocol. Study procedures posed no additional risk to the child. Blood tests done were in keeping with the standard KNH CCC protocols. No interference was made in the routine clinical management of the child by the primary KNH CCC doctors. Any clinical condition noted by the researcher requiring immediate medical attention was reported to the primary KNH CCC doctors.

All patients had access to free HAART drugs as standard of care of the hospital. Drugs were donated under United States government PEPFAR program. Patients were free to discontinue from the study at any point according to their wish. No material or financial incentives were given to the patients.

CHAPTER FOUR: RESULTS

4.1 SOCIODEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION

Table 4.0-1: Baseline Sociodemographic Characteristics Of Study Population (from initial assessment).

Characteristic	Frequency or Median	Percentage or Range
INFANT FACTORS		
Age (in Months) (n = 36)		
< 6	7	19.4%
6 – 12	14	38.9%
13 – 18	4	11.1%
19 – 24	4	11.1%
25 – 30	6	16.7%
30 +	1	2.8%
Sex (n = 36)		
Male	16	44.4%
Female	20	55.6%
BF (n = 24)		
Yes	10	41.7%
No	14	58.3%
Living with Mother (Currently) (n = 34)		
Yes	33	97.1%
No	1	2.9%
Baseline Characteristics of the Maternal Factors		
Education Level (n = 34)		
Primary & Below	21	61.8%
Secondary&Above	13	38.2 %
Ethnicity (n = 34)		
Bantu	22	64.7%
Nilotes	11	32.4%
Cushites	1	2.9%

We enrolled thirty six black African children into the study between March 2007 and March 2008. They were of median age 10.9 months ranging from 4.1 to 30.6 months and 55.6% were female. Sixty two percent of the mothers had a maximum of primary level education and 38% had secondary and above qualifications. Forty two percent of the

children were currently breastfeeding. Ninety seven percent were currently living with their birth mothers. Mothers were from various ethnic groupings with 65% Bantu, 32% Nilotes and 3 % cushites.

4.2 BIRTH CHARACTERISTICS OF STUDY POPULATION

Table 4.0-2: Birth Characteristics Of Study Population (from initial assessment)

Characteristic	**Frequency or Median**	**Percentage or Range**
PMTCT (n = 34)		
Yes	12	35.3%
No	22	64.7%
Birth History (n = 34)		
SVD C/S	29 5	85.3% 14.7%

The majority (85.3%) were born through normal vaginal delivery. All were HAART naïve, though 35.3 % of mother / child pair were exposed to nevirapine PMTCT around birth.

4.3 CLINICAL CHARACTERISTICS OF STUDY POPULATION

World Health Organization disease stages in these children were II in 5.9%, III in 32.4% and IV in 61.8%. Median CD4 counts were 715.5. Forty three percent had hemoglobin levels less than 10g/dl.

Table 4.0-3: Clinical characteristics of study population (from initial assessment)

Characteristic	Frequency or Median	Percentage or Range
Initial Staging (n = 36)		
II	4	5.9%
III	11	32.4%
IV	21	61.8%
HB g/dl (n = 20)		
≤ 10	8.5	4.3 – 9.3
> 10	11.1	10.2 – 17.2
CD4 count (n = 24) Mean 860 SD 621		
Absolute count	715.5	2.0 – 2,416
CD4% (n = 24)		
Mild	1	4.2%
Advanced	4	16.7%
Severe Immunosuppresed	19	79.2%

According to 2006 WHO HIV immunosuppression by CD4% classification, 4.2% had mild immunosuppression, severe immunosuppression 16.7% and advanced immunosuppression 79.2%.

4.4 PREVALENCE OF NEURODEVELOPMENT DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

Table 4.0-4: Prevalence Rates For ND Delay Among HIV Infected Children (From initial assessment)

Type of ND delay	N	Frequency	Percentage
Any delay	**36**	**32**	**88.9%**
Cognitive delay	36	22	61.2%
Language delay	36	24	66.6%
Motor delay	36	30	83.3%
SES delay	33	12	36.4%
Adaptive delay	33	20	60.6%

Twenty nine children of the thirty six had at least one extremely low qualitative assessment (composite score development quotient of 69 and less) in at least one ND parameter. Two others had at least two ND parameter assessments that fell in the borderline group (composite score of 70 to 79) and one other at least one. As a result only four out of the cohort of 36 children with HIV did not have any type of neurodevelopment delay in any one development constructs assessed. This put the overall prevalence rate at 88.9%. Motor delay was the highest specific type of neurodevelopment delay followed by language, cognitive and adaptive delay respectively.

4.5: SPECTRUM OF ND DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

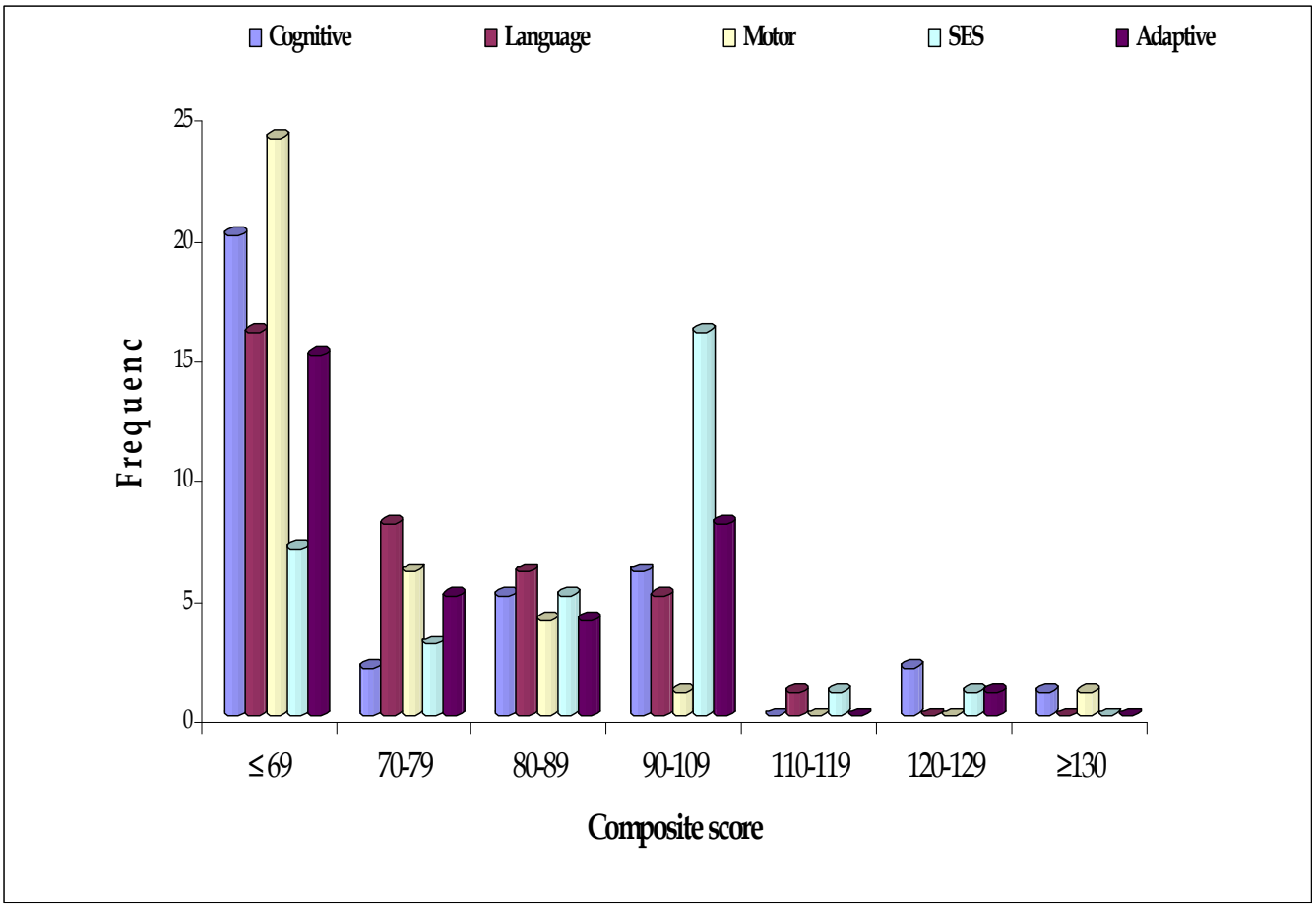


Figure 4.0-1: ND composite scores of study population (From initial assessment).

The full spectrum of neurodevelopment function was observed in the study population, ranging from extremely low qualitative description to very superior. All aspects of ND delay as assessed by the BSID III as noted by the columns showing composite scores of under 69 and 70 – 79 was also present. (See figure 4.1 above).

Table 4.0-5: Spectrum of ND Delay: Median Bayley Composite Score Summary (From initial assessment)

Parameter	N	Median score	IQR	Score qualitative description
Cognitive	36	65	55–88.75	Extremely low
Language	36	72.5	59–89	Borderline
Motor	36	61.0	49.75–78.25	Extremely low
SES	33	90	70-95	Average
Adaptive	33	76	58-95.5	Borderline

Median motor and cognitive scores were in the extremely low ND zone, language and adaptive scores fell in the borderline ND range. SES median scores qualitative description was normal (table 4.5). Using the definition of ND delay represented in table 3.1, median scores that are delayed are those of cognitive, language motor and adaptive parameters.

4.6 SEVERITY OF NEURODEVELOPMENT DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

Table 4-0-6: Severity of ND Delay: Qualitative Bayley Composite Score Distribution. (From initial assessment)

ND Classification	**Cognitive** Freq (**%**)	**Language** Freq (**%**)	**Motor** Freq **(%)**	**SES** Freq **(%)**	**Adaptive** Freq **(%)**
NEURODEVELOPMENTAL DELAYED					
Extremely low	**20 (55.6)**	**16 (44.4)**	**25 (69.4)**	**10 (30.3)**	**16 (48.5)**
Borderline	**2 (5.6)**	**8 (22.2)**	**5 (13.9)**	**2 (6.1)**	**4 (12.1)**
Sub Total	**22 (61.1)**	**24 (66.7)**	**30 (83.3)**	**12 (36.4)**	**20 (60.6)**
NOT NEURODEVELOPMENTALY DELAYED					
Low average	6 (16.7)	6 (16.7)	3 (8.3)	4 (12.1)	4 (12.1)
Average	5 (13.9)	5 (13.9)	2 (5.6)	15 (45.5)	8 (24.2)
Above average	3 (8.3)	1 (2.8)	1 (2.8)	2 (6)	1 (3)
Sub Total	**14 (38.9)**	**12 (33.3)**	**6 (16.7)**	**21 (63.6)**	**13 (39.4)**
Total	**36 (100)**	**36 (100)**	**36 (100)**	**33 (100)**	**33 (100)**

* SES: Socio-emotional status

*GAD: General Adaptive Behavior

Motor delay is severe with most of the children scoring in the extremely low qualitative description range. The same point is replicated in the cognitive, language and general adaptive scores. Social emotional mode lies in the average qualitative description range. This table and the prevalence data calculated earlier on summarises the fact that of the neurodevelopment delay that occurs most fall in the extremely low qualitative category

especially in the cognitive, language, motor and general adaptive constructs. These are the most affected of the ND parameters in the Kenyan child with HIV.

4.7 FACTORS ASSOCIATED WITH NEURODEVELOPMENT DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

Fischer's exact and Pearson's chi square statistics were done to determine factors associated with ND delay in this cohort. The definition of ND was that fell in the borderline and extremely low group (See table 3.1 in case definitions).

Fischer's statistics were used in data cells that had less than five children in this analysis. Those that did not have any with less than five, Pearson's chi square statistics were used.

Risk factors used in data analysis in this chapter are; age, sex, mode of delivery, PMTCT, maternal education, initial HIV WHO staging, initial CD4% and current infant breast feeding.

Table 4-0-7: Factors Associated With 'Any Delayed' ND Score (From initial assessment)

Risk Factors	Any ND Delay		χ^2	p-value
	Yes, n (%)	No, n (%)		
Infant Age				
• ≥ 18	11 (34.4)	-	0.33	0.220
• < 18	21 (65.6)	3 (100.0)		
Sex				
• Female	18 (56.3)	1 (33.3)	0.02	0.461
• Male	14 (43.8)	2 (66.7)		
Mode of Delivery				
• SVD	24 (82.8)	2 (100.)	0.12	0.434
• C/S	5 (17.2)	-		
PMTCT			0.36	
• Yes	10 (34.5)	1 (33.3)		0.968
• No	19 (65.5)	2 (66.7)		
Mother Education				
• Primary & Below	16 (55.2)	3 (100.0)	0.79	0.132
• Secondary & Above	13 (44.8)	-		
Initial Staging				
• ≤ II	27 (93.1)	3 (100.0)	0.16	0.639
• ≥ III	2 (6.9)	-		
CD4%				
• **Other**	18 (81.8)	1 (50.0)	0.02	0.289
• **Severe**	4 (18.2)	1 (50.0)		
Infant BF				
• **Yes**	6 (20.7)	3 (100.0)	4.99	**0.004**
• **No**	23 (79.3)	-		

*****Fischers exact chi square statistics

This analysis shows that not breast feeding was associated with a higher risk of having any ND delay in any one development parameter as assessed by the BSID III (100% of those who did not breastfeed developed delay as opposed to 67.7% of those who did, p value of 0.004).

Table 4.0-8: Factors Associated With ND delayed Cognitive Scores (From initial assessment

Risk Factors	Cognitive delay			p-value
	Yes, n (%)	No, n (%)	χ^2	
Age in months			4.25	
• ≥ 18	10 (45.5)	1 (7.1)		**0.015**
• < 18	12 (54.5)	13 (92.9)		
Sex			0.04	
• Female	12 (54.5)	8 (57.1)		0.577
• Male	10 (45.5)	6 (42.9)		
Mode of Delivery			0.28	
• SVD	18 (90.0)	10 (76.9)		0.306
• C/S	2 (10.0)	3 (23.1)		
PMTCT			0.78	
• Yes	5 (25.0)	6 (46.2)		0.208
• No	15 (75.0)	7 (53.8)		
Mother Education			6.97	
• Primary & Below	8 (40.0)	12(92.3)		**0.003**
• Secondary & Above	12 (60.0)	1 (7.7)		
Initial Staging			0.18	
• I or II	1 (5.0)	1 (7.7)		0.751
• III or IV	19 (90.9)	12 (92.3)		
Immunosuppression by CD4%			0.78	
• Severe	14 (87.5)	5 (62.5)		0.155
• Non – severe	2 (12.5)	3 (37.5)		
BF			0.58	
• Yes	4 (20.0)	5 (38.5)		0.245
• No	16 (80.0)	8 (61.5)		

*****Fischers exact chi square statistics

Table 4.8 shows a child who is 18 months and above is more likely to have scores that fall in the extremely low cognitive delay range than one who is under 18 months (90.9% versus 48.0%, p-value 0.015). Children from mothers educated to a maximum of primary level are less likely to get extremely low cognitive delay in this cohort than those whose mothers had a higher education (40% versus 92.3%, p-value 0.003).

Table 4. 0-9: Factors Associated With ND delayed Language Scores (From initial assessment)

Risk Factors	Language delay			p-value
	Yes, n (%)	No, n (%)	χ^2	
Age in months				
• ≥ 18	11 (45.8)	-		**0.005**
• < 18	13 (54.2)	12 (100.0)	5.91	
Sex				
• Female	13 (54.2)	7 (58.3)		0.813
• Male	11 (45.8)	5 (41.7)	0.01	
Mode of Delivery				
• SVD	20 (90.9)	8 (72.7)		0.170
• C/S	2 (9.1)	3 (27.3)	0.74	
PMTCT				
• Yes	6 (27.3)	5 (45.5)		0.296
• No	16 (72.7)	6 (54.5)	0.43	
Mother Education				
• Primary & Below	12 (54.5)	8 (72.7)		0.314
• Secondary & Above	10 (45.5)	3 (27.3)	0.40	
Initial Staging				
• III or IV	21 (95.5)	10 (90.9)		0.606
• I or II	1 (4.5)	1 (9.1)	0.07	
Immunosuppression by CD4%				
• Severe	15 (88.2)	4 (57.1)		0.088
• Non – severe	2 (11.8)	3 (42.9)	1.33	
BF				
• **Yes**	5 (22.7)	4 (36.4)		0.407
• **No**	17 (77.3)	7 (63.6)	0.17	

*****Fischers exact chi square statistics

Being over 18 months of age is a risk factor for developing language ND delay in this cohort (100% versus 52%, p-value 0.005).

Table 4.0-10: Factors associated with ND delayed motor scores (From initial assessment)

Risk Factors	Motor delay		χ^2	p-value
	Yes, n (%)	No, n (%)		
Age in months			0.10	
• ≥ 18	10 (33.3)	1 (16.7)		0.418
• < 18	20 (66.7)	5 (83.3)		
Sex			0.02	
• Female	16 (53.3)	4 (66.7)		0.549
• Male	14 (46.7)	2 (33.3)		
Mode of Delivery			0.27	
• SVD	22 (81.5)	6 (100.0)		0.252
• C/S	5 (18.5)	-		
PMTCT			0.23	
• Yes	9 (33.3)	2 (33.3)		1.000
• No	18 (66.7)	4 (66.7)		
Mother Education			0.02	
• Primary & Below	16 (59.3)	4 (66.7)		0.737
• Secondary & Above	11 (40.7)	2 (33.3)		
Initial Staging			0.07	
• III or IV	26 (96.3)	5 (83.3)		0.229
• I or II	1 (3.7)	1 (16.7)		
Immunosuppression by CD4%			0.81	
• Severe	17 (85.0)	2 (50.0)		0.116
• Non – severe	3 (15.0)	2 (50.0)		
BF			0.77	
• **Yes**	6 (22.2)	3 (50.0)		0.167
• **No**	21 (77.8)	3 (50.0)		

*****Fischers exact chi square statistics

There were no factors in this analysis that showed any association with motor delay despite the fact that it is the most prevalent type in this cohort.

Table 4.0-11: Factors associated with ND delayed SES scores (From initial assessment)

Risk Factors	SES delay		χ^2	p-value
	Yes, n (%)	No, n (%)		
Age in months				
• ≥ 18	7 (58.3)	3 (14.3)		***0.008***
• < 18	5 (41.7)	18 (85.7)	5.08	
Sex				
• Female	7 (58.3)	11 (52.4)		0.741
• Male	5 (41.7)	10 (47.6)	0.00	
Mode of Delivery				
• SVD	10 (90.9)	17 (85.0)		0.639
• C/S	1 (9.1)	3 (15.0)	0.01	
PMTCT				
• Yes	4 (36.4)	7 (35.0)		0.939
• No	7 (63.6)	13 (65.0)	0.10	
Mother Education				
• Primary & Below	6 (54.5)	13 (65.0)		0.567
• Secondary & Above	5 (45.5)	7 (35.0)	0.03	
Initial Staging				
• III or IV	10 (90.9)	19 (95.5)		0.657
• I or II	1 (9.1)	1 (5.0)	0.10	
Immunosuppression by CD4%				
• Severe	6 (75.0)	12 (80.0)		0.782
• Non – severe	2 (25.0)	3 (20.0)	0.06	
BF				
• Yes	2 (18.2)	7 (35.0)		0.324
• No	9 (81.8)	13 (65.0)	0.33	

*****Fischers exact chi square statistics

*SES Socioemotional status

Age, being older than 18 months once again is significantly associated with social emotional delay (70.0% versus 21.7%, p-value 0.008). None of the other risk factors seem to statistically increase the chances of a child having a lower socio-emotional score.

Table 4.0-12: Factors associated with ND delayed GAD scores (From initial assessment)

Risk Factors	GAD delay			p-value
	Yes, n (%)	No, n (%)	χ^2	
Age in months			5.93	
• ≥ 18	9 (44.5)	-		**0.005**
• < 18	11 (55.0)	13 (100.0)		
Sex			0.09	
• Female	11 (55.0)	7 (53.8)		0.948
• Male	9 (45.0)	6 (46.2)		
Mode of Delivery			0.04	
• SVD	16 (88.9)	11 (84.6)		0.726
• C/S	2 (11.1)	2 (15.4)		
PMTCT			0.46	
• Yes	5 (27.8)	6 (46.2)		0.291
• No	13 (72.2)	7 (53.8)		
Mother Education			0.01	
• Primary & Below	11 (61.1)	9 (69.2)		0.641
• Secondary & Above	7 (38.9)	4 (30.8)		
Initial Staging			0.03	
• III or IV	18 (100.0)	12 (92.3)		0.232
• I or II	-	1 (7.7)		
Immunosuppression by CD4%			0.00	
• Severe	12 (85.7)	6 (75.0)		0.531
• Non – severe	2 (14.3)	2 (25.0)		
BF			0.05	
• Yes	5 (27.8)	4 (30.8)		0.856
• No	13 (72.2)	9 (69.2)		

*****Fischers exact chi square statistics

*GAD General Adaptive Behaviour

Children older than or equal to 18months are significantly more likely to have general adaptive delay (100% versus 45.8%, P-value 0.005). None of the other risk factors seem to have a statistically significant role in this cohort.

4.8 COMPOSITE SCORES AFTER AT LEAST 6 MONTHS OF HAART

Only 12 children out of the 36 completed the follow up after at least six months of HAART.

Table 4.0-13: Trend In Composite Score Over The Study Period (N = 12) (From both initial and final assessment)

Summary Scaled Score	Mean (SE)	95% CI	P-value
Cognitive			
Initial	69.58 (±486)	(-15.40 to -2.10)	**0.015**
≥ 6 months of HAART	78.33 (±4.23)		
Language			
Initial	67.00 (±3.37)	(-19.20 to -4.14)	**0.006**
≥ 6 months of HAART	78.37 (±2.80)		
Motor			
Initial	62.75 (±3.85)	(-13.58 to 3.08)	0.193
≥ 6 months of HAART	68.00 (±3.68)		
Socio-emotional			
Initial	81.25 (±6.03)	(-34.67 to -2.00)	**0.031**
≥ 6 months of HAART	99.58 (±5.13)		
General Adaptive			
Initial	67.25 (±5.93)	(-16.35 to 6.69)	0.376
≥ 6 months of HAART	72.08 (±4.33)		

A paired t test comparing the means of the 12 patients who had results at baseline and after at least 6 months of ART realized an improvement in cognitive, language and socio-emotional scores. It is however important to note that apart from SES, all other ND

parameter's scores after at least six months of HAART fell in the ND delay range (See table 3.1).

Though the power of this test is limited, it is in keeping with other studies who realized similar results as discussed in the following chapter.

Table 4.0-14: Comparison between demographic characteristics of those who did and did not complete study (From initial / baseline assessment visit)

Study completion status					**P-value**
Factors	**Completed**		**Lost to follow-up**		
	n	%	**n**	%	
Age: n = 36					
≤ 5	-	-	3	12.5	0.121
6 – 10	3	25	10	41.7	
11 – 15	2	16.7	6	25	
16 – 20	1	16.7	1	4.2	
21 – 25	2	16.7	1	4.2	
25 +	4	33.3	3	12.5	
Sex: n = 36					
Male	7	58.3	9	37.5	0.406
Female	5	41.7	15	62.5	
Birth History: n = 34					
SVD	10	83.3	19	86.4	1
C/S	2	16.7	3	13.3	
PMTCT : n = 34					
Yes	3	25	9	40.9	0.465
No	9	75	13	59.1	
Initial Staging: n = 34					
II	1	8.3	1	4.5	0.576
III	5	41.7	6	27.3	
IV	6	50	15	68.2	

A paired t test comparing demographic characteristics of those who failed to and those who completed the study was done (table 4.14 above). It shows that there is no difference

in the age, sex, birth history, PMTCT and initial staging characteristics of the two populations. One can then assume that the results of those lost to follow - up are similar to those who completed the study.

4.9 MORTALITY

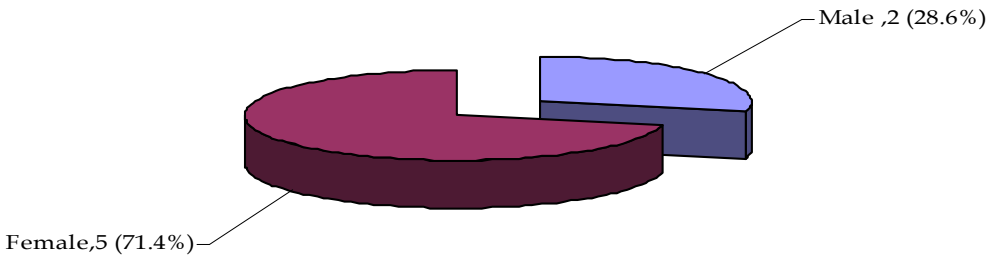


Figure 4.2: Mortality Distribution By Sex (N = 7)

Of the children who did not finish the study, seven are known to have died. Of these most were in WHO stage four (71.4%).

Table 4.15: Neurodevelopmental Delay And Mortality (from initial assessment)

Developmental Delay	Dead				p-value
	Yes		No		
	N	%	N	%	
Cognitive	6	27.3	16	72.7	0.137
Language	5	20.8	19	79.2	0.766
Motor	6	20.0	24	80.0	0.851
SES	1	8.3	11	91.7	0.171
GAD	3	15	17	85	0.279

*****Fischers exact chi square statistics

*SES Socioemotional status

*GAD General Adaptive Behaviour

This table shows of the 22 children who had cognitive delay in the initial assessment, as defined as extremely low and borderline cognitive score (see table 4.6) six died. Likewise using table 4.6 in language five out of the 24 with language delay died; Motor six out of the 30 with motor delay died; SES one out of the 12 with delay in this construct died; and three out of 20 with the ND delay died in adaptation.

There is however no association between mortality and any of the ND constructs assessed. These numbers are too low to make any conclusion.

CHAPTER FIVE: DISCUSSION OF RESULTS

This protocol's research question sought to unravel the prevalence, spectrum and severity of the Kenyan HIV infected child's neurodevelopment delay and factors that affect it. A standardized tool the BSID III third edition was employed.

5.1 PREVALENCE OF NEURODEVELOPMENT DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

Of the 36 children in this cohort only four did not need any intervention for neurodevelopment delay (Table 4.4) according to the AAMR (see chapter 2.3). This is a very high overall prevalence of 88.9%. Motor delay is especially prevalent 83.3%, while cognitive, language and adaptive delay present in this cohort were 61.2%, 66.6% and 60.6% respectively (Table 4.4).

Other neurodevelopment studies in Africa have also realized high prevalence rates. Potterton in South Africa using BSID II, had a prevalence rate of 78% cognitive delay and 87% motor delay (Potterton, 2006). Most studies however use a development quotient two SD's below the mean as a definition of ND delay in accordance with the APA. Figures falling in the above definition are those that are in the qualitative description of 'extremely low' (table 4.6). Extremely low percentage rates were 55.6%, 44.4%, 69.4%, 30.3% and 48.5% for cognitive, language, motor, SES, adaptive ND parameters respectively.

A study in DRC using BSID II had severe ND delay prevalence rates of 60% cognitive and 28.6% motor (Van Rie et al 2008). These rates changed to 91% cognitive and 82% motor delays in their lower age range, 18 to 29 months (Van Rie et al, 2008) which is part of this Kenyan cohort's age range.

A meta analysis reported by Van Rie et al 2006, had prevalence rates ranging from under 8% to over 60 % in motor, cognitive and speech delay. In this systemic review Rwanda with a small cohort and simple screening tools reported prevalence rates of 15% to 40% of mainly gross motor delays. Uganda studying HIV infected children by 12 months had rates of 30% and 26% of motor and cognitive delay respectively (Van Rie et al 2006).

5.2 SPECTRUM OF NEURODEVELOPMENT DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

All aspects of ND delay as measured by BSID III was realized in this cohort. Table 4.5 show that motor, cognitive, language and adaptive delay are more likely to occur as evidenced by their median scores. One has to plan to manage these delays as well as the primary condition of HIV. It is clear that a holistic management approach that addresses all these abnormalities is mandatory as one handles a child living with HIV (Van Rie et al, 2006; Forster et al, 2006).

5.3 SEVERITY OF NEURODEVELOPMENT DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

These results also point out that most of those with neurodevelopment delay had the severest of the malady. Many of their scores fell in the extremely low qualitative range at least in the motor, cognitive, language and adaptive parameters (Table 4.6). This is the group with a development quotient of 69 and less and falls in the neuropsychological profiling that places them at the highest risk for later disease progression (Pearson et al 2000).

Globally several studies have reported lower neuropsychological scores in HIV infected children (Knight et al, 2008; Forster et al, 2006 ; Lindsey et al, 2007) and it has been proven that these assessments have useful disease progression predictive value and monitoring information (Pearson et al 2000). While the Bayley III was not standardized for Kenya purposeful enabling easy comparison of these results with other global studies, this study shows that there is a possibility of increased holistic follow up of HIV children in Kenya if neurodevelopment assessments are incorporated into the standard of care in children represented by this cohort.

5.4 FACTORS AFFECTING NEURODEVELOPMENT DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

This study also looked as some risk factors and their effect on ND of children infected with HIV in Kenya. Fischers exact chi square analysis per each category of 'extremely low' ND scores were done. This is to enable favourable comparisons with other studies who analyse using these scores.

5.4.1 FACTORS AFFECTING OVERALL DELAY PICTURE

Table 4.7 shows breastfeeding is protective against developing any delay in any one ND parameter (p value 0.004). Breast feeding has been linked to low mortality in HIV infected children from resource poor countries who lack the resources to buy formula in the first six months of life (ANECA, 2006; Nduati et al, 2001; Mbori Ngacha et al, 2001). It is also an important MTCT route (ANECA, 2006; Nduati et al, 2001; Mbori Ngacha et al, 2001). To balance the two previous points HIV mothers without alternative food have been advised to exclusively breastfeed for the first six months of life and then wean abruptly (ANECA, 2006).

5.4.2 FACTORS AFFECTING SPECIFIC DELAY PARAMETERS

5.4.2.1 AGE

It is interesting to note that the older child (18 months or more in age) was more at risk of getting cognitve, language, SES and adaptive delay (tables 4.8, 4.9, 4.11 and 4.12). Possible explanations lie in the fact that this being a HAART naïve population, we captured most of the ones whose disease progression was at an advanced stage with most of the rapid progressors having died in their infancy (Obimbo et al, 2004). These children are also more at risk of being affected by socio-enviromental factors. Van Rie et al reports results of a study in Tanzania whose older children had lower Bayley scores. These are more vulnerable to the combined effect of poverty, HIV illness and family stress on neurodevelopment (Van Rie et al 2006, Van Rie et al 2008). Many other studies however report the reverse with younger children being at a higher risk of ND delay. Most of their young children fall in the 18 to 24 months category and is in keeping with our 'older' population of over 18 months.

5.4.2.2 MATERNAL EDUCATION

Maternal education affects baseline cognitive scores with those of lower education better than their counterparts, tables 4.8 ($p = 0.005$). This is unlike the systemic review results of Van Rie et al 2006. The poorly educated mothers in this cohort have no careers, are stay at home mums therefore have a lot of time and love to invest in their children. These children benefit from a secure attachment and the most of the available mental stimulation from their mothers hence the better cognitve scores. One can postulate that

presence of the mother to the child overrides a higher maternal education and socio-economic status in the overall cognitive development of the child.

In Kenya the more educated counterparts in this cohort fall in the lower middle class and have careers that take up most of their day. House helps with lower socio-economic and educational levels are employed to baby sit and perform household chores. There is usually a high turnover of these house helps, additional household chores reduce time spent with the children and any mental stimulation from them is definitely of a lower quality than that from the mother had she been more available.

5.4.2.3 IMMUNOSUPPRESSION BY CD4%

Immuno-suppression by CD4% did not realize any significant p values in this cohort. Forster et al 2006 concluded that the worse the immunological compromise the more the abnormal neurological functioning. Other studies have realized definite association with immunosuppression as defined by higher viral loads and neurodevelopment delay (Chiriboga et al, 2005; Jeremy et al, 2005).

5.4.2.4 BREAST FEEDING

Breast feeding was associated with better outcome against having ND delay in any one ND parameter as assessed by BSID III. In this population the fact that breast milk is free, nutritionally complete and not expensive either to acquire or maintain is important. It also ensures bonding and a secure attachment for the child. This ensures adequate stimulation which improves all aspects of ND functioning. Formula is expensive and all those

children who were not breast fed may not have had access to nutritional optimum alternatives. They also would lack the special mother child bonding and are at risk of attachment disorders. This may explain why 100% of them had ND delay in any one parameter as assessed by the BSID III.

5.4.2.5 TREATMENT

All these children received medical treatment that included HAART. Involvement of the rehabilitational sciences was minimal if any. Some services like speech therapy are not developed. Physio and occupational therapy services which are available in KNH involve frequent hospital visits. This means many bus fares making the financial obligation out of reach for most of these mothers. Being out of the home several days a week or month may also not be feasible for these mothers. These children were followed up for a period of at least six months post HAART. Loss to follow up was massive with only 12 out of the original 36 finishing the study period. Table 4.15 however shows there was no difference in the baseline age, HIV stage, sex, PMTCT status and birth history of the population who completed the study and those who did not.

After at least six months of Art, ND constructs that improved were cognition, language and SES (table 4.14). Improvement is limited in keeping with results of other studies (Potterton 2006; Lindsey et al, 2007; Forster et al, 2007;). HAART did not improve the motor delay which was the most severe and prevalent.

This data is of clinical significance because while there was improvement in the cognitive, language and general adaptive mean composite scores they still fell in the

borderline qualitative distribution. These means these parameters were still delayed (see chapter 2. on AAMR definition of ND). Extra therapeutic measures apart from HAART are needed to adequately address these delays. Other studies with similar results include Forster et al, 2007 who followed up 62 children under three years using BSID II. A systematic review by Van Rie et as, 2006 validated these findings. Potterton realized that a home developmental stimulation program added to HAART had a bigger ND function improvement over one years follow up (Potterton, 2006). The general adaptive delay was also not improved by HAART.

Further research is needed to validate this data statistically in the Kenyan population but clinicians can review the management of these aspects of neurodevelopment delay in the HIV infected child.

5.5 LIMITATIONS OF STUDY

5.5.1 STUDY DESIGN

This was a prospective cohort study. The study heavily depended on the follow up of recruited study subjects. The study design therefore exposed research to loss of follow up which affected this particular study.

5.5.2 VARIABLES MEASURED

The Bailey Scales are a standardized tool whose interpretation is dependent on the uniformity of their applications. This is a limitation as it was not possible to adapt them to the Kenyan population without compromising on the data collected. The variables

measured were authentic especially when compared with results from other studies chapter 5.1, 5.2 and 5.3.

5.5.3 LOSS TO FOLLOW UP

One of the major limitation of this study was the political environment in which the study period fell. The cohort was drawn from the KNH, CCC patronized mainly by patients at the lower end of the socioeconomic spectrum. These people live in the slum and estates bordering them. Slum populations are hetero ethnic but each has one particular dominant tribe. Kenyan politics in the year 2007 divided the country along ethnic lines and slum population migration was taking place even before the vote casting day. This complicated the follow up of patients a fact made worse by the post election violence which resulted in many internally displaced persons. As a result only 12 patients out of the initial 36 were able to have follow-ups of at least 6 months after ART initiation, despite all efforts to follow them up.

5.6 RECOMENDATIONS.

5.6.1 CLINICAL RECOMMENDATIONS

Table 4.5 shows that in this cohort 89% of these children need the services of an early intervention center. Children respond to interventions carefully directed to specific or pervasive neurocognitive dysfunction irrespective of aetiology (Willen, 2006). Specialised rehabilitational services are important in HIV as these children are now

surviving longer and will need an optimal ND functioning to integrate and contribute to society (Forster et al, 2007). Rehabilitaion optimizes performance breaking the vicious cycle of poverty so prevalent in HIV infected children (Van Rie et al, 2006) especially in Sub Saharan Africa.

Kenya, like many sub Saharan countries have not made the strides in rehabilitational sciences so evident in the West. This makes these services either not present or under utilized even in other neurodevelopmental pathologies not necessarily HIV. Clinicians in Kenya have to use more of the rehabilitational sciences and make use of neurocognitive profiling to monitor progress of the HIV infected child's ND status with time.

5.6.2 RESEARCH RECOMMENDATIONS

The mainstay of HIV treatment in Kenya is HAART. Though the loss to follow up was colossal and data from the 12 children who at least completed six months of follow up (table 4.14) has limited statistical power it is in keeping with results from many other studies (Chiriboga et al, 2005; Jeremy et al, 2005; Van Rie et al, 2006; Potterton,2006; Lindsey et al, 2007) that show that HAART does not adequately address the neurodevelopment abnormalities prevalent in children infected with HIV.

Further research needs to be done on the effect of HAART on the ND of Kenyan child infected with HIV.

5.7 CONCLUSION

5.7.1 PREVALENCE OF ND DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

ND delay in this cohort of Kenyan children with HIV is very prevalent. Those who had ND delay in any one parameter as assessed by the BSID III were 88.9%. Motor delay had the highest specific prevalence of 83.3% followed by language delay at 66.6%, cognitive delay at 61.2%, adaptive delay at 60.6% and SES delay at 36.4% respectively.

5.7.2 SPECTRUM OF ND DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

The spectrum of ND delay in this cohort of Kenyan children infected with HIV, encompasses all aspects of ND delay as measured by the BSID III. These are cognitive, language, motor, SES and general adaptive delays.

5.7.3 SEVERITY OF ND DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

The severity of ND delay this cohort of Kenyan children infected with HIV is high with most of those with neurodevelopment compromise falling in the extremely low as

opposed to the borderline group (see table 4.4). Those with severe delay (extremely low) as opposed to mild (borderline) ND delay were 69.4% versus 13.9% for motor delay; 55.6% versus 5.6% for cognitive delay, 44.4% versus 22.2% for language delay; 48.5% versus 12.1% for adaptive delay and 30.3% versus 6.1% for SES delay.

5.7.4 FACTORS ASSOCIATED WITH ND DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

Important factors associated with ND delay this cohort of Kenyan children infected with HIV were breast feeding, age and maternal education. Breast feeding was associated with protection from developing ND delay in any one parameter as assessed by the BSID. Being older than 18 months was associated with worse cognitive, language, SES and adaptive outcomes. Lower maternal education was associated with better cognitive results in this cohort.

5.7.5 TREATMENT AND ND DELAY AMONG A COHORT OF KENYAN CHILDREN INFECTED WITH HIV

Data concerning treatment in this cohort of Kenyan children infected with HIV was affected by the loss to follow up. For those study subjects with a BSID III assessment after at least six months of HAART, their ND outcome showed that this treatment alone was not sufficient to make it normal. This is an interesting hypothesis that can be used for future research.

APPENDICES

Appendix I: Ethics Approval University of Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Kigira

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M060134**
PROJECT	Neurodevelopmental Status of Kenyan Childen Infected with the Human Immunodeficiency Virus
INVESTIGATORS	Dr MMM Kigira
DEPARTMENT	Department of Paediatrics
DATE CONSIDERED	06.01.27
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06.02.17 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : E Obimbo

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix II: Ethics Approval University of Nairobi

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH-ERC/ 01/ 4153

7th March 2007

19/3/07
Authorised to carry out Research in the CCC.
CCC Staff Requested to Cooperate.

Dr. Mary Madumadu Kigira
Dept. of Paediatrics & Child Health
School of Medicine
University of Nairobi

Dear Dr. Madumadu

RESEARCH PROPOSAL: "NEURODEVELOPMENTAL STATUS OF KENYAN CHILDREN INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS BEFORE AND AFTER ANTIRETROVIRAL THERAPY" (P214/09/2006)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above cited research proposal for the period 7th March 2007 – 6th March 2008.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH-ERC

c.c. Prof. K.M.Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Paediatrics & Child Health, UON
Supervisor: Dr. Elizabeth Obimbo,Dept. of Paediatrics & Child Health, UON

Appendix III: WHO 2006 immunological classification for established HIV infection

HIV-associated immunodeficiency	Age-related CD4 values			
	<11 months (%CD4+)	12 - 35 months (%CD4+)	36 – 59 months (%CD4+)	>5 years (absolute number per mm3 or %CD4+)
None or not significant	>35	>30	>25	>500
Mild	30 -35	25 – 30	20 – 25	350 – 499
Advanced	25 – 29	20 – 24	15 – 19	200 – 349
Severe	<25	<20	<15	<200 or <15%

Appendix IV: Demography form

Study number;…. Age;…. Date of birth;…. Tribe;… Telephone number;…

Birth order; Birth history; svd.. c/s.. Pmtct;yes.. no.. Live with birth mother;yes.. no..

Main systemic complaints…….……

Breast feeding currently; yes… no… stopping date& age…

Food supplements; yes… no… type…

Last evening meal contents:……..

Previous hospital admissions; give dates & length of hospital stay.

Siblings; number ages on arv's

Mother's education level

Appendix V: Information Sheet

My name is Dr Mary Mupa Madumadu Kigira. Current research has shown that HIV treatment improves the development and working of childrens' nervous systems. I am carrying out a study to measure this improvement in Kenyan children.

I will use a specialized test known as the Bayley Scales of Infant Development to measure this. The test is harmless, painless and will take about an hour to perform. If you allow your child to participate in this study, this test will be performed on your child free of charge. The results of your child's test and their meaning will be explained to you. I will also study your child's medical records for research purposes only and will maintain strict confidentiality.

It is not a must to include your child and you are free to withdraw your child from this study whenever you feel like. Whether you choose to participate or not will not affect the quality of care your child will get at the clinic. If you have any questions feel free to call me at 0722 786 220. If you agree in your child's participation kindly sign below.

SIGNED DATE

Appendix VI: Consent form

I the mother/ father/ legal guardian of

Agree to let Dr Mary Mupa Madumadu Kigira carry out the Bayley Scales of Infant Development on my child. I also allow her to study my child's medical records for research purposes. The study has been explained to me and I fully understand it's purposes and procedures. The information will be used for research purposes.

SIGNED DATE

WITNESS DATE.

Appendix VII: Demographic data extraction sheet

NAME OF PATIENT; STUDY NUMBER;

DATE OF BIRTH;

HIV RESULTS: - ELISA (IF >18 MONTHS OF AGE);

PCR (IF < 18 MONTHS OF AGE);

INITIAL WHO CLINICAL STAGE;

LABARATORY RESULTS PRESENT IN FILE:

- FULL HAEMOGRAM:
    - White cell count
        - Total count
        - Polymorph percentage
        - Lymphocyte percentage
        - Monocyte percentage
        - Eisinophil percentage
        - Basophil percentage
    - Haemoglobin
    - Mean corpuscular volume
    - Mean corpuscular haemoglobin
    - Mean corpuscular haemoglopbin concentration

- UREA & ELECTROLYTES:
    - Urea
    - Creatinine
    - Potassium

    - Sodium
    - chloride
- LIVER FUNCTION TESTS:
    - Alanine transferase
    - Aspartate transferase
- CD4 COUNT:
    - Total
    - Percentage
    - CD4/CD8 ratio

Appendix VIII: Computer generated Bailey Report.

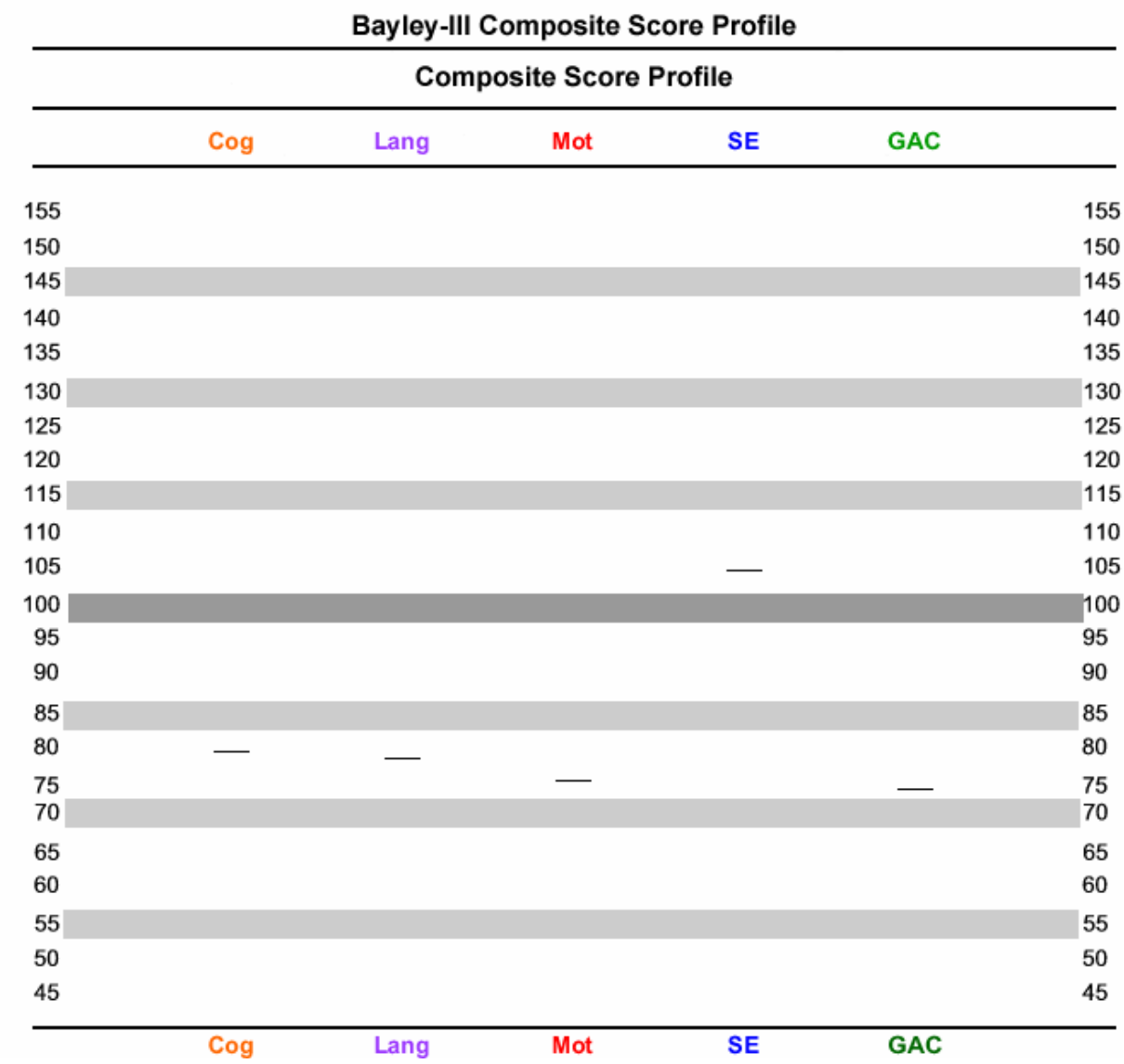
Reason for Referral:

Other Examiners:

Composite Score Summary

Composite	Sum of Scaled Scores	Composite Score	Percentile Rank	90% Confidence Interval	Qualitative Description
Cognitive	6	80	9	75–89	Low Average
Language	13	79	8	74–87	Borderline
Motor	12	76	5	71–84	Borderline
Social-Emotional	11	105	63	97–112	Average
General Adaptive	69	75	5%	72-78	Borderline

Cognitive and Social-Emotional Composites are converted from their respective Scaled Scores.



Composite	Score	Composite	Score
Cognitive	80	Social-Emotional	105
Language	79	General Adaptive	75
Motor	76		

Subtest Score Summary

Subtest	Raw Score	Scaled Score
Cognitive (Cog)	66	6
Receptive Communication (RC)	28	6
Expressive Communication (EC)	35	7
Fine Motor (FM)	42	6
Gross Motor (GM)	58	6
Social-Emotional (SE)	158	11
Communication (Com)	45	6
Community Use (CU)	25	6
Functional Pre-Academics (FA)	40	11
Home Living (HL)	43	7
Health and Safety (HS)	50	9
Leisure (LS)	47	7
Self-Care (SC)	37	2
Self-Direction (SD)	45	7
Social (Soc)	52	7
Motor (MO)	62	7

Subtest Level Discrepancy Comparison

Discrepancy Comparisons	Scaled Score 1	Scaled Score 2	Diff.	Critical Value	Sig. Diff. Y/N	Base Rate
Cognitive vs. Receptive	6	6	0	2.98	N	
Cognitive vs. Expressive	6	7	-1	2.72	N	43.5%
Cognitive vs. Fine Motor	6	6	0	2.95	N	
Cognitive vs. Gross Motor	6	6	0	2.61	N	
Cognitive vs. Social-Emotional	6	11	-5	2.70	Y	12.7%
Receptive vs. Expressive	6	7	-1	3.06	N	41.2%
Receptive vs. Fine Motor	6	6	0	3.27	N	
Receptive vs. Gross Motor	6	6	0	2.96	N	
Receptive vs. Social-Emotional	6	11	-5	3.05	Y	12.9%
Expressive vs. Fine Motor	7	6	1	3.03	N	41.9%
Expressive vs. Gross Motor	7	6	1	2.69	N	42.7%
Expressive vs. Social-Emotional	7	11	-4	2.79	Y	17.7%
Fine Motor vs. Gross Motor	6	6	0	2.93	N	
Fine Motor vs. Social-Emotional	6	11	-5	3.02	Y	13.7%
Gross Motor vs. Social-Emotional	6	11	-5	2.68	Y	14.5%

Statistical Significance (Critical Values) at the .05 level

Subtest	Score	Subtest	Score
Cognitive (Cog)	6	Functional Pre-Academics (FA)	11
Receptive Communication (RC)	6	Home Living (HL)	7
Expressive Communication (EC)	7	Health and Safety (HS)	9
Fine Motor (FM)	6	Leisure (LS)	7
Gross Motor (GM)	6	Self-Care (SC)	2
Social-Emotional (SE)	11	Self-Direction (SD)	7
Communication (Com)	6	Social (Soc)	7
Community Use (CU)	6	Motor (MO)	7

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