THE EFFECT OF SERURES / EPILEPSY ON THE ARCHIEVEMENT OF DEVELOPMENTAL MILESTONES IN CHILDREN WITH HIV.

BY

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A Dissertation Submitted to the University of Zambia in Partial Fulfilment of the Requirements for the Award of the Degree of Master of Arts in Child and Adolescent Psychology

THE UNIVERSITY OF ZAMBIA

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DECLARATION

I, Namwiya Musonda declare that this dissertation:

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APPROVAL

This dissertation of NAMWIYA MUSONDA has been approved as fulfilling the requirements for the award of Master of Arts Degree in Child and Adolescent Psychology by the University of Zambia.

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ABSTRACT

Seizures and epilepsy are associated with a range of psychosocial difficulties and developmental delays. Infants and preschoolers with epilepsy are at elevated risk for developmental difficulties such as social, language and motor skills and school-related problems. It is therefore necessary to study whether the achievement of developmental milestones in HIV + children presenting with/without seizures/epilepsy in Zambia. This study aimed to find out the developmental milestones attainment in HIV+ children with and without seizures/epilepsy. It answered the following questions; how is the achievement of the fine motor developmental milestone in HIV+ children with/without seizures/epilepsy? How is the attainment of the gross motor developmental milestone in HIV+ children with/without seizures/epilepsy? How is the achievement of the language developmental milestone in HIV+ children with/without seizures/epilepsy? What was the medical personnel's observation towards their child's behavior in relation to developmental milestones? This was a case study that was conducted at the Pediatric Center of Excellence at the University Teaching Hospital. It included a sample size of 8 participants of which 4 were presenting with seizures/epilepsy and 4 were not presenting with seizures /epilepsy of ages 4-6 years old, mean age of 5 and standard deviation of 0.76. The achievement of the developmental milestone was assessed using the Malawian Development Assessment Tool (MDAT) and the Vineland Adaptive Behavioral Scale (VABS). The MDAT is a standardized tool developed by Gladstone et al (2009), after careful qualitative evaluation of culturally appropriate developmental domains for rural Malawi. The VABS is a standardized tool that was developed by Balla, Cichetti and Sparrow in (2005); it is administered to the parents, caregivers or the guardians of the child and intends to give information about the child's adaptive behavior and developmental life. From the findings, it was evident that there were delays in the achievement of developmental milestone between children who were presenting with seizures/epilepsy and those that were not presenting with seizures/epilepsy. Particularly in the language domain it was found that ¾ participants presented to be delayed, in the gross motor domain it was found that 2/4 participants and ¼ participants performed to be delayed in the fine motor domain. Additionally HIV+ children who were presenting with seizures/epilepsy were found to be delay in at least one of the domains that were being assessed. The findings from this study motivate the need to carry out another study with a large sample size so as to generalize the results.

Key words: Seizure, Epilepsy, Development, Milestones

DEDICATION

I dedicate this paper to my late dad, Mr. Charles Kawama Musonda. He always has been the reason why I always want to keep pushing forward because of his wise words and encouragement. It's a pity he died before I could make him proud, regardless am so proud of him because of the knowledge he has inculcated in me.

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LIST OF ABBREVIATIONS AND ACRONYMS

AEDs	Anti-Epileptic Drugs
AIDS	Acquired Immune Deficiency Syndrome
ART	Anti-Retroviral Therapy
BSID-II	Bayley Scales of Infant Development, Second Edition
CDC	Center for Disease Control
CHER	Children with HIV Early anti-Retroviral therapy
CHASE	Cohort for HIV Associated Seizures and Epilepsy
CNS	Central Nervous System
CSF	Cerebral Spinal Fluid
HIV	Human Immune Virus
HUU	HIV-unexposed uninfected
IQ	Intelligent Quotient
IQR	Intelligent Quotient Ratio
MDAT	Malawian Development Assessment Tool
MoH	Ministry of Health
PCOE	Pediatric Centre Of Excellence

PMTCT	Prevention of Mother-To-Child Transmission
TB	Tuberculosis
USA	United States of America
UTH	University Teaching Hospital
VABS	Vineland Adaptive Behavior Scale
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1.Background

Human Immunodeficiency Virus (HIV) is a virus that causes Acquired Immune Deficiency Syndrome (AIDS). Acquired Immune Deficiency Syndrome is a disease that affects the immune systems. Worldwide an estimated number of 1.8 million children (< 15 years) are living with HIV, most of these infected by their HIV+ mothers during pregnancy, childbirth or breastfeeding (UNAIDS, 2017). The Joint UN Program on HIV and AIDS (UNAIDS) estimates that between 900,000 and 1,100,000 people in Zambia live with HIV, which represents approximately 13% of the country's total population. Urban areas still have higher HIV prevalence rates than rural areas (18.2% and 9.1%, respectively), and females (15.1%) are more likely to be HIV positive than males (11.3%) (National AIDS Council, 2015). Among children born to mothers infected with HIV, the percentage of infants contracting HIV has reduced over the years, from about 6.14% in 2000 to 1.7% in 2011, and was estimated of 1.49% in 2015. According to the National AIDS Council, the main reason for this reduction has been the decrease of HIV infections among pregnant women and prophylaxes administered to those infected in the prevention of mother-to-child transmission program (PMTCT) of HIV. In the same fashion, the percentage of dying infants has also reduced, by more than 51% between 2010 and 2016, (National AIDS Council, 2017).

The central nervous system is affected by the human immunodeficiency virus. This first involves HIV-infected CD4 T cells crossing the blood–brain-barrier (BBB) (Davis et al., 1992; Martin-

Blondel et al., 2011) and HIV then infects the perivascular macrophages and microglia (Koenig et al., 1986; Martin-Blondel et al., 2011). Inflammatory cytokines secreted by these infected cells increase the permeability of the blood-brain-barriers (BBB). Two main mechanisms may be involved in central nervous system (CNS) complications: 1) the direct viral infection of CNS cells which initiates a cascade of immune reactions to control viral replication and leads to by-stander CNS lesions; and 2) opportunistic infections and lymphomas that complicate the prolonged immune suppression and evolve on their own. As a consequence, a large range of cognitive disorders is associated with HIV before appropriate drugs are made available. The proportion of involved patients markedly increases with the disease stage (Antinori et al., 2007 as cited in Bonnan, Barroso, Demasles, Krim, Marasescu & Miquel, 2015). For example, 15% of asymptomatic HIV-infected patients suffer from neuropsychological (NP) impairment (Bonnan, Barroso, Demasles, Krim, Marasescu, Miquel; 2015).

Infection of the central nervous system (CNS) is a nearly universal feature of systemic human immunodeficiency virus (HIV) infection. It develops early in systemic HIV infection (Valcour et al., 2012 as cited in Gisslén, Price, Andreasson, Norgren, Nilsson, Hagberg, Fuch, 2016) and continues throughout its untreated course. While often seemingly innocent, this infection can evolve to a form that is associated with CNS injury, most severely manifesting as HIV-associated dementia (HAD) with high morbidity and mortality (Gisslén, Price, Andreasson, Norgren, Nilsson, Hagberg, Fuch, 2016). However, infected individuals can also manifest less severe CNS injury that elides detection (Antinori et al., 2007; Heaton et al., 2011). Individuals with HIV infection can suffer CNS dysfunction from a variety of other conditions that can confuse diagnosis.

HIV and AIDS have many opportunistic infections associated with them; seizures and epilepsy are among them. New-onset seizures occur in 8% of adults and up to 20% of children who have HIV infection, although among patients followed regularly in HIV care clinics, the prevalence of seizures is lower (2%–4%). Most seizures are generalized tonic-clonic seizures that can progress to status epilepticus in 8% to 18% of instances (Shanbhag, Rutstein, Zaoutis, et al; 2005). There are many potential causes for seizures in HIV-seropositive patients, including opportunistic infections, medications, substance use or withdrawal, metabolic disturbance, HIV infection, and pre-existing disorders. The opportunistic infections most commonly associated with seizures are toxoplasmic encephalitis, followed by cryptococcal meningitis and primary CNS lymphoma. The seizure may be the only sign that the patient is suffering from an infectious or malignant process, especially in the case of CNS lymphoma. Without treatment, there is a high likelihood that the seizures will recur. Because HIV-seropositive patients inherently have an increased rate of adverse drug reactions, up to a quarter of these patients will develop a rash with phenytoin, (Van Rie, Harrington, Dow, et al; 2007).

Epilepsy is a common, largely invisible, chronic neurological condition, with estimated childhood prevalence rates ranging from 3.6 to 9.0/1000 population internationally, (Waaler, Blom, Skeidsvoll, Mykletum, 2000; Oka, Ohtsuka, Yoshinaga, Murakami, Kobayashi, Ogino, 2006; Linehan, Kerr, Walsh, Brady, Kelleher, Delanty, et al. 2010; Pandey, Singhi, Bharti, 2014 as cited in Benson, O'Toole, Lambert, Gallagher, Shahwan, Austin, 2015). Epilepsy is a chronic condition characterized by recurrent unprovoked seizures displaying the clinical manifestation of excessive, abnormal, unprovoked, synchronous discharges of neurons, (Lai & Mak; 2009). As one of the most common neurological disorders, epilepsy affects more than approximately 1% of the population worldwide (Engel, 1989). This wide-spread disorder is characterized by episodic

interruptions of cerebral electrical activities caused by abnormal hyper synchronous discharges of neuronal populations, commonly referred to as seizures (Jackson, 2005). The diagnosis of epilepsy during childhood or adolescence is not only contending with the medical aspects of the condition, but also with the impact that the condition can have on psychosocial wellbeing.

Seizures affect 2%–8% of children aged between 6 months and 6 years, (Sadleir & Scheffer, 2008). Whether prolonged or complex seizures cause long-term injury to medial temporal structures, including the hippocampus, is a critical question concerning the neurocognitive outcome of these seizures. Researchers have proposed that complex seizures are a risk factor in human temporal lobe epilepsy and temporal lobe sclerosis. Evidence from magnetic resonance imaging (MRI) studies has revealed focal hippocampal atrophy after prolonged seizures in some children and abnormal T2 signal enhancement in the limbic structures in children with febrile seizure and a rat febrile seizure model, Sadleir & Scheffer, (2008).

Chang et al (2008) found that the results of studies examining the cognitive effect in children with complex seizures have been inconsistent. Earlier studies had reported that children with prolonged seizures exhibited significantly reduced nonverbal intelligence and abnormalities in other neuropsychological tests compared with controls and children with simple seizures. However, some published population-based studies found no increase in the risk of unfavorable neurodevelopmental outcome according to the Wechsler Intelligence Scales for Children (WISC-III) in patients with seizures Knudsen, (2000). Nevertheless, a higher incidence of behavioral disturbances, sleep problems, learning and developmental difficulties have been reported in children with seizures (Knudsen; 2000 as cited in Hung, Tsai, Tsan and Tung; 2015).

Correspondingly it has also been shown that the presence of seizures is a negative prognostic factor for rehabilitation of neurodevelopmental disorders (Chiappediet al., 2011). Most recent investigations have considered seizures as comorbidity in neurodevelopmental conditions, rather than neurodevelopmental comorbidities in people with seizures or epilepsy. Comparisons of neuropsychological functioning and behavioral and academic performance at the time of seizure onset to healthy siblings and to individuals with chronic epilepsy have revealed an elevated risk for neurodevelopmental dysfunction already at the time of onset (Austin et al., 2011; Baumet al., 2010; Dunn et al., 2010; and Guilfoyle et al., 2012).

The prevalence of epilepsy in sub-Saharan Africa seems to be higher than in other parts of the world, but estimates vary substantially for unknown reasons. The prevalence of epilepsy is highest in poor countries and in rural areas, particularly in sub-Saharan Africa, (Ngugi, Bottomley, Kleinschmidt, Wagner, Newton, et al, 2013). The prevalence of epilepsy in Africa is estimated to be around 11.29 per 1000 population (Global Campaign Against Epilepsy, 2005). In Zambia, epilepsy continues to be one of the most common non-communicable diseases although the exact prevalence is unknown. However, a study in the rural parts of the Southern Province showed a prevalence of 14.5 per 1000, in a catchment area of about 55,000 people (Birbeck et al, 2004). Reported prevalence varies between studies in sub-Saharan Africa, but the cause of this variation is unknown. Differences in methodology and case definition could partly explain this heterogeneity, but the epidemiology of parasitic diseases (particularly malaria, cysticercosis, onchocerciasis, toxocariasis, and toxoplasmosis, perinatal events, head injuries, HIV infection, and hereditary factors might also contribute, (Ngugi et al, 2013). Previous studies in sub-Saharan Africa have focused on a small number of risk factors in areas with high

prevalence of epilepsy (Preux &, Druet-Cabanc, 2005), but none have examined a wide range of potential risk factors.

Fine motor skills are the collective skills and activities that involve using the hands and fingers (Amundson & Weil, 2001; Case-Smith & Shortridge, 1996). That is, fine motor skills are those skills that require the small muscles of the hand to work together to perform precise and refined movements.

Gross motor skills are the skills used to move the whole body, arms & legs. They include running, jumping, walking & balance. The development of these skills begins when the child is in the womb & continues throughout life. Gross motor skills generally develop in an order and build upon each other. As a result, if a stage of development is missed or delayed, the higher level skills will also be delayed or may never develop at all, (Bee; 2000). Delay in achievement of the gross motor milestones may be an indicator of neurological abnormalities and is sometimes associated with a global developmental delay. Although the correlation between gross motor skills and global developmental level is weak, there is usually an impact on assessment of skills that depend on an intact motor system for their expression. Evaluation and interpretation of test needs to be accommodated accordingly, (Bee; 2000). Developmental assessment involves establishing the child's progress in the sequence of development and a qualitative description of the child's mobility. Clinical interpretation requires combining this information with the findings of physical examination.

Language domain involves a child to be able to communicate in a certain manner in accordance with their age. Identification of language impairment needs to combine information from parents, and observations/assessment. Parents' reporting of expressive language is

improved by making lists of spoken words or phrases. As children have good understanding of daily family routines, their language comprehension is often overestimated by parents, (Bee, 2000).

Infants and preschoolers with epilepsy are at elevated risk for developmental difficulties such as social and language, motor skills and school-related problems, (Jones, Siddarth, Gurbani, Sheilds & Caplan, 2010). Epilepsy is associated with a range of psychosocial difficulties and cognitive deficits. Active epilepsy decelerates and obscures the development of children. Delay of language development and motor development are some of the symptoms of active epilepsy in children. As such, language and motor impairment may simply be part of a global developmental arrest or delay that occurs in many children with epilepsy, (Overvliet et al; 2010). Problems with both cognitive and motor development have been reported in children with epilepsy, even in children without obvious neuro-impairment. Many explanations have been proposed for these problems, (Reijs, van Mil, van Hall, Arends, Weber, Renier, et al; 2006 as cited in Reijs, de la Parra, van Mil, van Hall, Arends, Weber, Renier & Aldenkamp; 2010). They may reflect brain dysfunction that is also held accountable for the epilepsy. They may be a side-effect of the antiepileptic drugs (AEDs). They can be also a direct effect of the epileptic seizures, and therefore be related to the severity of the seizures, or to factors such as seizure frequency and seizure type, (Maalouf, Takahashi, Reinkensmeyer, Cooper & Rho; 2006 as cited in Reijs, de la Parra, van Mil, van Hall, Arends, Weber, Renier & Aldenkamp; 2010).

However, several studies have demonstrated cognitive impairment in children with epilepsy, in particular language impairment may occur. Nicolai et al concluded that, although the full scale intelligent quotient (IQ) is often in the normal range in children with epilepsy, language delay, learning disabilities and educational problems have been reported. Language delay is

significantly more frequent in children with epilepsy with atypical seizures (Nicolai, Aldenkamp, Arends, Weber, Vles; 2006 as cited in Overvliet, Aldenkamp, Klinkenber, Vles & Hendriksen; 2011). Overvliet et al concluded in their review that language is often affected in children with epilepsy, although the type of impairment varies over the different studies. Impairment of phonological and literacy skills are most frequently reported. Early onset of seizures and epilepsy have larger impact on language skills, and language skills that are acquired in later phases of development are more vulnerable, (Overvliet, Besseling, Vles, Hofman, Backes, van Hall, et al; 2010 as cited in Overvliet, Aldenkamp, Klinkenber, Vles & Hendriksen; 2011).

Although the risk of perinatal HIV transmission has been reduced from 1% to 2% with ART, among children who are congenitally infected with HIV, a progressive encephalopathy can develop as a frank encephalopathy or as neurodevelopmental delays in motor, language, and cognitive milestones, (Tardieu, Le Chenadec, Persoz, et al 2000). The prevalence of neurologic involvement in HIV-infected children can be as high as 50% depending on the level of immunosuppression and treatment, usually in the first 2 years of life. Neurologic features of congenital HIV infection include microcephaly, delayed developmental milestones, spastic paraparesis, and rarely seizures. Risk factors for the development of neurologic disease in children include high cerebral spinal fluid (CSF) viral load and maternal high viral burden at the time of birth. The neuropathology in children who have HIV infection differs from adults in that there is typically high viral abundance and frequent infection of astrocytes together with basal ganglia calcification and cortical atrophy that is also evident on neuroimaging, (Shanbhag, Rutstein, Zaoutis, et al; (2005). The prognosis for congenital HIV infection with encephalopathy is poor, with survival ranging from 6 to 24 months in untreated individuals. With the availability

of ART, outcomes have improved, although residual neurocognitive impairment continues to be an ongoing problem, with associated behavioral complications.

1.2.Statement of the Problem

Early childhood is a period of rapid development of language and motor skills. Most of the time, these skills develop naturally without any need for special attention. However, CNS diseases such as epilepsy can affect the achievement of these developmental milestones and later the development of age-appropriate cognitive competences and skills. Childhood onset seizure and epilepsy is associated with neurocognitive impairment, developmental disabilities, psychosocial problems in the long term and delayed achievement of the developmental milestones (Halma, de Louw, Klinkenberg, Aldenkamp, IJff &, Majoie; 2014). Research has shown that children with seizures and epilepsy have been found to obtain worse scores in language and motor domains, (Eddy et al., 2010). Seizures and epilepsy in children may impact a wide range of neuropsychological functions with high variability. In some patients, cognitive challenges could appear at or before seizure onset, suggesting the existence of an underlying condition that may manifest with seizures and developmental milestones.

In Zambia, there is no good access and use of antiretroviral therapy (ART), children with HIV and AIDS still demonstrate to have seizures and epilepsy. It has not been stated that seizures could be linked to the delay in achievement of developmental milestones or non-delay achievement in Zambia, particularly in the language domain, gross motor domain and fine motor domain. It is therefore necessary to study the how attainment of developmental milestones is in HIV positive children who are presenting with seizures/epilepsy in the motor and language domains. This study addressed the issue at hand by administering the development assessments

to find out the achievement of developmental milestones in HIV+ children presenting with/without seizures/epilepsy.

1.3.Justification of the Study

The choice of the topic on which this research was based on, emerged as a concern from studies of other countries which had reviewed HIV+ children with seizures and epilepsy showed delay in their achievement of developmental milestones, this had led to find out the case for Zambia. The study was aimed at helping HIV+ children and their caregivers understand the importance of seizures/epilepsy on the achievement of developmental milestones functioning. An early identification and assessment of the developmental milestone often related to seizure and epilepsy in childhood may lead to the implementation of specific and appropriate rehabilitative treatment, in order to promote learning and social functioning, allowing children to develop normally. Children with new onset seizure should undergo a rapid neuropsychological assessment to detect possible neuropsychological deficits linked to associated seizure and epilepsy related factors to identify specific interventions that could improve outcome. This study is therefore necessary in order to better understand if there are any possible delays in children with seizures/epilepsy who are HIV positive on the developmental milestones achievement and later the development delays. It was expected that information from the study may help in clinical management of HIV+ children presenting with seizure/epilepsy by providing sufficient knowledge on the importance of developmental milestone in children.

1.4.Aim of the study

- To determine the achievement of developmental milestone in HIV+ children with seizures/epilepsy.

1.5.Research questions

i. How is the achievement of the fine motor developmental milestone in HIV+ children with/without seizures/epilepsy?

ii. How is the attainment of the gross motor developmental milestone in HIV+ children with/without seizures/epilepsy?

iii. How is the achievement of the language developmental milestone in HIV+ children with/without seizures/epilepsy?

iv. What is the medical personnel's observation towards their child's behavior in relation to developmental milestones?

1.6.Operational definition of terms

For purposes of this research:

Seizure defined as an abnormal movement or behavior caused by unusual electrical activity in the brain.

Epilepsy has been defined as more or less incessant seizures, a neurological disorder marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain..

Development has been defined as the gradual accumulation of relatively permanent, age-related changes through transactions with the environment (Krantz, 1943).

A **milestone** refers to an important stage or event in development.

CHAPTER TWO

LITERATURE REVIEW

2.1. Overview

Knowledge of the development and function of the normal central nervous system is important in gaining an understanding of its vulnerability in infants, and therefore how it can be affected by HIV infection. This literature review serves to discuss attainment of developmental milestones in HIV presenting with seizures/epilepsy in relation to the gross motor, fine motor and language domains to be specific. From the literature search that was done there seems to be a gap in relation to the topic under discussion, therefore this chapter looks at the developmental milestones in HIV positive children, effects of seizures/epilepsy on the neurocognitive functioning in HIV positive children, motor development and language development coupled with empirical reviews that were done in children in relation to HIV, its effect on the developing nervous system, and therefore the outcomes on cognitive, language and motor development.

2.2. Developmental milestones in HIV positive children

The central nervous system of HIV positive children is influenced to a larger extent than the peripheral nervous system, which is influenced more in adults (Davis-McFarland, 2000). This causes the virus to be more prominent in the developing nervous system of a child, which, in turn, results in the deficiencies in developmental milestones (Davis-McFarland, 2000; Blanchette *et al*., 2001; Wachsler-Felder & Golden, 2002). Motor developmental deficiencies are mainly the result of gross motor deficiencies rather than of fine motor deficiencies (Msellati *et al*., 1993; Parks & Danoff, 1999). This conclusion is attributed to the fact that gross motor skills

require the use of large-muscle groups and physical effort, whereas fine motor skills require less strength (Parks & Danoff, 1999). HIV is associated with exhaustion and a decline in physical functioning, which restrict the person in performing life-sustaining activities (Crystal *et al*., 2000; Keyser *et al*., 2000; Cade *et al*., 2004; Storm *et al*., 2005). Research reveals that 50% of HIV infected children's physical functioning is restricted and that 58% have one or more restriction concerning school activities (Storm *et al*., 2005). A loss of muscle mass contributing to a decrease in strength and functionality is also reported (Grinspoon & Mulligan, 2003).

Botha & Pienaar, conducted a study that was aimed to determine the level of gross motor and fine motor development of 2 to 6-year old children affected by and infected with HIV, and to compare it with children not affected by this disease, (Botha & Pienaar; 2008). It was clearly indicated that the infected group already exhibited serious motor deficits compared to other children of the same chronological age, especially the unaffected children; their development is already below average in comparison to the other two groups, who exhibited average development. Researchers point out that such deficiencies are already noticeable in the first three months of an infected baby's life (Blanchette *et al*., 2001), while these results are also confirmed by researchers who studied 28 infected and 98 uninfected children (Gay *et al*., 1995). These researchers also found that motor deficiencies were already evident during the first three months of the baby's life and that it deteriorates in time.

The gross and fine motor quotients indicated that the infected group performed below average with regard to the gross motor, while their performance was average in the fine motor skills. Furthermore, the infected group performed worst with regard to their gross motor skills. A reasonable difference was also recorded between the fine motor and gross motor skills development of the infected group in comparison to the other two groups that obtained more or

less the same percentile values for fine motor and gross motor development. It can be concluded that the gross motor skill development of the HIV infected group is influenced to a greater degree than their fine motor skills development, although their total development was also below average. These results are in agreement with other literature findings, indicating that the gross motor skills of infected children are affected most by the virus (Msellati *et al*., 1993; Parks & Danoff, 1999).

In a retrospective study that aimed to screen a large cohort of children infected with HIV to identify the prevalence, etiology, and semiology of seizures, conducted by Samia and colleagues, (Samia et al; 2008). A sequential folder review of patients attending the general pediatric HIV clinics was undertaken from January 2008 to January 2009. A total of 354 records were reviewed, patients with seizures were further assessed for seizure type, etiology, epilepsy evolution, and antiepileptic drugs used. It was found that, features of developmental delay were documented in 107 of 354 (30%) records. Among those assessed, 23 children were classified with mild developmental delay, 7 children had moderate developmental delay, whereas 9 children were classified as having severe developmental delay. It was also found that, features of developmental delay in the seizure cohort were documented twice as frequently as that of the non-seizure group. It was concluded that, only 30% of the population was noted to have features of developmental delay. Developmental delay and neuro-regression were documented presenting features of HIV encephalopathy in children with cognitive delays and are reported in up to 80% of cases in some studies.

In a study that was done by Benki-Nugent et al (2007), to determine the extent to which effective antiretroviral therapy (ART) prevents the delayed developmental milestone attainment, ages at attainment of milestones were compared between HIV-infected (initiated ART by age <5

months), and HIV-unexposed uninfected (HEU) infants. The results showed that, seventy-three HIV-infected on ART (median enrollment age 3.7 months) and 92 HEU infants (median enrollment age 1.6 months) were followed prospectively. HIV-infected infants on ART had delays in developmental milestone attainment compared to HEU: median age at attainment of sitting with support, sitting unsupported, walking with support, walking unsupported, monosyllabic speech and throwing toys were each delayed (all p-values <0.0005). From this study it was concluded that, HIV infected infants with viral suppression on ART had better recovery of developmental milestones than those without suppression, however, deficits persisted compared to uninfected infants. Therefore, ART may be required for optimized cognitive outcomes in prenatal HIV-infected infants.

Correspondingly, Van Rie, Dow, Mupuala, and Stewart (2009) studied 160 18–71 month old children in the Democratic Republic of Congo (DCR) with baseline and two follow up measures and showed that the HIV positive children had lower mean scores than both control groups (HIV affected and HIV unaffected) at all three time points for both motor and mental development. Van Rie, Mupuala, and Dow (2008), appearing to use the same sample as Van Rie et al. (2009), explored the severity of delay in a study of 160 children (35 HIV positive, 35 HIV affected and 90 controls) who were clustered into three age bands (18–72 months; 18–29 months and 30–72 months). They found significantly more HIV positive children were severely delayed 60% versus 40% in the affected group and 24.4% in the control group on mental development in the first age group. The pattern was repeated for motor delay with 28.6% of the HIV positive children delayed compared to 14.3% of the affected children and none of the control children. Of interest was that the differences seemed to dissipate over the time periods (significantly worse at the second time period, but a trend at the third).

2.3. Effects of seizures/epilepsy on cognitive functioning in HIV positive children

It must be noted that, there is a proposed relationship between motor development and cognitive development, with early studies by Piaget (1953) suggesting that activity and sensorimotor experiences influence cognitive ability. Since then, several studies have examined the association between motor skill development in infants, toddlers and young children and cognitive ability in later life (Burns et al., 2004; Williams & Holley, 2013). Brain imaging shows that brain regions associated with primitive motor and sensory functioning mature first, followed by brain regions associated with cognition and action (Casey et al., 2005) supporting the argument that basic sensory-motor skills form the foundation for higher-order cognitive abilities (Diamond, 2000). Support for the inter-relationship between motor and cognitive development comes from a summary of neuroimaging studies, which found that mutual brain structures are used for both motor and cognitive functioning and suggest that when deficits in motor ability are observed, so too are reductions in cognitive ability and vice versa (Diamond, 2000; Wassenberg et al., 2005). One implication is that gross motor skill acquisition in early childhood may be a better predictor of cognitive performance at school than fine motor skill, suggesting the need for teachers to encourage development of gross motor skills in early childhood programs.

Research supports a link between early movement and later cognitive learning. Infants, toddlers and young children who have increased opportunities to move and to improve motor skills may be more likely to develop greater cognitive and academic skills, than those who experience limited opportunities for physical activity, (Burns et al., 2004).

Developmental milestone challenge in children refers to failure to gain developmental abilities or to gain this at a different rate in comparison with other children. There is a body of knowledge from the child development literature describing multiple factors contributing to

development milestone or developmental delay (Davis et al., 1992). Many of these factors can be found within families affected by HIV and AIDS. Children with HIV are subject to the potential impact of the virus, of antiretroviral treatment (ART) and environmental factors that are known to affect developmental milestones. There are a lot of predictors of poor cognitive performance, reduced stimulation being one of them (Bonnan, 2015).

Since the beginning of the pandemic, with continuing advances in the development and increased use of ART, there has been a noticeable reduction in the prevalence of HIV-associated neurological disease in developed countries, from 60–50% to 23–13%, (Hamid; 2008). In the developing world, there is still a relatively high prevalence of neurological disease associated with pediatric HIV disease. Neurological disease is three times more common in children than adults, and is often the initial presentation of HIV disease, with 75% of cases occurring within the first 2 years of life, (Chase; 2000 as cited in Chang, Christie, Pierre & Walker;2013). The majority of children with HIV-associated neurological disease are infected by maternal–fetal transmission (Chang, 2013). Through this route, there is an increased risk of irreversible brain damage, as well as various degrees of developmental delay and cognitive impairment (Charurat; 2000).

Epilepsy is a symptom rather than the cause of brain dysfunction. The most prominent feature of epilepsy are the seizures, but mental health may be also involved, including memory deficits, learning disabilities, behavioral problems, motor deficit and poor social outcome, (Smith, Elliott & Lach; 2002). Epileptic seizures can cause both morphological and functional changes within the brain as well as cognitive and neuropsychological alterations. The short- and long-term consequences can be influenced by several factors, especially the epilepsy syndrome. If most of the changes are transient and seizure related, mental health problems may persist even

if the patient achieved seizure freedom or may be present with a history of a few seizures. Major cognitive complaints are reviewed in regard to the epilepsy syndrome, with a particular attention to the malignant epilepsies in infancy and childhood, (Bjoernas et al; 2001).

The most reported cognitive complaints in adults are mental slowness, memory impairment and attention deficits. However, because early seizures can induce permanent deficits and increase seizure susceptibility and that prolonged exposure to abnormal neural activity during a critical period of cerebral maturation may disrupt the structural and functional changes in the brain, diffuse impairments, (Nolan et al; 2003) are more often documented in children with additional troubles (compared to adults) such as learning disabilities, poor academic outcome, behavior problems, motor deficit and language stagnation or deterioration.

The developmental deficits associated with HIV infection in children include impaired language and motor skills, cognitive deficits, impaired visual–spatial integration ability and impaired executive functions, (Wolters, Brouwers, Civitello and Moss 2007). Children tend to be more impaired than adults, (Janszky et al: 2005). More common language problems are poor lexical knowledge, word-finding difficulties and anomia, (Silvia et al: 2003). However, there is evidence that reading and spelling are also affected. This may be attributable to atypical language distribution with increased right activation. Using functional magnetic resonance imagery (fMRI) in epilepsy patients, several language patterns differ from normal control with atypical language activation in about one-third of patients or atypical language dominance in one-fifth of patients, (Thivard et al; 2005). This reorganization is more likely to occur with epilepsy onset before 6 years of age; however, late reorganization has been described in specific cases as in late-onset left Rasmussen syndrome, (Loddenkemper et al: 2003). Patients with atypical language location had better cognitive measures, suggesting a deleterious cognitive

effect on those unable to transfer and compensatory mechanisms on those able to dislocate, (Billingsley et al: 2001: Gaillard et al: 2003).

Problems in motor function are frequently reported in children with epilepsy (Gloersen & Nakken 2000). It is sometimes claimed that motor disability is one of the most common types of comorbidity associated with epilepsy (Cowan et al. 1989). These consist of problems in balance, coordination, and impairments of fine and gross motor skills, even in those without learning disability and cerebral palsy. Epir et al. (1984) report a deficit in perceptuo- and fine motor skills as the dominant motor impairment in children with epilepsy. Several studies confirmed this finding (Gloersen & Nakken 2000). In addition, psychomotor slowing is often reported as a prevailing impairment in children with epilepsy. For example, slowing on simple reaction time tasks was found (Beckung & Uvebrant 1993, 1997). Some studies have related this slowing to the epilepsy (Vermeulen et al. 1994) or the postictal effect of frequent epileptic seizures (Aldenkamp et al.1999); others hold the use of antiepileptic drug (AED) treatment responsible (Aldenkamp et al. 1993, Vermeulen and Aldenkamp 1995, Braathen et al. 1997).

Delays in motor development, especially gross motor skills, most strongly differentiate HIV infected from HIV-exposed children, and are seen more frequently in infants than school-aged children, (McNeilly; 2000). Children demonstrating motor dysfunction, including abnormal muscle tone, less muscle bulk or less muscle strength, have been shown to be at an increased risk for disease progression. Delays in mental development occur later in infancy and most often present as a global cognitive deficit (Pearson, McGrath, Nozyce, et al; 2000).

Chang, Christie, Pierre & Walker (2013), conducted a study for the Caribbean in particular, aimed to describe the neurological outcomes of HIV-infected children in Jamaica and determine

their neurocognitive function. A nested case–control study was conducted between July and September 2009 where 15 randomly selected encephalopathic HIV-infected children aged 7–10 years and 15 matched controls who were non-encephalopathic HIV-infected. Data for 287 HIV-infected children presenting between 2002 and 2008 were reviewed and neurological outcomes characterized.

From the same study the median age of tested children was 8.7 years (IQR 7.6–10.8 years) in the encephalopathic group and 9 years (IQR 7.4–10.7 years) in the non-encephalopathic group. The encephalopathic group achieved lower test scores than their non-encephalopathic peers in the Raven's Progressive Coloured Matrices. Additionally, they achieved lower test scores in the Corsi Block, Digit Span, and Map Search tests. They also took longer times to complete the motor tests such as the grooved pegboard, posting coins, and the hand pronation–supination tests. Two encephalopathic children were unable to complete the grooved pegboard test due to significant motor impairment; they were severely spastic. It was concluded that a high prevalence of HIV encephalopathy was noted, and significant neurocognitive dysfunction identified in encephalopathic children. Optimized management through the early identification of neurological impairment and implementation of appropriate interventions is recommended to improve quality of life.

2.4. Motor development (fine and gross)

Fine motor development is the development and control of small movement skills, such as reaching and grasping, while gross motor development refers to control over larger movement skills that tend to be less refined, such as crawling, standing and walking (Berk, 2005). Early views of child development were based on the achievement of developmental milestones, largely centred on the research of Gesell (1925). Later on, Mercer (1998) had suggested that there are

two major categories of development: maturation and learning. Maturation describes the developmental changes that occur due to the instructions built into DNA (Harris & Liebert, 1992), which include changes attributed to growth. Learning describes the permanent changes that occur in thinking and behavior when children play an active role in their own development, when both perceptual and social incentives promote the progression of skills (Bruner, 1973). Child development is increasingly recognized as a dynamic system, strongly influenced by a variety of factors, including interaction with peers, families, societies and cultures (Thelen et al., 1991; Greenfield & Cocking, 2014). The dynamic perspective recognizes that even small differences in experience or environment at a young age can result in dramatic differences in later behavior (Smith & Thelen, 2003).

As dynamic perspectives of development suggest, all children develop at different rates and, while there is a typical order of development due to maturation (Brierley, 1993), patterns or milestones may vary in children from different cultures, ethnicities and communities because different opportunities in individual contexts also lead to the development of different physical skills or proficiencies (Adolph & Berger, 2005). One implication of this is that in the early years of life, developmental age is often deemed to be a more relevant assessment measure than chronological age (Foster & Hartigan, 2006), especially for children born pre-term or with very low or extremely low birth weight (VLBW and ELBW, respectively). Therefore, some researchers report findings in terms of developmental age as opposed to chronological age.

Although the sequence of motor development is fairly uniform, children develop at different rates and in different ways, influenced by factors such as environment, experience and culture, as well as genetics and growth (Berk, 2005; Thelen et al., 1991; Greenfield & Cocking, 2014). Both fine and gross motor development are influenced by cephalocaudal development and

proximodistal development in the typically developing child (Berk, 2005; Adolph & Berger, 2005). Through these cephalocaudal and proximodistal trends, upper body control is achieved first, followed by arm control, and then finger control (Berk, 2005). For toddlers (1 - 3 years-old) development is rapid, with the most obvious changes occurring in language and motor skills (Colson & Dworkin, 1997). Toddlers' motor development is typically characterized by the commencement of walking and other gross motor skills such as running, jumping and hopping (Cardon et al., 2011). Fine motor skills, such as writing, drawing or manipulating blocks, also develop and progress during the toddler period (Cardon et al., 2011).

As children grow, their bodies become less top heavy and more streamlined, their perceptual and cognitive capacities grow, and building on existing motor skills, they learn more complex movement patterns (Berk, 2005). Children's more complex motor skills are sometimes referred to as fundamental movement skills , and further categorized as locomotor skills and object control skills. Locomotor skills involve body movement and include skills such as running, skipping and jumping (Barnett et al., 2008a). Object control skills are those that involve manipulation of an object, for example throwing, catching and kicking (Barnett et al., 2008a).

In another study, that was conducted in South Africa, aimed to determine the extent of delay in acquisition of language, cognitive and motor skills of HIV positive children, (Nicole; 2005). The data was collected from 40 HIV positive infants fitting the inclusion criteria ages between 18 and 3 months. It was determined in this study that infants were delayed in motor development, which was statistically significant ($p<0.001$), of which 77.5% of the sample was significantly delayed according to their PDI scores. On descriptive analysis, gross motor function was found to be affected in 85% of the population, whereas fine motor function was only affected in 12.5%. The results of this study confirmed that children with HIV have language

delays, and descriptive analysis of the data revealed that 82.5% of the sample had delays in language development. It was postulated that motor delays may be attributed to decreased strength, as the most adversely affected skill in this sample was gross motor development. The cognitive delays noted may be due to disease progression and structural damage to the brain, as well as socio-economic factors. The language delays noted could be due to neurological impairment, cognitive delay or environmental deprivation.

2.5. Language development

There has been very little research conducted in Africa regarding the extent of delay of language, motor, and cognitive development in HIV-positive infants. Overall development of HIV-infected infants has been found to be delayed,(Blanchette et al, 2001), but there is a need for the assessment of the above-mentioned skills to facilitate a better understanding of where the most significant developmental problems lie(Bissiachi et al, 2000). Therefore, the purpose of this study was to determine the extent of delay in acquisition of language, cognitive, and motor skills of children infected with HIV.

In a cross-sectional study that was conducted by Baillieu & Potterto, they used a sample of convenience, in South Africa, which consisted of 40 consecutive children with vertically transmitted HIV, between the ages of 18 and 30 months,(Baillieu & Potterto;2008). The neuropathogenesis of language problems in HIV is unknown.14 Speech and language acquisition is sensitive to a variety of neurodevelopmental abuses, including global cognitive delay, central disorders of language function or auditory perception, central or bulbar disorders of motor functio, and hearing loss. HIV CNS disease in children is associated with deficits in both receptive and expressive language, although expressive language skills are more severely impaired, (Brouwers et al; 1995). The results of this study confirm that children with HIV have

language delays, and descriptive analysis of the data revealed that 82.5% of the sample has global language delay. The infants may have structural damage to the brain caused by HIV CNS infection, and there is cognitive impairment in this sample, which may interfere with language development. The results of this study are similar to findings by Webster et al (2005) who found a relationship between gross motor and communication performance, suggesting that factors critical to gross motor function may also lead to language impairment.

The findings of this study support previous research, which has demonstrated that children with HIV have significant delays in language development. Problems with language development are also seen, which may be because of CNS involvement or oral-motor problems that stem from decreased muscle strength. Cognitive delays may be affected by CNS involvement, as well as socioeconomic problems encountered in this population. These findings are in keeping with studies done in other parts of the world.

In a systematic review, (Abubakar; 2008) aimed to determine the degree of motor, cognitive, language and social-emotional impairment related to HIV infection in children living in sub-Saharan Africa (SSA). All studies that investigated motor development (Msellati et al. 1993; Boivin et al. 1995; Drotar et al. 1997; McGrath et al. 2006) reported significant differences between HIV-infected children and controls. In the language domain, two studies of infants (Msellati et al. 1993; Boivin et al. 1995) found that there were no significant differences in the language scores of children at 6 and 18 months of age. However, the Rwandan study (Msellati et al. 1993) reported a significant effect at 24 months of age severe impairment, whereas Boivin et al. (1995) did not find significant language deficits in a pre-school population. From the data it was concluded that the magnitude of impairment in motor and mental development is similar to that observed in children who are HIV-positive. Motor development was the most frequently

measured area of functioning, providing consistent evidence of delay in HIV-positive children across all ages.

Ferguson and Jelsma (2009) studied 86 (1–33 month old HIV positive and healthy children in South Africa 51 HIV positive, 5 affected and 20 HIV status unknown and found that significantly more HIV positive children were ‘significantly delayed compared to the healthy children 66.6% versus 5.7%. Similarly, Baillieu and Potterton (2008 as cited in Fergusonn and Jelsma; 2009) studied 40 ((18–30 months old HIV positive children in South Africa and found significantly lower cognitive development than the children's cognitive development for their chronological age in 97.5% of the sample, more especially in the language domain.

Bradshawa et al (2014) conducted a systematic review to explore developmental effects of HIV including cognitive, behavioral, developmental and psychological function as measured by the various studies and standardized child developmental inventories. The review covered studies on effects of HIV for the period 2008 to 2013. This review aimed to provide a more detailed understanding of concepts under the cognitive development umbrella such as language development, motor skills, memory, executive function, spatial abilities, information processing and other cognitive processes that would affect how a child gains access to their learning curriculum and functions in the emerging adult world. The majority of the studies (17/21) (80.1%) showed that HIV was associated with some form of detrimental effect on cognitive development, across a wide range of different measures. Eight studies (38%) reported detrimental effects on all measures and a further 10 (totaling 48%) reported detrimental effects on at least one measure. Of these eight, seven emanated from Sub-Saharan Africa. Only three studies found no significant differences or effects of HIV between the HIV positive group and a comparison group (14%).

From the studies that were reviewed, seven provided specific data on language scores. Rice et al. (2012) carried out a comprehensive language assessment linking this with hearing impairment and environmental variables on 437 HIV positive and affected 7–16 year old children in the USA and Puerto Rico. They found elevated language impairment among both HIV positive and HIV affected children (40% prevalence rate which is much higher than the 16% expected rate based on country norms). In the same study, on the cognitive/executive functioning categories, only one study explored pattern recognition as a specific sub-item (Koekkoek et al., 2008 as cited in Bradshawa; 2014) and found HIV positive children significantly lower in both speed and accuracy than 'norms'. Executive function is usually measured by attention variables, visual-spatial abilities and working memory. Koekkoek et al. (2008) found that executive functioning and processing speed were specifically challenged for HIV positive children. In the same study that was conducted by Bradshawa, it was concluded that they found significantly lower scores for almost all the domains that were explored in HIV positive children.

In conclusion, the above studies that have been reviewed i.e. the neuropsychological measures, HIV in children, and the developmental difficulties in HIV children have focused much on the attainment of developmental milestone in HIV positive children. A clear tendency of poorer motor development is apparent in young children infected by HIV. The necessity of motor intervention for children with HIV to promote their development and quality of life can therefore be emphasized. Nonetheless, it must be noted that within the HIV positive children, there are those that are presenting with other opportunistic infections that are not outlined and their attainment of developmental milestones are not reviewed either, because this has not been reviewed it gives the more reason of conducting this research more especially here in Zambia.

CHAPTER THREE

METHODOLOGY

3.1. Overview

This study was part of a bigger project that is being conducted at the University Teaching Hospital. The bigger study is a cohort study looking at HIV associated seizures and epilepsy. This study was part of the bigger study in that; the participants that were recruited in the bigger project are the same participants were data were collected for this study too. In relation to finding out the neurodevelopment of children in the core study, two test batteries were used which is the Malawian Developmental Assessment Tool (MDAT) (Gladstone et al, 2009) and the Unit, (Balla, Cichetti & Sparrow, 2005). But for the case of this paper only the MDAT was used. This part of the proposal outlines the methods that were used to collect data as well as methods that were used for data analysis.

3.2.Study design

The study was a case study design. Using a case study design enabled the researcher to focus on in-depth data on single cases and participants that were under study. The purpose of this design was to learn more on unknown information. This design was carried out so as to generate findings of relevance beyond the individual cases, and also to arrive at a comprehensive understanding of the events under study but at the same time to develop more theoretical statements about regularities in the observed phenomena. It too provided clues for further research into the etiology of HIV associated seizures and epilepsy. This design was appropriate for the study because it brought out more detailed information in each case that was studied.

3.3.Participants

3.3.1. Core study sample

The core study, from which the sample was derived, had intended to collect data from a prospective 100, with only 45 enrolled in the study over a two year period while recording a 45% mortality rate. This sample was selected from the University Teaching Hospital (UTH) pediatric Admission Ward. This was done in a way that the nursing staff and other medical personnel placed in various centers did the recruitment on behalf of the bigger study and the researcher. The core study for this project was determined to find the epidemiology effects of long term antiepileptic drug (AED) treatment for HIV+ individuals who experience a first seizure. The goal of the study was to determine the causes of seizures in children with HIV and the outcomes including mortality and seizure recurrence. The core study aimed to identify seizure etiology in those without a history of epilepsy, to determine the incidence of seizure recurrence for those without a history of epilepsy, and also to identify risk factors for recurrent seizures among those without a history of epilepsy. The study also aimed to assess clinically relevant interactions between anti-retroviral therapy (ART) and anti-epileptic drugs (AEDs) in the Zambian setting.

3.3.2. Current study sample

The current study aimed at collecting a total of 20 participants for the study however, due to the high mortality rate in the core study, the sample size was reduced to fit in the current study format. The total sample for this study was 8 participants, of which 4 were those children who were part of the bigger study as well and were presenting seizures/epilepsy and the other 4 were those without seizures/epilepsy who receive their antiretroviral therapy (ART) through the PCOE of ages 4-6 years old, mean age of 5 and standard deviation of 0.76. These participants were recruited from University Teaching Hospital (UTH) pediatric admission wards. The UTH

pediatric ward is the largest referral ward in Lusaka Province. After the eligible participants had been identified and they had consented for the study, the recruitment was done in a way that those patients who come in as out-patient or are admitted in any of the above mentioned wards and meet the inclusion criteria were recruited. The recruitment was done by medical nurses and doctors and the consenting was done by one of the medical staff members who were part of the cohort for HIV associated.

3.3.2.1.Inclusion Criteria for the A participants presenting with seizures

The A participants were those who were from the bigger study and were presenting with seizures/epilepsy.

The participants' inclusion criteria in these participants was

- HIV positive children - HIV positive status confirmed by medical records.
- Ages between 3 to 6 years old – was confirmed by the caregivers report.
- Had experienced a seizure not more than 6 weeks prior to referral for recruitment.
- Had presented with a febrile seizure or provoked seizure.
- Stable enough to be assessed – were able to participate in the study well
- Caregiver's who had given consent

3.3.2.2.Exclusion Criteria for A participants presenting with seizures

An exclusion criterion for these participants was that they;

- Presented with any history of any neurological conditions confirmed from their medical reports.

- ❖ Presented with any head injuries.
- ❖ Had any seizures before confirmed from the medical history
- ❖ Caregiver's who had not given consent

3.3.2.3.Inclusion Criteria for the B participants presenting without seizures

The B participants were those who were not from the study and not presenting with seizures/epilepsy, they were a comparison

The B participants' inclusion criteria were;

- ❖ HIV positive children- HIV positive status confirmed by medical records
- ❖ Ages between 3 to 6 ages old- confirmed from the caregivers report
- ❖ Not presented with experiencing any seizures- confirmed from their medical history
- ❖ Children who received their antiretroviral therapy through PCOE
- ❖ Had close matching demographics (e.g. age, sex, caregivers) with the participant in group A
- ❖ Caregiver's who had given consent

3.3.2.4.*Exclusion Criteria for B participants presenting without seizures*

Exclusion criteria for the B participants were;

- ❖ Presented with any history of any neurological conditions
- ❖ Presented with any head injuries

- ❖ Had any seizures before
- ❖ Mismatched demographics with the participant from group B

3.4.Procedure

The study procedure for participants who were presenting with seizures/epilepsy in the core study had a number of steps which were undertaken and these are:

Step1.

Recruitment of the participants for the study was done from UTH Filter Clinic and UTH Pediatric Admission Ward. This recruitment was done by medical personnel on behalf of the researcher. Recruitment of the participants was based on the inclusion and exclusion criteria and all medical personnel in various clinics were informed of the procedure. The criteria were helpful in identifying eligible participants for the study from those who visit the health centers for their care, support and treatment. Participants' caregivers were provided with information on the study by the medical personnel as well as the researcher. Consent was also obtained from the participant's caregiver by the researcher and they were made to sign an informed consent before the assessment started. (A copy of the informed consent can be found in appendix 1). Only participants' caregivers who consented took part in the study.

Step2.

All medical assessments were conducted by well trained and qualified medical practitioners. The medical practitioners were responsible for all evaluations and biological specimens for example, collect blood from the participants which was used to make a number of examinations like CD4 count, viral load and other necessary laboratory examinations.

Step3.

The neurodevelopmental test battery was administered to all participants while still in the ward for in-patient after they were stable enough or on discharge day. For out-patient participants the neuropsychological assessment was administered on the date of their appointment that was given to them by medical staff from the PCOE. According to neuropsychological battery participants were asked to perform some tasks and some questions were asked to their caregivers concerning certain tasks that cannot be asked to be performed there and then while administering the tool. The whole assessment took approximately 30-45 minutes.

Step4.

After the assessment was done with the participant, the researcher then administered the Vineland Adaptive Behavior Scale to the caregivers, which is basically a behavioral checklist that tends to understand the behavior of the child which is administered to the caregivers about the child's information. This interview took approximately 20-30 minutes.

Step5

After the assessment was done with the child and the caregiver, the medical personnel was then later interviewed concerning the child's development specifically with the cases that were under study who were presenting with seizures/epilepsy.

3.5.Data collection tools or instruments

The data collection tools used in this was the CHASE neuropsychiatric assessment questionnaire (appendix 2) where demographic data was obtained from, the Malawian Development Assessment Tool, (Gladstone et al, 2009) (appendix 3), the Vineland Adaptive Behavior Scales (Balla, Cichetti & Sparrow, 2005) (appendix 4) and the interview guide that was used to interview the medical personnel, (appendix 5), the interview guide with the medical personnel provided qualitative data. The CHASE neuropsychiatric assessment questionnaire is a semi-structured questionnaire that was administered to the participants' caregivers.

3.5.1. The Malawian Development Assessment Tool

The Malawian Development Assessment Tool (MDAT) is a standardized tool and it is a culturally specific tool developed by, after careful qualitative evaluation of culturally appropriate developmental domains for rural Malawi. The original tool was created by adapting items from Western tools such as the Denver II and the Griffith's (Gladstone et al. 2008), but after substantial re-adaptation and in-depth qualitative work, the newer MDAT was created (Gladstone, Kayira, Lancaster, Nyirenda, Smyth, Umar & Van den Broek 2010).

On the MDAT's reliability, children were invited to participate in reliability testing as follows. The first child on the testing day was assessed for inter-observer immediate reliability, the second child for inter-observer delayed reliability, and the third child for intra-observer delayed reliability, with a good fit, good to excellent reliability (kappa > 0.6), few problems when rated subjectively, and no effect of gender. Inter-observer immediate reliability was measured by assessing the same child independently on the same occasion by two observers (56 children). Inter-observer delayed reliability was measured by observing the same child independently on the same day at different times by two observers (52 children). Intra-observer

delayed reliability by the same observer assessing the same child 2 weeks apart (124 children). Reliability testing was carried out on all 185 items in the Draft MDAT III in Malawi.

The MDAT was validated once the final set of items was chosen; children were then scored in two ways. Firstly a score was generated by a categorical pass or fail assessment, and each score was used to validate the tool in a series of tests. All items relevant to the age of testing were scored in a similar way to the Denver II screening test. If the child failed two items or more in any one domain at the chronological age at which 90% of the normal reference population would be expected to pass, then they failed the test. Secondly, a continuous score was obtained by adding up the total number of items passed by the child per domain and in total. These scores varied with the age of the child.

Using this tool, each objective was measured in each domain, a child was expected to do the tasks, two items below their age and then keep going till they fail to perform three tasks consecutively. A child was required to complete all the four domains that the MDAT has, but only three domains for the sake of this paper were analyzed which was the language domain, gross motor domain and fine motor domain.

3.5.2. The Vineland Adaptive Behavior Scale

The VABS is a standardized tool that was developed by (Balla, Cichetti & Sparrow, 2005). The VABS is administered to the parents, caregivers or the guardians of the child, which intends to give information about the child's adaptive behavior and developmental life. The VABS has 5 domains, but for the sake of this paper only 3 domains were be analyzed, and these were communication domain, daily living skills and motor skills. All the 3 domains that were analyzed in this paper included their subdomains that are age related too. Using this tool, the

fourth objective was measured. The caregiver or the parents or guardian of the child were expected to give information about the child in relation to what the researcher asked them. It was noted to the parents or caregiver or guardian too that there was no wrong or right answer.

3.6.Data analysis

Data collected from the MDAT was in the raw score form, then was scored according to the standard norm performance of the tool, and then compared between the two groups. This was done in a way that, first the scores from each participant in group A was recorded then the scores from each participant from group B was second. Each pair was compared in line with their performance after the assessment from each group.

The data that were collected using the Vineland Adaptive Behavior Scale were analyzed using the raw scores, and then scored them using the standardized scoring form in relation to the performance levels in each pair from both groups.

Qualitative data that was collected from the medical personnel were subjected to thematic content analysis; this process involved first the researcher reading of the transcript in order to find meaning, there after qualitative themes were extracted. Thematic Analysis was used to identify, analyze and report recurring patterns or themes within the collected data. The interviews were transcribed, and then later picked out the most common words from what was said and grouped into themes. Similar responses were grouped together for ease of presentation and understanding as described in the results, (see appendix 6).

3.7. Limitations

There are a number of limitations that were faced during the course of the research but only the key ones will be highlighted

1. In the study, with the participants that were presenting with seizures/epilepsy it was recorded that there was high mortality rate, which later even affected the study size sample. The participants that were enrolled in the study could not survive till the time they are assessed because of their condition.

2. The use of qualitative approach to report findings that use quantitative instruments may have reduced the ability to detect the delays in the developmental milestone domains that were assessed.

3. The results from these cases cannot be generalized.

3.8.Ethical considerations

Voluntary informed consent was required and obtained from the participants' caregiver and also a written informed consent was required to be signed for enrollment of participants in the study. Participants' caregivers were told about the study and their right to refuse participation if they felt that participating would have violated their rights in one way or another. Participants' caregivers were voluntarily enrolled in the study without any coercion and were free to withdraw anytime. The children were also informed about the assessment their wiliness and cooperation was asked from them too.

Participant privacy and confidentiality was also observed in that participant's information was only accessed by the members of staff for the study and was kept within the circles of the members of staff and was not publicized. Confidentiality was maintained by ensuring that information collected from participants was used solely for research purposes of the study, both the core study and current study. Information obtained was not shared or broadcasted or passed into the hands of persons other than the members of staff and the researcher part of the study.

Participants were anonymous and were not required to provide their names during the assessment apart from the study identity number.

Participant safety was also promoted because participants' caregivers knew (if any) available risks to them, it was ensured that participants' caregivers knew the benefits (part of consent), referral system was put in place if needed and they were also reporting of adverse events to research ethics.

The participants' caregivers were being thanked after the assessment with their children for their time and patience that they exercised, and also for making it possible for the researcher to collect the necessary data.

CHAPTER FOUR

RESULTS

4.1. Overview

This chapter presents the analysis of data in accordance with the following research questions: - How is the achievement of the fine motor developmental milestone in HIV+ children with/without seizures/epilepsy? How is the attainment of the gross motor developmental milestone in HIV+ children with/without seizures/epilepsy? How is the achievement of the language developmental milestone in HIV+ children with/without seizures/epilepsy? What is the medical personnel's observation towards their child's behavior in relation to developmental milestones? From the simple descriptive that was analyzed, the sample consisted of 8 participants of which 4 were in group A (were presenting with seizures/epilepsy) 1 boy and 3 girls and 4 participants were in group B (were not presenting with seizures/epilepsy) 1 boy and 3 girls. In group A, which had participants who were presenting with seizure/epilepsy the data was analyzed in cases. The cases are presented in the order of their participant ID. In group A, which was presenting seizures/epilepsy after a comprehensive analysis of the cases in relation with the relevant information that, was collected, these were the findings. Below is the description of the participants.

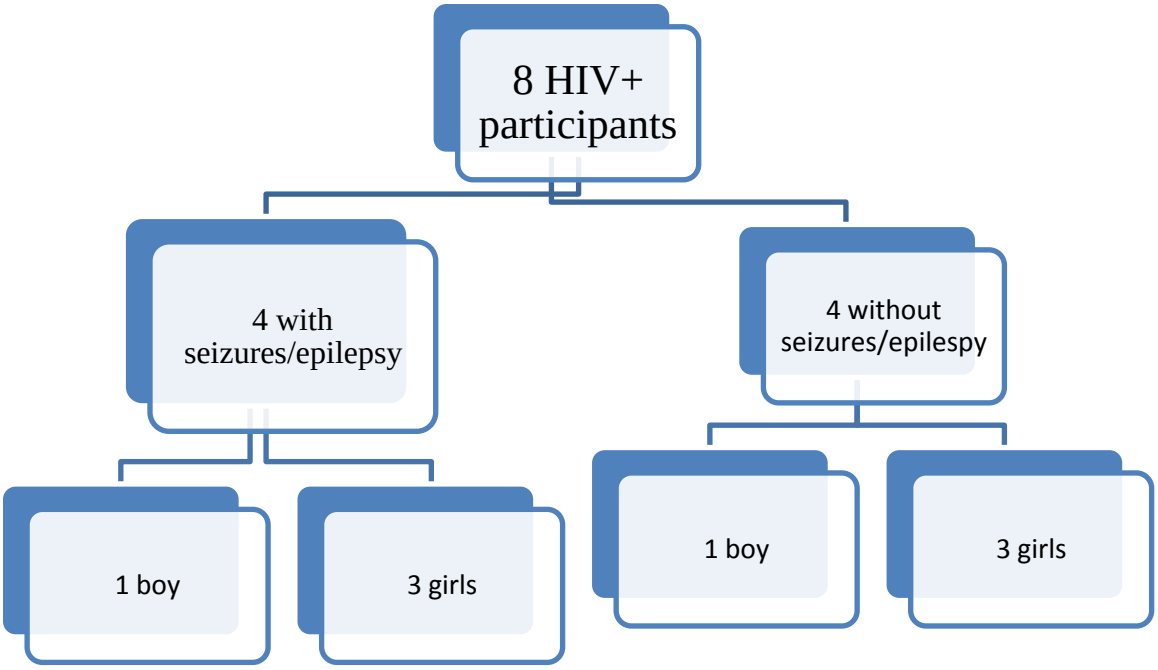

Figure1. Shows the summary of participant's characteristics

3.2.Case series

Case 1

A 4 years (49 months) old boy, presented with fever and seizure consisting of left sided jerking followed by secondary generalization and status lasting for 1 hour 30 minutes. HIV + diagnosed when he was 2 years 8 months and the antiretroviral therapy (ART) was initiated at the same time, with a CD4 count of 25% and viral load of over a million copies. Medical history was that had completed treatment for TB meningitis and had WHO stage IV level of HIV. No PMTCT services were received by the mother. The developmental assessment on the child showed to be severely delayed in all the domains that were assessed.

On the child developmental information that was collected from the mother, she reported that, comparing her son to other children of his age, her child seemed to have delayed motor skills in

tasks like sitting, standing or walking. This child also reported to have noticed that her son had hearing difficulties. Before hospitalization and enrollment in the study, the mother described that her son used to learn to do things and understood like children of his age. The child was scheduled for a follow-up assessment after 3 months which was supposed to be in August, but unfortunately passed away on their way to the hospital.

Table 1: shows the case summary for the participant 1 presenting with seizures/epilepsy.

CASES	AGE/SEX	HIV/ART	PMH	CD4	VIRAL LOAD	ASSESSMENT SUMMARY
Case 1	4y/M	Worst WHO stage IV. ART initiated the same period after HIV diagnosed	TB Meningitis-completed treatment 3 months prior to enrollment	451(25%	1,597,452	Fine motor-severely delayed Gross motor-severely delayed Language domain- severely delayed

Case 2

A 5 years (64 months) old girl, presented with fevers, headache and two seizures characterized by body stiffening and eyes rolled upward/unresponsive with second seizure appearing more generalized tonic for 10minutes. The HIV + diagnosis and ARV initiation was done almost at the

same period. The child had a CD4 count of 23% with a viral load which was not detected due to insufficient sample. The participant had WHO stage II level of HIV. No PMTCT services were received by the mother. In the developmental assessment she reported to be fairly developed in other domains because she performed the expected tasks that were appropriate for her age based on the test norms, except in the language domain. In the language domain she had low scores. Unfortunately the child had hearing loss affecting the language abilities.

Table 2: shows the case summary for the participant 2 presenting with seizures/epilepsy.

CASES	AGE/SEX	HIV/ART	PMH	CD4	VIRAL LOAD	ASSESSMENT SUMMARY
Case 2	5y/F	Worst WHO stage IV. ART was initiated at the same period.	stroke w/ residual (r) hemiparesis, severe malnutrition	633	undetectable	Fine motor skills- performed well. Gross motor skills- performed well. Language domain-delayed

Case 3

A 6 years (76 months) old girl, presented with fevers and meningitis with 2 generalized tonic lasting 2-3 minutes. ARV was initiated at the same age. The child had a CD4 count of 459 with insufficient viral load. Had WHO stage I. No PMTCT services were received by the mother. In the developmental assessment it was reported that she performed fairly well in other domains,

except in the language domain. This child recovered well and was sent home. At follow-up, it was reported that there was no seizure but with signs of hearing problems on screening exam.

Table 3: Shows the case summary for the participant 3 presenting with seizures/epilepsy.

CASES	AGE/SEX	HIV/ART	PMH	CD4	VIRAL LOAD	ASSESSMENT SUMMARY
Case 3	6y/F	HIV - diagnosed in October 2016 Worst WHO stage I. ART-initiated October 2016.	NONE	459(25%)	Insufficient sample	Fine motor skills- performed well. Gross motor skills-performed well. Language domain- delayed

Case 4

A 6 year (78months) old girl, presented with body stiffened with eyes rolling to back and to the right, none responsive when called to, there were several episodes of this, lasting 5mins each with no return to baseline in between with fevers. The HIV history was that the participant was initiated on ARV a month after the HIV+ diagnosis. Had a CD4 count of 556, with a viral load of

above 5 copies. Past medical history stated that the participant had TB meningitis and was on treatment for one year, had WHO stage IV. The mother received ART and other PMTCT services. After the developmental assessment the child performed fairly well in other domains, except in the gross motor domain. No seizure was reported then and the patient had been doing well.

Table 4: Shows the case summary for the participant 4 presenting with seizures/epilepsy.

CASES	AGE/SEX	HIV/ART	PMH	CD4	VIRAL LOAD	ASSESSMENT SUMMARY
Case 4	6y/F	HIV-diagnosed in August 2015 Worst WHO stage IV. ART- Jan 2017	HIV and TB Meningitis – 1 YR (AUG 2015 – AUG 2016)	556(35%)	507. 025	Fine motor skills- delayed Gross motor skills-performed well Language domain-performed well

4.3.Fine motor domain

Motor milestones are useful in organizing a developmental assessment. Children move through these motor stages in an orderly fashion; attainment of these functions is a clear-cut and dramatic.

The motor development in this paper was in accordance with the assessment tools that were used which were divided into two parts which is the gross motor development domain and fine motor development domain. The first research question was to find out the achievement of the fine motor developmental milestone in HIV+ children with seizures/epilepsy and those that were presenting without seizures/epilepsy. In this domain the first participant in A1 was assessed and the other participant in B 1 was assessed later. The participant A1 scored 17/34 items while, the participant B1 scored 29/34 items. The participant A in the fine motor domain, was unable to make circular or straight scribble on the paper, build tower of 2, 4, and 6 with the blocks toys, could not put pegs in board in a longer or short time, failed to unscrew and screw back cap on the chiponde (peanut butter) bottle and also could not thread 6 beads on a string, while participant B1 managed to perform all the tasks.

The second analysis was for the second participant A2 then, B2. The comparison of the two assessments showed that A2 and B2 both performed as expected by the test norm. Both participants from both study groups scored 34/34 items from the tool.

The third analysis was A3 and B3, the comparison of the two assessments showed that A3 and B3 both performed as expected by the test norm. Participant A3 scored 32/34, while B3 scored 33/34 items from the tool.

The fourth analysis was A4 and B4, the comparison of the two assessments showed that A4 and B4 both performed as expected by the test norm. Both participants scored 34/34 items from the tool.

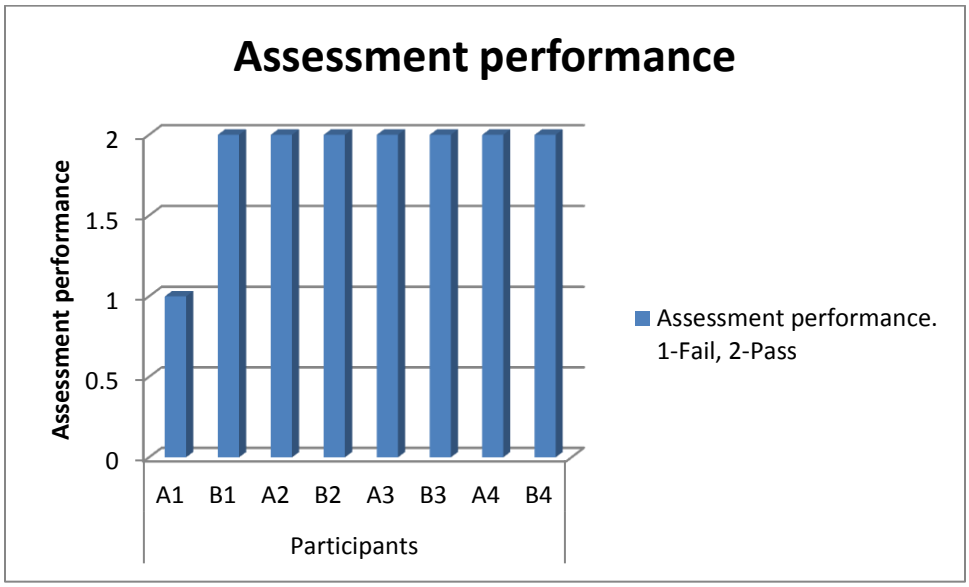

Figure 2: Shows the MDAT performance summary

With the use of the VABS the motor domain was also assessed. In the fine motor domain after the VABS was administered to the caregivers it was observed that participant A1 on the adaptive level was moderately low with the score of 40; the participant in group B1 on the adaptive level was also adequate with a score of 56.

The second analysis was collected from participant A2, whose adaptive level was adequate with a score of 60, while participant in the comparison B2 on the adaptive level was adequate with a score of 58.

The third participants' analysis showed that participant A3 scored 50 which was adequate on the adaptive level, while participant in the comparison participant B3 scored 50 which was adequate on the adaptive level.

The forth participants A4 scored 60 with which was moderately high on the adaptive level; while participant B4 scored 62 which was high on the adaptive level.

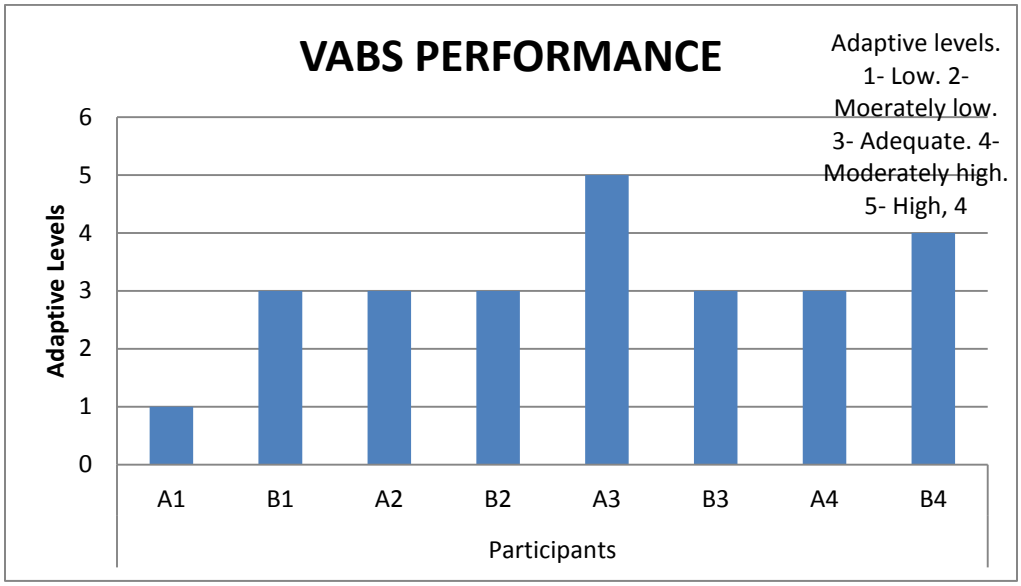

Figure 3: Shows the participants performance with the VABS

4.4.Gross motor

The second research question was to find out the achievement of the gross motor in children presenting with seizures/epilepsy and those that are presenting without seizures/epilepsy. The findings showed that the first participant in A1 was assessed and then B1. The comparison of the two assessments from the scores that were collected using the MDAT showed participant A1 was performed poorly in the gross motor skill, while participant B1 performed better. The participant A1 scored 10/34 items while the participant B1 scored 28/34 items. The participant A1 in the gross motor domain was unable to pull himself to stand, unable to stand if holding on to things, could not walk using both hands of someone, could not walk without falling over time and stoop and recover, while the participant B1 managed to perform all the tasks in accordance with his age.

The second analysis was for the second participants, which was A2 and B2. The comparison of the two assessments from the MDAT showed that A2 and B2 both performed as expected by the test norm. Both participants scored 32/34 items from the tool.

The third analysis was for the third participants which was A3and B3. The comparison of the two assessments from the MDAT showed that A3 and B3 both performed as expected by the test norm. Both participant scored 32/34 items from the tool.

The fourth analysis was for the fourth participants A4 and B4, the comparison of the two assessments showed that A4 had low scores, performed to be delayed in the performance of the gross motor tasks, while B4 performed as expected by the test norm. Participant A4 scored 27/34, while participant B4 scored 34/34 items from the tool. In this domain, participant A4 from was unable to walk on heels for 6 steps, could not jump over the paper, failed to walk on tip toes 6 steps, could not stand on 1 foot for more than 5 seconds, could not catch the ball after throwing it in the air and failed to heel/toe walk precisely with one foot behind.

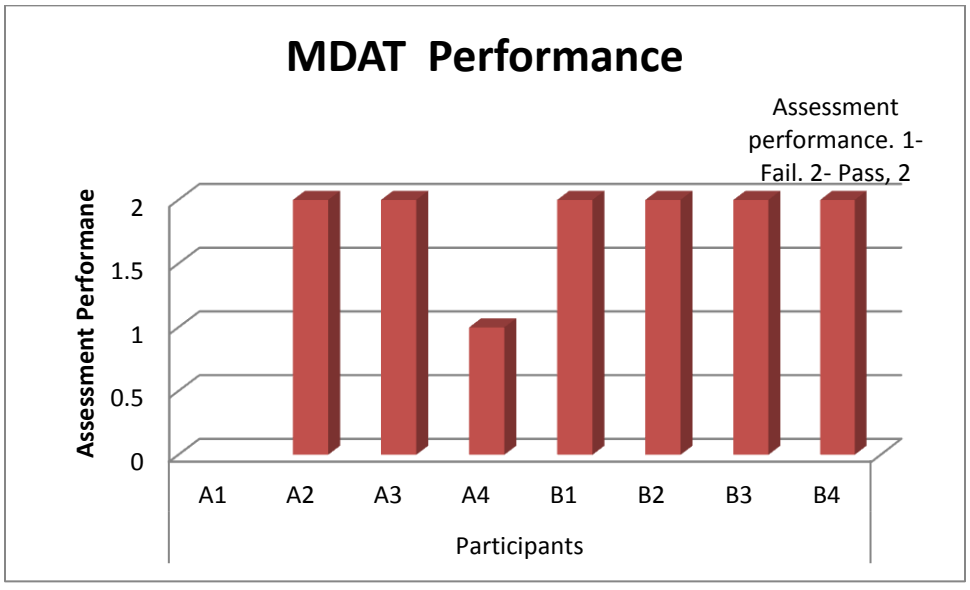

Figure 4: Shows participants' performance with the MDAT

With the data that was collected using the VABS from the caregiver in the gross motor domain it was found that participant A1 on the adaptive level was moderately low with a score of 70, while the comparison participant B1 on the adaptive level was adequate with a score of 80.

With the second analysis, participant A2 on the adaptive level was adequate with a score of 84, while the comparison participant B2 on the adaptive level was adequate with a score of 84. In this domain both participants scored the same.

In the third analysis, the participant in the study group A3 was adequate on the adaptive level with a score of 70, while participant from the comparison participant B3 sored 80 which was moderately high on the adaptive level. From these two participants it was observed that they both performed well.

The forth analysis was of participant A4 which was moderately low on the adaptive level with a score of 72, while the participant B4 scored 84 which was moderately high score.

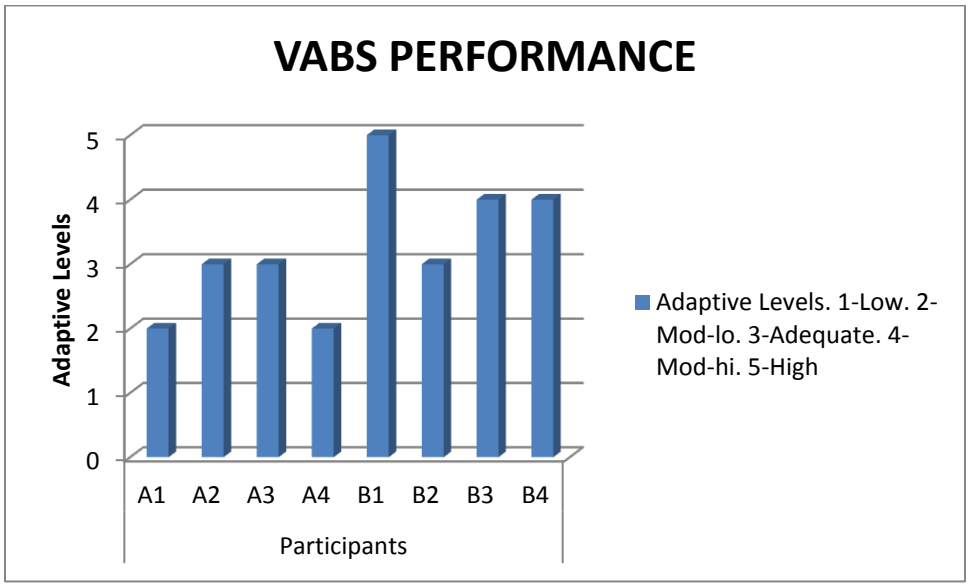

Figure 5: Shows participants' performance using the VABS

4.5.Language domain

The third research question was to find the achievement of the language developmental milestone domain in children who were presenting with seizures/epilepsy and those without seizures/epilepsy. Children's' language development is a function of both innate communication abilities and the environment that may or may not support their development. An assessment of language needs to incorporate both the extent of the child's language performance (which is expressive as well as receptive and the characteristics of the environment in which the child is learning. Children in the three-five-years range are in a critical period for language development.

In line with the MDAT's domains, the findings in the language domain showed that the first participant in A1 was assessed and the first participant B1 was assessed later. The comparison of the two assessments from the MDAT showed that A1 performed poorly while, B1 performed as expected by the test norm. Participant A1 scored 22/34 while, participant B1 scored 31/34 items from the tool. Participant A1 in the language domain was unable to know actions of objects, was unable to identify at 10 objects from the basket and failed to mention names of 10 objects in the basket.

The second analysis was A2 and B2. The comparison of the two assessments from the MDAT showed that A2 could not perform as expected by the test norm, while participant B2 performed as expected by the test norm. Participant A2 scored 26/34 items, while participant B2 scored 33/34 items from the tool.

The third analysis was for the third participants A3 and B3. The comparison of the two assessments from the MDAT showed that A3 could not perform as expected by the test norm,

while B3 performed as expected by the test norm. Participant A3 scored 30/34 items, while B3 scored 34/34 items from the tool.

The fourth analysis was for the fourth participants A4 and B4. The comparison of the two assessments from the MDAT showed that A4 and B4 both performed as expected by the test norm. Both participants from both study groups scored 34/34 items from the tool.

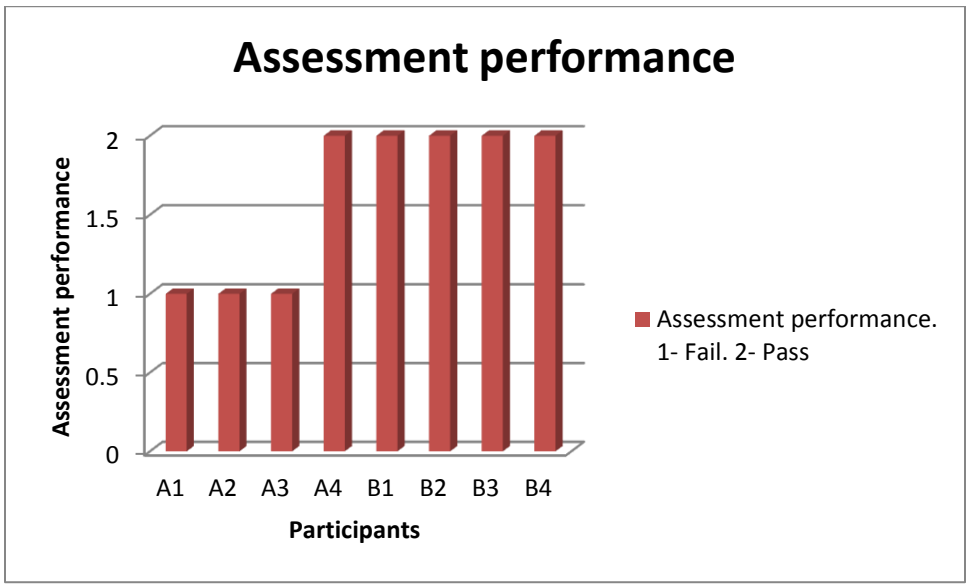

Figure 6: Shows the assessment performance using the MDAT

The language domain in the VABS was assessed in the communication domain which has three subdomains namely the receptive, expressive and written but for the sake of this paper only receptive and expressive subdomain were taken into consideration because they assessed skills mostly in line with the language skills. With the use of the VABS, the language domain was being observed in the communication domain which had subdomain like the receptive

subdomain, which involved the participant to be able to understand, listen, attend and follow instructions. In the receptive subdomain the participant A1 of the adaptive levels showed to be low which was observed in the score that was obtained which was 33, while participant in group B1 of the adaptive level was moderately high with the score of 46. In the expressive subdomain of the communication domain, which involved expressing complex ideas and interactive speech, the participant A1 on the adaptive level showed to be moderately low as 100 was scored, while B1 was high as the adaptive level showed with a score of 150.

With the data that was collected using the VABS the participant A2 in the receptive subdomain on the adaptive scale was low with a score of 30 while participant B2 on the adaptive level was 44. In the expressive subdomain, the participant A2 on the adaptive level was moderately low with a score of 126, while the comparison B2 on the adaptive level was moderately high with a score of 150.

From the data that was collected using the VABS, in the receptive subdomain, participant A3 on the adaptive level was moderately low with a score of 40, while participant B3 was adequate on the adaptive level with a score of 44. In the expressive subdomain, participant A3 was low on the adaptive level with a score of 120, while the participant B3 was high on the adaptive level with a score of 152.

From the forth analysis in the receptive subdomain the participant A4 on the adaptive level was adequate with a score of 40, while with the participant B4 on the adaptive level was adequate with a score of 46. In the expressive subdomain the participant A4 on the adaptive level was adequate with a score of 150, while the participant B4 was adequate on the adaptive level with a score of 150.

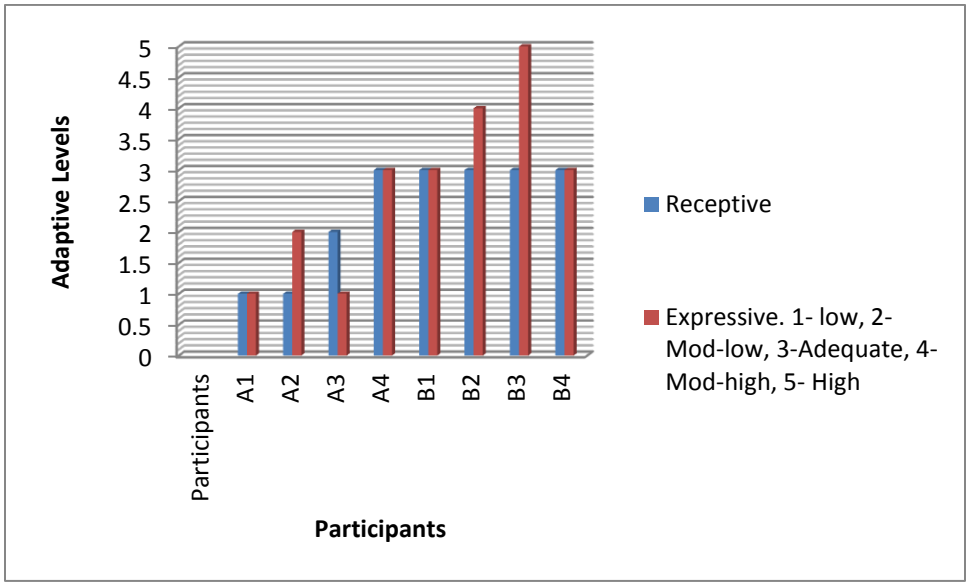

Figure 7: Shows the assessment performance of participants using the VABS

4.6.The medical personnel's observation

The fourth research question was to find out what the medical personnel's observation towards their child's behavior in relation to developmental milestones. From the information that was reported from the interviews. In order to establish the medical personnel's observation towards their child's behavior in relation to developmental milestones several themes emerged from the interview data. These themes included severely delayed, non-medical adherence, late ART initiation and ART withdraw.

Table 5: shows the medical personnel's explanation in relation with the observed delayed developmental milestone in child with seizures/epilepsy.

THEMES	NUMBER OF TIMES
Birth weight	1
Healthy	1
Normal development	3
Severely delayed	2
Non-medical adherence	3
Late ART initiation	1
Malnutrition	1
Cell damage	1
Weakened immune system	1
Opportunistic infections	3
ART withdrew	2

N.B. Numbers of the themes do not add up to 4 as the medical personnel used more than one theme for each case.

From the medical personnel's observation, it was stated that these children who later presented with seizures/epilepsy in their childhood had earlier normal birth weight and used to be very healthy. As stated on one of the case, it was illustrated that, '*this is a child who was born with a very good birth weight and was very healthy his first three years'.* This description meant that this child's early years development was normal just like those of an uninfected child would be.

From the four cases, in three cases which was case 1, case 2 and case 3 it was reported that their children had normal development which was described in different ways. For example, in one case it was explained by the medical personnel that, ‘ *according the mother's words though she concentrated much on the point of time when the child was sick referring to hospitalization that previously the child was developing normally'* . In another case, it was illustrated that, ‘the developmental growth of this child is well in some areas and not well in some areas. According to the mother, the child was developing normally till the time the child had seizure that was when she observed some delay in performance of some tasks. In a different case it was also explained that, ‘*the first few days of admission this child was critically ill but, after recovering this child was not so delayed in all the developmental domains it was in correlation with her age'*. In all the cases that were reported, it was explained that the child had either a normal development from the onset but later was altered with the presenting of the seizure or the child is recovering well and is moving in the right direction now.

It was reported in two cases that the children were severely delayed. As illustrated by the medical personnel, *'but not following the mother's words from my own observation and interaction with the child, he was delayed in all his developmental participation in his life'*. This was equally noticed in how these children would perform during the assessment test. Non-medical adherence was also observed in three cases, which is the inconsistence in taking of ART. This meant that the immune system is really disturbed and the recovering process is delayed too. In one case, late ART initiation was said to be the reason for the noticed delay in development. This was the case in that, the mother knew the status for the child a long time but could not take up the step of initiating the child on ART and this delayed the boosting of the immune system for the child.

In one case, malnutrition was mentioned as one of the reasons for the delayed development that was noticed. It was also reported that, they could have been cell damage on the brain caused by the illness which could have affected the child's developmental growth. This was illustrated as, 'the reason could be that there was cell damage in the brain due to the illness because this child was brought in critically ill and had number seizures'. The medical personnel also explained that these children were brought in with a weakened immune system that could not fight other infections easily. The other reason was that, due to opportunistic infections like meningitis and tuberculosis, as it was narrated, '*HIV lowers the immune system of someone. Henceforth making that person susceptible to any infections that can end up the seizure. The CD4 count was very low and after other medical investigations it found that seizure was due other opportunistic infections such meningitis due to weak immune system*.' The other reason that was attributed to the observed delay in developmental task was due to the ART withdraw.

CHAPTER FIVE

DISCUSSION

5.1. Overview

This part of the report discusses the results that are presented in chapter four. The aim of this research was to determine the achievement of developmental milestones in HIV children with seizures/epilepsy. The findings are presented in line with the research questions in chapter one, which included the following; How is the achievement of the fine motor developmental milestone in HIV+ children with/without seizures/epilepsy? How is the attainment of the gross motor developmental milestone in HIV+ children with/without seizures/epilepsy? How is the achievement of the language developmental milestone in HIV+ children with/without seizures/epilepsy? What is the medical personnel's observation towards the child's behavior in relation to developmental milestones? The discussion will first and foremost outline a summary of the main findings. In relation with the aim of the study, it is evident based on the results that the aim was accomplished. The acquisition of developmental milestones was impaired in our sample of individuals; this was especially true for those that were presenting with seizures/epilepsy, unlike the other group that was presenting without seizures/epilepsy.

This study looked at 3 developmental milestones domains that were assessed with the use of the 2 developmental tools. The MDAT was first used which was administered to the children and then later the VABS which was administered to the parents/caregivers. Afterwards some interviews were conducted with the medical personnel who had frequent interaction with the children while in-patients and with the caregivers. With the use of the MDAT with the children, the tool required most of the tasks to be performed by the children in each domain in relation to the age of that child. With the use of the VABS with the parents/caregivers, this tool contains

questions about the child's development and behavior in relation to their growth. This is only administered to someone who spends much time and knows the child very well; no wonder it can only be administered to the parents or caregivers. It was found that children who were presenting with seizures/epilepsy had delayed achievement of developmental milestone in comparison with those children who were not presenting with seizures/epilepsy. Results indicated that all the cases of children presenting with seizures/epilepsy had delay in at least one domain that was assessed.

5.2.Attaining the fine motor developmental milestone

In line with the aim of the study which was to find out the attainment of developmental milestones in the specific domains, the first research question was to find out the achievement of the fine motor developmental milestone in HIV+ children presenting with/without seizures/epilepsy. The fine motor skill is the ability to use small muscles (fine motor) particularly in the hands. The fine motor domain is an important domain because it is helpful with the daily living skills activities. Babies use fine motor skills to grasp objects. Toddlers and preschoolers use them to do things like hold utensils, work with objects and draw. Being delayed in the fine motor domain for this child, it is possible that this would affect the child's life by interfering with writing and other academic activities or preventing the child from participating at their classmates' level in sports and play. The delay in fine motor skills might show evidence of hand dexterity (fine motor) control problems, such as untidy writing.

Two different tools were used to assess the same domain in the same participant with different tasks. From the results that were collected using the MDAT, it was found that case 1 a 4 year old boy a participant who was presenting with seizures/epilepsy (A participants) was delayed in achieving the fine motor skills unlike the participants who were in the other group (B

participants) which had no one with delays in the fine motor domain. The results that were collected using the VABS also showed that the same participant which is case 1 who was presenting with seizures/epilepsy had a low adaptive level in the fine motor domain. It confirms with the literature in that, these results suggest that among HIV-infected infants who often had HIV symptoms prior to initiation of ART, neurodevelopmental delays may not be completely resolved despite effective ART responses, and more especially in the fine motor domain (Govender et al; 2011).

The same case of a child who had poor fine motor skills that survived to the assessment, later died. This is in line with other studies that showed that poor fine motor skill is a predictor of mortality in children living with HIV (Pearson et al. 2000). This result is also in line with other studies that show that fine motor skills domain is one of the most affected neuropsychological domains associated with pediatric HIV (Knight et al. 2000; Lindsey 2007; Van Rie et al. 2008; Abubakar, 2008). Literature indicates that, fine motor development is a most frequently measured area of functioning, providing consistent evidence of delay in HIV-positive children across all ages. Differences in outcome may be attributable to sample characteristics, such as biomedical factors (e.g. viral load, CD4 count, timing of infection and disease stage), which are known to influence intellectual and psychological outcome (Smith et al. 2000, 2006). With regard to case 1 which had delayed fine motor skills, this was a child who has a CD4 of 51 with viral load over 1 million copies, the worst world health organization (WHO) stage IV and whose medical adherence was not good. This child was also on TB treatment prior to enrollment in the study, the co-occurrence of HIV/AIDS and seizure could have led to the poor performance of the fine motor skills by the child.

5.3.Attainment of the gross motor developmental milestone

The second research question was to find out the achievement of gross motor domain development milestone in HIV+ presenting with/without seizures/epilepsy. Gross motor domain involves the use of large muscles (gross motor) in the body like throwing the ball and catching it, kicking the ball and jumping. The gross motor domain is important because it is helpful for babies to use the gross motor skills to sit up, roll over and begin to walk. Older children use them to do things like jump, run and climb stairs (Mitchell, 2001). It is possible that a child who shows delayed attainment of gross motor skills would have a lack of hand-eye coordination, which causes problems with basic skills such as throwing and catching. The delay in the gross motor skill might as well lead to uncoordinated physical movements, awkward postures and running styles. The gross motor skill is very important in our daily lives because inadequate whole body (gross motor) control skills for example, they may find it difficult to stand on one leg or handle equipment like a bat or racquet. Also requiring more than typical time and effort to master a new physical skill might be one of the consequences for having delayed motor skills. By adolescence, most children with motor skills disorder not only perform poorly in physical education classes, but may also have a poor physical self-image and perform below expectations academically, (Lindsey; 2007).

Gross motor skills delays involve a developmental disorder of movement and posture that leaves children with coordination substantially below that of others of their age and intelligence level. From the data that was collected from the MDAT it was evident that 2 participants who were presenting with seizures/epilepsy were delayed in this domain. These 2 participants were cases 1 who was a 4year old boy and case 4 of a 6 year old girl. This was evident due to the fact that they failed to perform the tasks that they were supposed to in line with their developmental

age and according to the test batteries that were administered to them. When the VABS was used it confirmed with the finding from the MDAT in that the same 2 cases (2 participants) who were delayed in the gross motor domain showed to be moderately low on the adaptive scales of the VABS.

Children's motor development, coordination, muscle tone and reflexes are most consistently and strongly affected by HIV infection (Drotar et al, 1997). The delay is either a reflection of the chronicity of the disease or a direct expression of CNS involvement (Msellati et al, 1993, Bisiacchi et al, 2000). Motor function is compromised early in development in infants with HIV and it is mainly gross motor skills that are delayed (Nozyce et al, 1994; Chase et al, 1995). This may be that gross movements require muscle groups and some degree of physical effort; whereas fine movements are associated with more precise outputs but lower force. Therefore gross motor performance deficits may be related to an overall loss of strength (Parks et al, 1999). The child in this case who had poor gross motor skills had a low CD4 count of 556 and this is the child who performed poorly in all the domains that were assessed. Prior to the enrollment in the study, the participant had TB meningitis and was on treatment for one year from August 2015 to August 2016. The participant had WHO stage IV up to date of HIV. This could be attributed as to why the child had poor gross motor skills.

5.4.Attainment of language developmental milestone

The third research question was to find out the achievement of the language developmental milestone in HIV+ children presenting with seizures/epilepsy. Language skills are the abilities to use and understand language. For babies not older than a year, this includes cooing and babbling. In older children, it includes understanding what's said and using words correctly and in ways that others can understand. This specific domain of the developmental milestone is important in

that it helps with the communication at different levels in our daily living and increasingly for social interactions. For the children that showed delayed achievement of the language skills it might mean that they are much more at risk for reading and psychosocial problems. Children with delayed language domain might have difficulties entering in peer group conversations and can in turn be excluded; giving them less opportunity to learn and practice the social skills they need for peer interaction, (Mitchell, 2001). From the results, children who were presenting with seizures/epilepsy (in A participants) showed to be developmentally delayed in their attainment of language developmental milestone when compared to children who were not presenting with seizures/epilepsy (in B participants). As it was evident from the results, 3 cases of children from (A participants) showed to be delayed in the language domain. The first was case 1 of the 4 year old boy, the second was the case 2 of the 5 year old girl and the third was case 3 the 6 year old girl. Language is a broader system of expressing and receiving information, such as being able to understand gestures, it can be said that it has different subdomains that are specific.

The findings in this domain are similar to the findings of Elley (2011), who found that there were differences in the language score among HIV-infected children who had ART at a mean age approximately 5 months comparing them with HIV-exposed uninfected infants. Three cases showed a marked delay in the language domain, this is not surprising as most seizures are present in the temporal lobe which is associated with the development of language and this is an impairment that is seen in children who presented with seizures without an HIV diagnosis (Abubakar, 2007).

From the results, it was evident that children who were presenting with seizures/epilepsy (A participants) at a delayed performance in their language domain in comparison with the other children who were not presenting with seizures/epilepsy in (B participants). From the scores that

were obtained from both developmental tools administered to the participants, it was noticed that the same participants who were delayed on the MDAT showed to be low to moderately low on the adaptive level of the VABS. This was much proof that those that were presenting with seizures/epilepsy (A participants) were delayed in achieving the developmental milestone in the language domain than those that were presenting with no seizures/epilepsy. The first three cases that performed poor in the language skill were case 1, case 2 and case 3. The children in these cases had late ART initiation which could be associated with their poor performance in this domain. As of case 2 to be specific, this child had the seizure which affected the left side of the brain, which is responsible for language. It must be definite because this child had a hearing problem even at follow up.

The findings in this study are similar with that of (Samia, 2011), who found that the features of developmental delay in the seizure cohort were frequent as compared to that of the non-seizure group. Literature indicates that, developmental delay and neuro-regression are expected features of HIV encephalopathy in children with language delays and are reported in up to 80% of cases in some studies, (Bavdekar, 2003). There are complex layering etiologies that are frequently part of managing patients with HIV. Multiple pathologies occur independently and in response to the consequences of HIV. These pathologies potentially contribute to the delay of developmental milestone achievement. In addition, children with HIV are more likely to have poor nutrition and to live in demographically distressed areas known to predispose them to developmental delay. From the results, the participants' cases who were presenting with seizures/epilepsy in (A participants) were reported to have insufficient sample to examine the viral load, for this case epilepsy in children with HIV infection could be related directly to viral damage, or could be secondary to acquired pathology, (Sinha, 2005).

5.5.Medical personnel's observation towards the child's behavior

The fourth research question was to find the medical personnel's observation towards the child's behavior in relation to achievement of developmental milestones. The results as observed from the medical personnel reported a number of reasons that can be attributed to the developmental delay in children who were presenting with seizures/epilepsy. The medical officer reported that the delay was also due to opportunistic infections, this is similar to literature which states that etiologies among children patients with HIV and seizures include incidental association, direct effects of HIV-1 disease, opportunistic infections, cerebrovascular disease, drug toxicity, and metabolic derangements. Opportunistic infections are considered the commonest cause of seizures in resource-poor countries, (Shanbhag; 2005). The results are in line with results from other studies that have shown that children living with HIV are at risk of having neuropsychological impairment as well as developmental delay (Samia et al. 2013; Rajeshree et al; 2011).

Most of the children in the study had a late initiation on ART and all had delay in achieving developmental milestones. Research has indicated that children who have late ART initiation are prone to developmental delay and poor neurocognitive functioning (Donald et al. 2014; Faye et al. 2004). From the results in both compared groups, it was found that children who were HIV and presenting with seizures/epilepsy were delayed in at least one of the domains that were being assessed unlike those children that were HIV and not presenting with seizures/epilepsy. It was also noticed that those that were presenting with seizures/epilepsy were initiated on ART late in comparison with those that were not presenting with seizures/epilepsy. This might be added to the reason why those who were presenting with seizures/epilepsy were impaired in comparison with the other group that was normally developing. This finding confirms with Benki-Nugent;

(2017) in that, they showed that early ART-treated HIV-infected infants had measurable neurodevelopmental differences compared with HIV-unexposed uninfected infants in the first years of life.

These results are consistent with the findings from the Children with HIV Early antiretrovial (CHER) randomized trial in South Africa, in which infants randomized to deferred ART had lower motor scores at 11 months of age compared with HIV-uninfected infants, (Laughton; 2012). In addition, a second South African study found differences in language and motor scores among HIV-infected infants who had initiated ART at a mean age of approximately 5 months and were followed for six months, compared with HIV-exposed uninfected infants, (Whitehead, Potterton and Coovadia; 2014).

In contrast to CHER, which did not find deficits in other domains, in this paper there was persistent delay. These delays were seen in the language domain in which 3 of the 4 cases that were assessed (A participants) showed to be delayed in this same domain, as compared to those (B participants) that was presenting without seizures/epilepsy with evidence of good ART response with viral suppression, immune recovery and growth. Compared with HUU infants, HIV-infected infants with both viral suppression and immune reconstitution had significantly language impairment. These results suggest that among HIV-infected infants who often had HIV symptoms prior to late initiation of ART, neurodevelopmental delays may not be completely resolved despite effective ART responses.

Delays in milestone attainment in spite of systemic viral suppression or immune reconstitution may reflect early viral penetration to the central nervous system or poor clearance from the CNS following late ART initiation. Furthermore, a study that was conducted by Samia

et al (2012) concluded that children with good medical adherence on both antiepileptic drugs and antiretroviral medications had virologic suppression. This was most likely related to good adherence with medication regimes.

Data from previous studies suggest a narrow window of time during infancy in which developmental deficits due to HIV may be reversed by ART. Thus, among children over 1 year of age, neurodevelopmental effects of HIV may not be reversed by ART in the same way as among infants receiving ART in the first months of life. Therefore, late milestone attainment in HIV-infected infants may reflect poor early infant health, which may have delayed physical and social play activities important for speech and walking attainment.

The data from the present study, showed an abnormal developmental profile for the participants presenting with seizure/epilepsy in (A participants). Despite comparable ages and educational backgrounds, their performance in all of the language and motor tests was significantly below that of their non-seizure/epilepsy peers. The seizure/epilepsy group achieved significantly lower scores for tests of general developmental milestones. They were slower in all or at least one of the domains that was being assessed. These differences may not only be explained by language impairments, but also by deficits in hearing and processing speed in seizure/epilepsy children.

The results above mirror the experience of others in the developed world, Chang (2003), who had reported significant impairment in motor function and language in HIV-infected children when compared to non-infected group.

CHAPTER SIX

CONCLUSION

6.1. Conclusion

Children who are HIV positive are more prone to various opportunistic infections, which is the cause of those children who were presenting with seizures/epilepsy in the study. There's no one specific cause of delays in achieving the developmental milestone. Delay in attaining developmental milestone might be an early sign of a learning or attention issue. Early detection and intervention is important to help children develop the necessary skills. `The etiology and natural history of developmental milestone delays associated with HIV infection in young children remain difficult to identify and predict, because development in these children is determined by the interaction of multiple genetic, health, disease, treatment, and psychosocial factors that may vary in their impact during infancy and childhood.

HIV-infected children who presented with seizures/epilepsy performed poorly compared with HIV-affected children who were not presenting with seizures/epilepsy on assessments of fine motor, gross motor and language development. HIV infected children who had their ART initiation late and had bad medical adherence, achieved lower scores for gross motor and language development. The researchers' results suggest that HIV and the presence of seizures/epilepsy affects the achievement of developmental milestones in children through a direct or indirect pathway (i.e., the presence of HIV in the CNS) and its effect on the child's living conditions.

6.2.Recommendations

This study is the first of its kind to be carried out in Lusaka; it would be more helpful if the study was replicated in other parts of Zambia especially in other urban areas of the country and rural areas. Replication of the study would be helpful in generalizing these results to all citizens of Zambia. A study like this in other parts of the country would help in determining which developmental milestones domains are more affected by the presence of seizures/epilepsy in HIV-infected children.

This information is needed for planning targeted interventions to meet the special needs of HIV-infected children presenting with seizures/epilepsy in various developmental milestones.

There is a need for forthcoming studies to review the efficacy and interactions of antiepileptic drugs and antiretroviral drugs used in children with HIV and seizures/epilepsy. This study support a need for caution and regular monitoring of antiepileptic drug levels when used concurrently with certain antiretroviral agents for optimal seizure control.

The developmental delay in HIV-infected presenting with seizures/epilepsy as compared with HIV-infected presenting without seizures/epilepsy highlights the need for screening and prevention of developmental delay at an early age and calls for access to early interventions for these affected children.

The finding in this study has important clinical implications. To predict risk for later disease progression most accurately, referrals for psychological assessment, motor functioning and language testing should be considered in the initial evaluation of infants, children, and adolescents with HIV infection, these findings also suggest that these assessments should be repeated during antiretroviral therapy.

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