

**THE PREVALENCE AND SEVERITY OF MOTOR
DYSFUNCTION AMONGST HIV-INFECTED CHILDREN AGED
6 TO 12 YEARS IN KATUTURA HOSPITAL
WINDHOEK, NAMIBIA.**

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**A research report submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of
Master of Science in Medicine in Child Health Neurodevelopment**

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DECLARATION

I, Goodluck Nwagboso, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in Child Health Neurodevelopment in the Faculty of Health Sciences at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signed:.....*gcnwagboso*.....Date: 15.11.2017.....

ABSTRACT

Context: Human Immunodeficiency Virus (HIV) has both direct and indirect effect on the growing immature brain that could lead to impaired neurodevelopmental outcome in children. The extent of the motor dysfunctions becomes a matter of concern as the children grow up to school age.

Objective: Our objective was to determine the extent and severity of motor dysfunctions in HIV-infected school-age children at a referral centre in Namibia.

Methodology: A cross sectional prospective study of 60 HIV-infected children aged 6-12 years attending the paediatric HIV clinic in Windhoek was conducted. Severity of motor dysfunction was assessed using the Gross Motor Functional Classification System (GMFCS) and the Manual Ability Classification System (MACS), and clinical data were collected from medical records and from a care-taker questionnaire.

Result: Of the 60 children enrolled in the study, 28(46.67%) were males. The mean age of the children was 9.73 years (S.D = 2.024). The median age at the time of diagnosis was 12 months, with a range of 1 to 73 and a SD of 16.11months. The median age at the time of commencement of treatment was 20.5 months (males) and 35 months (female) with a P-value of 0.0039.

Over five percent (5.1%) of HIV-infected school age children had motor dysfunction scored at Level II of the GMFCS while 7% had a score of Level II on the MACS. A positive correlation existed between time of start of intervention with antiretroviral therapy (ART) and motor function outcomes ($p < 0.0001$), the serum viral RNA load and the presence of seizures in the children (correlation coefficient = 0.31; $P = 0.00327$); serum viral load and developmental delays among the children (correlation coefficient = 0.4; $p\text{-value} = 0.00159$). The CD4 cell count and motor dysfunctions were correlated (correlation coefficient: 0.37; $p\text{-value} < 0.0001$). The CD4 cell count at diagnosis had a significant inverse correlation to the outcome of behavioural problems in the children as well (coefficient = - 0.22; $P\text{-value} = 0.004912$).

Conclusion: A significant proportion of school-age HIV-infected children have neurodevelopmental challenges and gross motor dysfunction in particular. A study with standardized tools to ascertain the extent of impairment in the other domains of development is needed for a more comprehensive understanding of the effects of HIV infection on school-age children.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal Care
ART	Antiretroviral Therapy)
ARV	Antiretroviral
ARVs	Antiretroviral medicines
AZT	Zidovudine
BBB	Blood-Brain Barrier
CDC	Centres for Disease Control and Prevention
CNS	Central Nervous System
C-section	Caesarean section
CT scans	Computerized Tomography Scan
DNA	Deoxyribonucleic Acid
ECD	Early Child Development
EEG	Electroencephalogram
ELIZA	Enzyme-linked Immunosorbent Assay
FM	Fine Motor

GM	Gross Motor
HAART	Highly-Active Antiretroviral Therapy
HAZ	Height-for-age z-score
HCZ	Head circumference-for-age z-score
HIV	Human Immunodeficiency Virus
HIVE	Human Immunodeficiency Virus Encephalopathy
IUGR	Intrauterine Growth Restriction
LPVr	Lopinavir
LBW	Low-Birth Weight (<2.5kgs)
MACS	Manual Ability Classification Scale
MRI	Magnetic Resonance Imaging
MTCT	Mother-to-Child Transmission (of HIV)
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NtRTIs	Nucleotide Reverse Transcriptase Inhibitors
NVD	Natural Vaginal Delivery
NVP	Nevirapine

OPD	Out patient Department
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother-to-Child Transmission (of HIV)
RNA	Ribonucleic Acid
UNAIDS	Joint United Nations Programme for HIV/AIDS
UNICEF	United Nations Children's Fund
USA	United States of America
USD	United States Dollar
WAZ	Weight-for-age z-score
WHO	World Health Organization
WHZ	Weight-for-height z-score

CHAPTER ONE: INTRODUCTION

1.1 Introduction

The burden of the Human Immunodeficiency Virus (HIV) infection has continued to plague countries across the world. In 2015, it was estimated that there were about 36.7 million people infected with the HIV across the world with 22.5 million found in the Sub-Saharan Africa (1,2) Children aged 0-14 years account for about 3.1 million worldwide; 2.9 million are in sub-Saharan Africa.

HIV is a multi-systemic infection with diverse organ-specific manifestations (2, 3). Neurological manifestations may be the presenting signs in about 18% of childhood infections (3, 4).

HIV is both neurotropic and neurotoxic, affecting the central nervous system (CNS) by direct (nerve toxicity) and indirect (chemical) effects (5, 6). HIV crosses the blood brain barrier and invades the CNS through infected macrophages (5). The cumulative effect of these assaults on the immature CNS results in encephalopathy, characterized by delayed or defective motor, speech and neurocognitive development (7). Encephalopathy is either static or progressive. Children with static encephalopathy have slow progression of the disease but still retain acquired skills while those with progressive type exhibit rapid decline and loss of acquired skills.

HIV-infected children show more delay in their development than their HIV-exposed and uninfected peers. The range of neurological deficits varies but manifestations include neurocognitive deficits, motor delays and language delay (8).

The degree of CNS manifestation is often related to the severity of the infection as measured by CD4 count and the viral load. Mode of transmission and the age at infection play a role in severity of infection. Infants and younger children manifest the most severe and global neurological dysfunction, while older children have more specific neurological dysfunctions. Children with early onset of HIV encephalopathy have smaller head circumferences, lower birth weights, and more severe neurological disease (4, 9). School-age children display similar patterns and the true extent of the detrimental effect become more pronounced as they start school activities (10).

Most paediatric infections are vertically transmitted from mother to child in utero, at the time of birth or through breastfeeding, accounting for up to 90% of childhood HIV infections. Without treatment, approximately 25%–50% of HIV-positive mothers will transmit the virus to their newborns during pregnancy, childbirth, or breastfeeding (11). The third trimester is the period of highest transmission due to the ease of passage of the HIV through the placenta.

The initiation of Prevention of Mother to Child Transmission (PMTCT) programmes reduces the rate of transmission to as low as 1% in children (12, 13). The current World Health Organization (WHO) guidelines recommend that all pregnant and breastfeeding women living with HIV, regardless of CD4 count or the clinical stage should receive life-long ART. This reduces the risk of mother-to-child transmission (11).

ART alters the progression of paediatric HIV infection and reduces the prevalence and severity of neurological complications. Prompt initiation of the ART saves life, improves disease outcome and delays the onset of encephalopathy. ARV drugs with minimal side effect and effective blood brain barrier (BBB) penetrative abilities are preferred; AZT, ABC, LPVr are among the preferred first line ART drugs (14, 15).

Various tools have been used to assess the degree of neurological complications of paediatric HIV. The tools are dependent on the subject of interest and the design of the study. The motor functional ability can be categorized by various tools which give a standardized outcome when the degree of motor dysfunction of a child is assessed (16). Two of such tools have been commonly described and are used in the assessment of the child with motor dysfunction (16). The Gross Motor Function Classification (GMFCS) is designed for the measurement and classification of the motor functional ability of a child based primarily on truncal and lower limb movements. It defines the extent a child can perform or exhibit natural movements with or without assistance (16). In addition, the motor function of the child's hands can be assessed by the Manual Ability Classification System (MACS). MACS is a 5-level classification system that can be used for children in the age group of 4 to 14 years. It measures grossly what a child can do with one or both hands (17).

1.2 Research Question

With early initiation of ART, more HIV-infected children survive to the school going age. While there is notable progress in the management of the HIV-infected child, it is not known how many

of these children of school-age have motor complications resulting from the infection. More so, the prevalence and extent of motor dysfunctions in particular, remain largely unknown.

The school-going age of 6 -12 years is a very critical period in the formation of the intellectual, motor and psychosocial make up or identity of a child. HIV does impact on the motor function of these children, which in effect affects their performances at school, sports and social interactions, and integration in the learning community (6). However, it is not clear what might be the extent of the impact of HIV infection on the gross motor development of children in this age group. Most research reports focus on children within the first 2 years of life and on younger pre-school children under six years of age (10).

In our setting, there is lack of information addressing this subject. There is paucity of literature and research reports on the prevalence and severity of motor dysfunction amongst HIV-infected school-going children in this age bracket. Furthermore, there is paucity of studies that have assessed the functional abilities of children of school-going age using instruments that are care-giver and observer reportable like the GMFCS and the MACS. This particular research project therefore aims to contribute to the field of knowledge on the extent of motor dysfunction among HIV-infected school going age children and fill the identified gaps in research and literature.

It is hoped that findings from this study will provide information to care-givers, paediatric physicians and health planners on the extent and severity of HIV-induced paediatric motor dysfunctions and provide the basis for further research on the questions that might arise from the study.

1.3 **Aim of the Study**

The aim of the study is to describe the prevalence and severity of motor dysfunction amongst HIV-infected children aged 6 to 12 years in a paediatric clinic in Windhoek, Namibia.

1.4 **Objectives of the Study**

The objectives of the study are

To determine the prevalence of motor dysfunctions amongst children with HIV infection

To describe the severity of motor dysfunction in HIV-positive children

To describe the associated morbidities in the children with HIV infections

To describe the relationship between motor dysfunctions and:

- (a) Age at diagnosis,
- (b) Viral load;
- (c) CD4 Count at diagnosis
- (d) Compliance with Antiretroviral therapy (ART)

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of HIV

The burden of the Human Immunodeficiency Virus (HIV) infection has continued to plague countries across the world. In 2015, it is estimated that there are about 36.7 million people infected with the HIV across the world with 22.5 million found in the Sub-Saharan Africa (1,2) Children aged 0-14 years account for about 3.1 million worldwide; 2.9 million of them are in sub-Saharan Africa.

Namibia has an estimated 210,000 [200,000 – 230,000] people infected with the virus. The number of infected children under 15 years is estimated at 10,000 [9400 - 11 000] while 120,000 [110000 – 130,000] are women aged 15 years and above who are in the reproductive age bracket. The national survey in 2015 reported a sero-positive prevalence of 13.3% nationwide amongst the adult population with a national mortality of 3100 (2500 – 3900). Orphans due to AIDS aged 0 to 17 years are estimated at about 45 000 [36 000 - 52 000] While there is a decrease in the rate of new infections, the global prevalence continues to rise. As the ART becomes more accessible, the number of deaths from HIV/AIDS related conditions decrease and number of surviving people increase (1, 18).

Improved access to surveillance (testing) and ART options across many regions of the world have led to the global decrease in death rate. As a result, there are more of people with chronic illness than terminally ill persons (19). Countries are reporting decreasing numbers of new

infection. From 2010 to 2015, Namibia had a reduction in new infection rate of 4.7%, Sub-Saharan Africa 8-14%, and globally, 6%. The number of HIV-infected children has dropped by 50% over the same time period (18). This has been attributed to improving surveillance, testing, the PMTCT initiative and improving access to the ART in many countries, including resource – constrained nations (19).

2.2 Virology of Human Immunodeficiency Virus

HIV is a retrovirus composed of Ribonucleic Acid (RNA) instead of Deoxyribonucleic Acid (DNA). Retroviruses possess reverse transcriptase enzyme that gives them the unique property of transcribing their RNA into DNA after entering a cell. The retroviral DNA can then integrate into the chromosomal DNA of the host cell, express itself and replicate (20).

There are genetic variations among human immunodeficiency virus. There are five major subtypes of HIV, designated A through E, each known to predominate in different geographical areas of the world. The subtype B is more common in North America. In contrast, subtype C predominates in sub-Saharan Africa (21).

Significant variation occurs within each subtype leading to a situation where a person can be infected with several strains of the virus. These variant strains are attributed to the poor replication accuracy exhibited by the virus. The cumulative effect of these multiple strains of the virus is rapid progression in drug resistance (22).

HIV has several strains of which the most common affecting human beings are the Types 1 and 2. The HIV-1 was first transmitted from Chimpanzees to man. The HIV-2 infection is reported to be from the animal variety of the virus, the simian subtype, found in primates in Cameroon, West Africa where the first transmission from primates (monkeys) to human being allegedly occurred (23). HIV-2 is less infectious than HIV-1.

2.3 Transmission and acquisition of HIV

HIV can be acquired through vertical or horizontal routes. About 90% of adult HIV infection is acquired through horizontal transmission occurring through unprotected sex with a HIV-infected person, through transmission of blood and blood products, or sharing unsterilized sharps like needles (also by accidental pricks) or circumcision blades (24).

The majority of paediatric HIV transmissions in Sub-Saharan Africa, Namibia inclusive, are by the vertical route, that is, from mother to child (25). Interception of the vertical transmission can reduce the rate of childhood infection. Thus, the Prevention of Mother-to-Child-Transmission (PMTCT) initiative has become a cornerstone in the management of childhood HIV programme, and it has been referred to as one of the major breakthroughs in HIV/AIDS management (26).

There are several factors that increase the likelihood of mother to child transmission (MTCT) of the HIV. These include high maternal viral load, maternal malnutrition, untreated sexually transmitted infections (increasing the risk as much as 6-10 folds), prolonged rupture of

membranes during labour, invasive delivery procedures that increase the incidence of blood interchange between mother and infant. Malaria is known to increase the chances of MTCT due to its effect on the placenta (27, 28.).

Most vertical transmission occur either in utero, at the time of birth, or through breastfeeding, all accounting for up to 90% of paediatric HIV infections. Without treatment, approximately 25%–50% of HIV-positive mothers will transmit the virus to their newborns (11). It is estimated that 5-10 % of MTCT occur in utero, 10-20 % at birth and 10-20 % during breastfeeding (29).

2.3.1 Transmission in Utero

Mechanisms of transmission are thought to be related to breakdown of the integrity of the placenta, leading to microtransfusions of viremic maternal blood across the placenta to the foetus. Several factors are thought to increase the risk of transmission in utero (30, 31) in HIV infected mothers, such as concurrent maternal or foetal infection as well as infections that target the breast tissues, the placenta, amniotic fluid (chorioamnionitis), and the membranes. The co-infections increase the release of cytokinines and inflammatory agents which enhance the replication of the HIV locally and systemically, increase permeability, and reduce the natural defences in MTCT (30, 31). The third trimester is the period of highest transmission due to the ease of passage of the HIV through the placenta (32).

2.3.2 Transmission during labour

It is postulated that the mechanism of transmission during labour and delivery is through the contact of the infant mucosal membrane with the HIV and the vaginal secretions at the time of birth. Prolonged labour, and thus, prolonged contact period between the foetus and maternal blood materials, increases the risk of MTCT. Furthermore, it is thought that during labour contractions, there are microtransfusions through the placenta which increase the risk of MTCT (30, 31).

2.3.3 Transmission through breastfeeding.

Breast milk is the preferred nutrition for the newborn. It contains most of the nutritional requirements for the baby. The risk of transmitting the HIV to the baby by a HIV-infected mother through breastfeeding does exist (33). There is evidence that breast milk harbours the HIV, and breastfed children have higher chances of acquiring HIV than those not breast fed. There is also higher regional incidence of paediatric HIV infection where children are breastfed (34).

Factor that increase the risk of MTCT via breast feeding include early mixed-feeding, that is before six months of age when the infant's gastrointestinal tract is not matured and highly

susceptible to damage (35), abrupt cessation of breastfeeding, and mastitis or breast abscess (19,27) .

2.4 Neuropathogenesis of HIV in children

Human Immunodeficiency Virus is a multi-systemic infection with diverse organ-specific manifestations (3) including neurological manifestations occurring as presenting signs in about 18% of paediatric infections (4). HIV invasion of the CNS may lead to irreversible neuronal damages that may cause persistent neurological deficits even after the suppression of viral load with ART (6). The HIV enters the brain through the blood brain barrier, transported by infected macrophages and monocytes (36). There is a further passage of free HIV virions and viral proteins into the CNS through the blood brain barrier via transcellular and paracellular pathways (37). HIV infection causes a chronic low-grade inflammatory state, comprising persistent monocyte and macrophage activation, vascular endothelial activation, and a hypercoagulable state (6). Furthermore, the CNS is a special compartment where HIV can remain undetected by the ART thus causing continued neuronal injury, continued multiplication and mutation (6, 38, 39).

HIV affects astrocytes, microglia, monocyte-derived macrophages oligodendrocytes, and neural progenitor cells. These cells produce viral products, chemokines, proinflammatory cytokines, and small molecules, such as platelet-activating factor and quinolinic acid that cause further

immune activation and cerebral injury. The fusion of these cells leads to the formation of giant multi-nucleated cells which are the hallmark of HIV encephalopathy (6, 40). HIV causes a decrease in the number of neural progenitor cells (responsible for neural regeneration and multiplication of astrocytes, oligodendrites). This leads to poor repair and regeneration of brain cells thus causing further insult to the CNS – encephalopathy (6). So the effect of HIV on the CNS is through direct HIV invasion of the brain and through chemical and immune responses.

2.5 Testing and Diagnosis

Diagnosis of HIV infection in children under the age of 18 months poses a challenge with the conventional available rapid tests due to the persistence of maternal antibodies in the child (20). The diagnosis of children over 18 months and older on the other hand are accurately made by HIV serological testing. Upon cessation of breastfeeding, confirmation of HIV in a child can be ascertained after six weeks, a period during which maternal antibodies are no longer detectable (41). Therefore, the presence of HIV antibodies in this population is a reliable means of definitive diagnosis.

So, for children younger than 18 months, a diagnosis of HIV infection is based on a positive virological test for HIV or its components (HIV RNA or HIV DNA or ultrasensitive [Us] HIV p24 Ag) confirmed by a second virological test performed on a separate specimen taken more than 4 weeks after birth. Serological testing for HIV is not applied for definitive or confirmatory

diagnosis of HIV infection in children until they are 18 months of age (42). In children older than 18 months and adults, the diagnosis of HIV is made with an enzyme-linked immunosorbent assay (ELISA) to detect HIV antibody; this can be followed by a confirmatory Western Blot test (20).

Early diagnosis and confirmation of HIV status facilitate prompt treatment and care of HIV-infected infants and children. This should be as early as two months of age (42). In children who continue to be exposed to HIV through breastfeeding, repeat testing should be done only six weeks after cessation of breastfeeding, as this window period reliably indicates the true status of infection (20, 41).

2.6 The effect of ART on the neurodevelopment of an HIV-infected child

ART causes a significant reduction in the MTCT of the virus (11) and has significant effect on the management of HIV-infected children. The ARV drugs alter the natural progression of the disease especially encephalopathy when commenced early in childhood (43).

The AZT and the newer combination therapy are known to have positive effect on the neurodevelopmental outcome of children with HIV infection. Few ARV medicines, including AZT, ABC and NVP, cross the blood brain barrier but resistance to NVP is a growing concern (19).

The effects of already established encephalopathy are often not reversed by the ARV due to a number of possible reasons. The causes of the continued manifestation of the neurocognitive deficits despite effective ART are multifactorial and may include continued irreversible CNS injury prior to ART initiation, continued viral replication in the CNS, ongoing neuroinflammation, neurotoxic effects of ART, and socioeconomic and psychosocial factors (43).

2.7 Manifestations of HIV Encephalopathy

It is estimated that about 20% to 60% of children infected with HIV have neurologic involvements, either as primary effect of the HIV or secondary effects mediated by the macrophages and cytokines (9). Majority of the children do not develop the severe forms of the neurological complications. Only about 18% of the children with CNS involvement develop the severe forms of the disease. In children, there is a predominant involvement of the CNS with sparing of the peripheral nervous system (PNS), and the brain being more affected than the spinal cord (9, 44).

HIV encephalopathy is the predominant presentation of neurological deficit in HIV-infected children and can start as early as in the first few months of life but manifestations occur in the second to third year of life (9,45,46). The risk factors for HIV encephalopathy include low weight, anaemia, constitutional symptoms, low CD4⁺ count, and high plasma HIV-RNA load

(46). With the introduction of Prevention of Mother to Child Transmission (PMTCT) of HIV programmes and routine HAART, there is however a continuous decline in the prevalence and severity of the CNS involvement in paediatric HIV infections, thus reducing the number of children that present with the severe forms of HIV encephalopathy (HIVE) (47).

The multiple effects of HIV infection on the CNS and the brain in particular generally result in the development of HIVE (35,48). Paediatric HIV encephalopathy is a clinical diagnosis that results from the various assaults, diseases, damage or malfunction of the brain caused by HIV on the immature brain of the child. HIV encephalopathy is a Clinical Stage 4 disease according to the WHO classification of AIDS defining illnesses (48).

According to the Centres for Disease Control and Prevention, HIV encephalopathy (HIVE) is defined by one or more of the following conditions:

- progressive encephalopathy over a period of two months in the absence of another causative illness
- Failure to attain, or loss of developmental milestones or intellectual ability
- Progressive impaired brain growth

Acquired symmetric motor deficits accompanied by paresis, pathological reflexes and /or gait disturbances (49, 50).

Neurological dysfunction is often one of the earliest signs of HIV infection in infants and young children (19) and can manifest as cognitive, language or motor delays. The neurologic

manifestations occur in two broad categories namely, conditions related directly to HIV-1 infection and secondly, those manifesting as complications secondary to the effects of the infection (9).

Vertically transmitted HIV infections in children differ in their characteristics from those found in adult infections because of the vulnerability of the immature brain tissue, nerves and supporting structures. Global motor deficits are noted in children due to impaired myelination which ultimately affects the fibre projections and commissural connections (9, 51).

Encephalopathy may present as a progressive or static type. In the progressive variety, the children manifest within 2-5 years post-infection. Those with progressive encephalopathy demonstrate a rapid decline and loss of acquired skills and milestones. Progressive encephalopathy can be acute or may progress slowly over the years (52).

Sherr, et al indicated that the HIV-infected children who function consistently below the level of the mean on standardised assessments, but continue to acquire fresh skills, may be regarded as having a static type of HIV encephalopathy (53). There is acquisition of fresh and new skills at a slower rate than normal as well as the retention of the previously acquired skills.

The behavioural aspects of the complication become obvious initially followed by developmental delays and then the more serious conditions like motor function and skills deficits

appear. With progression of the encephalopathy, extra-pyramidal and cerebellar signs like rigidity and ataxia begin to manifest (52,54). The major areas of dysfunction are impairment of brain growth, language impairment, decline of cognitive function and clinical motor dysfunction (49). The cognitive, language and motor delays and dysfunctions are discussed below.

2.7.1 Cognitive dysfunction

HIV-infected children exhibit cognitive deficits in the areas of language and fine motor skills, verbal and memory functioning, visual-spatial integrative ability, and executive functions (55, 56). These children show marked cognitive delay that may involve intelligence deficit, behavioural impairments, learning impairments, attention-deficit disorders, impairment of spatial memory, reduced intellectual function, with poor ability in sequential processing. Other behavioural problems associated with HIV encephalopathy include psychosomatic, learning, impulsive-hyperactive, conduct disorder, and anxiety problems (57).

2.7.2 Language Delay

Language delay is common in paediatric HIV infection. Language utilizes both motor and cognitive functions. Both expressive and receptive language impairments occur in HIV-infected children with the expressive impairment developing more rapidly than the receptive. Both impairments are worse after 2 years of age despite ARV treatment (58). Even clinically stable

HIV infected children can develop linguistic impairments. A clinical assessment is needed to identify such subtle impairments (59,60).

2.7.3 Motor delay

Motor delay in HIV-infected children may be an early indicator to a presumptive diagnosis of the infection (61). The delays are apparent in the early post-natal period as basic motor milestones are absent. Up to two thirds of the HIV infected children display significantly delayed motor performance (62). This damage may manifest as abnormalities in muscle tone, weakness and poor coordination causing impaired ability to achieve motor milestones. Gross motor delay is more prominent than fine motor activity delay (63).

2.8 Prevention of Mother to Child Transmission (PMTCT)

Initiation of PMTCT programmes could reduce the transmission to as low as 1% from 25-45% in untreated cases (12, 25). The basic model is to treat all pregnant women with a prophylactic ARV if the CD4 is normal, full ARV treatment to those with low CD4, and administration of ART during delivery and breastfeeding. It also involves monitoring the baby and providing prophylaxis to the baby (11).

The current WHO guidelines recommend two interventions: a) providing lifelong ART to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage or b) providing ART to pregnant and breastfeeding women with HIV during the mother-to-child transmission risk period and then continuing lifelong ART for those women eligible for treatment for their own health (11). The WHO guideline advocates

- Earlier antiretroviral therapy (ART) for a larger group of HIV-positive pregnant women to benefit both the health of the mother and prevent HIV transmission to her child during pregnancy and breastfeeding.
- Longer provision of antiretroviral (ARV) prophylaxis for HIV-positive pregnant women with relatively strong immune systems who do not need ART for their own health. This would reduce the risk of HIV transmission from mother to child.
- Provision of ARV prophylaxis to the mother and child to reduce the risk of HIV transmission during the breastfeeding period and beyond as there is now enough evidence for WHO to recommend life-long ARVs while breastfeeding (64).

The number of HIV-infected pregnant women who are on ART has increased worldwide, with improving access to PMTCT in many countries. It is estimated that 70% of HIV-infected mothers are on ART. This has good prognosis for the reduction of the transmission of the virus to the unborn child (65). Namibia has experienced this reduction in the MTCT with a drop in number of children living with HIV from 14,000 to 10,000 between 2013 and 2015 (2).

The key elements of Namibia PMTCT are the primary prevention of HIV infection; prevention of unintended pregnancy in HIV-infected women; prevention of HIV transmission from HIV-infected women to their infants; and provision of comprehensive care to mothers living with HIV as well as their children and families (14).

2.9 Treatment of Paediatric HIV

The WHO advocates the commencement of prophylaxis to children born to HIV-infected mothers, irrespective of the fact that the mother may have been on full treatment or on only prophylaxis. The treatment of both mother and child should continue throughout breastfeeding and weaning time until about 6 weeks after cessation of breastfeeding (64).

The Namibia treatment protocol calls for all HIV-infected children and adolescents <15 years to be initiated on ART irrespective of CD4 count and clinical stage. The choice of ARVs in children is informed by age, weight, previous PMTCT, Nevirapine exposure and comorbidities (14). The classes of ARV used in the Namibia context include the Nucleoside Analogue Transcriptase Inhibitors (NRTIs), Non-Nucleoside Analogue Transcriptase Inhibitors (NNRTIs) and the Protease Inhibitors (PIs).

The NRTIs class of ARV inhibits the transcription of viral RNA to DNA, a step necessary for the virus reproduction. Zidovudine (AZT), lamivudine (3TC), Stavudine (D4T), Abacavir

(ABC), and didanosine (ddl) are in this group. Tenofovir, though a nucleotide analogue, is included in this class of drugs (19).

The Non-Nucleoside Analogue Transcriptase Inhibitors (NNRTIs) are chemically different from the NRTIs but also inhibit the transcription of viral RNA to DNA by transcriptase enzyme. This class includes Nevirapine (NVP), Efavirenz (EFV), Etravirine and Delaviridine (DLV).

The Protease Inhibitors (PIs) act on the viral enzymes (protease) responsible for the cleavage of the long chain of amino acids produced by the virus. This stops the maturation of virions, and thus slows down viral reproduction. This class includes lopinavir (LPV), Ritonavir and Darunavir which are paediatric-friendly PIs (14, 19).

Combination therapy is advocated and it includes a combination of three ARV drugs. This is known as the highly active antiretroviral therapy (HAART) and may consist of two NRTIs and one NNRTI or two NRTIs and one PI. The combinations vary and are dependent on individual patients as well as guidelines established by the managing authorities.

In Namibia, the preferred first line ART regimens for children less than 3 years old or <10 kg is ABC/3TC/LPV/r. For children 3 to 9 years old and 10 kg to <35 kg, with no previous PMTCT NVP exposure, ABC/3TC/EFV is given, while those with previous PMTCT NVP exposure,

ABC/3TC/LPV/r is recommended. For children and adolescents ≥ 35 kg and at least 10 years old, the choice is TDF/3TC/EFV (14, 64).

2.10 The impact of HIV on growth and development

Research indicates that children born to HIV-infected mothers display poorer growth and have higher morbidity and mortality rates than children born to HIV uninfected mothers (66, 67). HIV infection has a direct effect on growth. Growth rate has been demonstrated to have an inverse relationship with viral load and viral genome replication rate. Growth failure, wasting and loss of active lean tissue are associated with increased mortality and accelerated HIV-AIDS progression in children. Growth failure is a prognostic indicator of mortality. Multiple causes of growth failure in HIV-infected children have been documented. Decreased nutrient intake, increased energy requirements, malabsorption and psychosocial issues, all being associated with HIV infection, may contribute to under-nutrition (68).

Both micronutrients and macronutrients are necessary for reduced morbidity and motility in HIV-positive infants and to improve growth. Micronutrients, including Vitamin A, reduce respiratory infections, and diarrhoeal illnesses. Zinc is known to reduce diarrhoea and multivitamins are associated with improved bone minerals. Macronutrients provide energy, fat and protein that are essential for improving the health and immunity of the child (69).

Poor growth pattern is noted in utero in HIV infected mothers, but cannot be entirely attributed to HIV infection since most of the infections in utero occur in the last trimester. However, it is reported that in the postnatal period, there is evidence of poor growth in weight and height in HIV-infected children as early as 3 months of age (68). Unlike protein-energy malnutrition where there is evidence of weight loss before height impairment, there is a concurrent impairment of weight and height in HIV-associated growth impairment. This suggests therefore that there are other mechanisms other than protein-energy deficiency that may account for this (70).

HIV-infected children have a higher risk of developing malnutrition due to the chronic nature of the infections, inducing poor appetite, poor nutrient absorption and risk of gastroenteritis. The effects of HIV on nutrition and growth are both direct and indirect. The direct effect of HIV on the gut and immature intestinal immune system leads to poor absorption of macro- and micro-nutrients, diarrhoea, infection and poor weight gain and growth (71). The indirect effects are associated with the general morbidity which compromises the child's ability to fight infections (72).

2.11 Effect of Nutrition on Neurodevelopment of HIV-infected children

Nutrition has profound effect on the neurodevelopment of children. Lack of certain nutrition and elements have far-reaching effect on the child. Cretinism, which is associated with severe

physical and mental development, is caused by lack of iodine in the diet of a child (69). Most of the early nutritional requirements of a child are available in the breast milk. Importance of breastfeeding and adequate nutrition in HIV infected children are highlighted in research (64).

2.11.1 HIV and Breastfeeding

Breast milk is the healthiest food for a child as it contains most of the nutrients required in the first 2 years of life. In addition, breast milk provides vital immunity through antibodies contained in the milk. It is recommended that even with HIV-infected mothers, babies should be fed exclusively with breast milk for 6 months despite the fact that transmission of the HIV occurs through breastfeeding. Research has indicated that the benefits of exclusive breastfeeding in children by HIV-infected mothers outweigh the risk of HIV infection in the child, especially when combination ART is provided to the mother and child (66).

The introduction of the PMTCT of HIV programme and the provision of ART to pregnant mothers have significantly reduced the transmission of the HIV to the children either in utero, at birth or during breastfeeding. Mounting evidence suggest that the impact of exclusive breastfeeding (where the child is breastfed only with breast milk , with no water or any other foods except for vitamin drops) for 6 months on HIV transmission in breast-fed children of HIV- positive mothers is very significant (64).

Literature indicates that up to 1.3m children are saved worldwide annually by implementation of the exclusive breastfeeding programme especially in resource-poor settings (73). The recommendations of WHO are that breastfeeding should be encouraged in HIV-positive mothers with HIV-infected and HIV-uninfected children provided ART is available to both child and mother throughout the period of breastfeeding.

Specifically, WHO recommendations are:

- In settings where health services provide and support lifelong ART, including adherence counselling, and promote and support breastfeeding among women living with HIV, the duration of breastfeeding should not be restricted.
- Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer (similar to the general population) while being fully supported for ART adherence .
- Mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first six months of life, introducing appropriate complementary foods thereafter and continue breastfeeding.
- Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided (64).

Research reports support the importance of the WHO initiative and guidelines on exclusive breastfeeding among HIV-infected and HIV-uninfected children (73).

2.11.2 Impact of nutrition on neurodevelopmental outcome in children

Adequate nutrition is very important in the developmental and motor outcomes in children in general. It is even more so in HIV infected children. As early as the 3 week of gestation, the neural tube and neural plate begin to develop into the future brain of the child. Nutritional deficiency at this stage impacts negatively on the development of the brain and the child may fail to reach their developmental potential in motor, cognitive, speech and socio-emotional developments (63, 72).

The major areas of brain development which are critically affected by poor nutrient supply are brain cell formation, neuron proliferation, axonal and dendrite formation and growth, myelination, synapse formation, arborization and pruning. These lead to reduced brain size and mass, and thus, reduced neurocognitive developmental potentials and function. Protein energy malnutrition, lack of zinc, iodine, choline, vitamin B and folic acid have detrimental effect on neurodevelopment. Lack of vitamin B and folic acid leads to neural tube defects like spina bifida; lack of zinc causes poor synaptic formation, impaired cell division and poor dendritic arborization. Lack of iodine may lead to decreased levels of IGF-1 and IGF-1 binding protein (73). Intervention with nutrient supplements in pregnancy and infancy leads to improve outcome in the neurocognitive and motor development of the children, especially in the HIV era.

Childhood growth is a challenge in Namibia. Report of a survey in 2013 indicated that 24 % of children under 5 years of age were stunted, 6 % were wasted, and 13 % were underweight (75). Drought and poor sanitation have been associated with the impaired levels of nutrition and thus, growth in the children. However, childhood HIV infection as an independent modifiable risk factor for poor nutritional outcomes (growth) has made substantial contribution to negative nutritional outcomes in children (71).

2.12 Disability amongst school going children in Namibia.

Fifteen percent of the world population lives with disability of which 2-4% suffers significant impairment and incapacitation (76). The estimated number of persons with disabilities in Namibia was 98,413 in 2011 with 59.74% being females. Children aged 0 - 4 years accounted for 6% while 5 – 14 year age group accounted for 16.3%. In all, about 22.3% of all disabled persons in Namibia are children from the ages of 0-14 years. This has serious impact on the education and training of the children. Only 13% of the children with disability aged 0-4years attend any form of Early Childhood Development programme but in the age group of 5-14 years, about 70% are enrolled in different forms of educational training programme (77).

Disabled people face limited access to basic amenities and are disadvantaged in society. Children are mostly affected. Disability correlates with poor and limited access to education, health, information, employment and transportation. They are often marginalized in the society; they

have poorer health status, live under poor socioeconomic conditions and underachieve in education (78).

The natures of the disabilities vary. While few of them may be apparent, every form of disability is a challenge. In Namibia, amongst the school-going age children (5-14 years), the distribution is as follows: physical limb impairment (27.95% - upper limb 9.83% and lower limbs 18.12%), visual impairment (17%), mental disability (12.76%), blindness (11%), hearing impairment (8.1%), deafness (5.58%), dumbness (5.01%) , speech impairment (4.98%), autism (1.08%) and albinism (1.01%) (76 , 77). Motor disability amongst the children is a significant portion of the overall disability, namely, 27.95%. That means that about one-third of school-going children have significant motor dysfunction.

The disabled school-going children face multiple challenges. Stigmatization, while being addressed, remains a major obstacle. Acceptance of these children into the main streams of education is an on-going challenge. Lack of disability-friendly institutions, infrastructure and transportation systems tend to hamper their assimilation into the schools. Limited funding makes the provision of specialized schools even more difficult. Additional challenges face the few disabled graduates including assimilation into the work place or schools of higher learning. Addressing these challenges will provide better opportunities for these children (78, 79).

CHAPTER THREE : METHODOLOGY

Introduction

This chapter reports on the method utilized in the research work. It highlights the research setting, ethical considerations in place, the study design, selection of the subjects, materials and measurements, as well as the procedures used to collect data and data analysis.

3.1 Research Setting

The paediatric department of Katutura State Hospital in Windhoek is a national referral centre. The study was conducted in the HIV unit of the department. The centre is run by medical doctors, assisted by trained senior nurses with supervising visiting paediatric specialists. The clinic renders out-patient services. It is located in the main hospital premises and has a dispensary. Other services including radiology, laboratory and other ancillary services are obtained from the main hospital facility.

3.2 Ethical Considerations

Ethical approval was obtained from the University of Witwatersrand Ethics Committee (Annexure 1) as well as from the Permanent Secretary, Ministry of Health and Social Services, Namibia; the Senior Medical Superintendent of the Katutura hospital and from the Head of

Department in Paediatric HIV Services at the clinic. These documents are all attached in the annexure.

Informed written and signed consent was obtained from the mother or care-taker of every child that was involved in the study. Every mother or care-taker had the option to decline participation, or exit the study and interview at any point. Anonymity of the children was ensured through the use of codes to represent each child while concealing the identity of the participants.

Psychological counselling services were made available to the mothers and children at the Department of Mental Health and Psychological Services if they required assistance. The phone numbers were supplied to them.

3.3 Study Design

This was a cross-sectional prospective study involving HIV-positive school-going children aged 6-12 years who are receiving treatment at the paediatric HIV clinic. The parents and care-takers were invited to participate if the child was registered with the clinic prior to the study. The participants represent the various ethnic groups and they live in the same community.

3.4 Participants/Subjects

The subjects were HIV-positive school-going children aged 6-12 years who are receiving treatment at the paediatric HIV clinic in Katutura Hospital. The study population consisted of 60

children who met the criteria for inclusion and who attended the clinic over the period of the study. No control subjects were included in the study as no comparative analysis was needed.

3.4.1 Sample Size

The sample size was determined by reviewing the pattern of attendance at the clinic over a three-year period. About 1350 patients are seen annually at the referral clinic, of which 20-22% is within the study age range. Over three months, it is expected that about 72-80 children in the study age group will attend the clinic. Adopting a confidence level of 95% (describing how sure one can be that the results are correct) and a margin of error (depicting the random sampling error that is possible in the study) of ± 5 , a sample size of about 61 children was computed, hence a sample size of 60 was decided upon by the researcher.

3.5 Exclusion Criteria

Children outside the age bracket, those with history and evidence of birth trauma or a head injury, cerebral palsy, Down's syndrome and other genetic disorders as well as those with incomplete records or unconfirmed diagnosis were excluded from the study.

3.6 Inclusion Criteria

The inclusion criteria accommodated children who fell within the specified age range, those diagnosed with HIV through two positive DNA-PCR tests, HIV antibody detection after 18 months of age (ELISA); those with AIDs-defining symptoms and those with clearly documented clinical records, who attended the clinic within the specified period and registered prior to the commencement of the study.

3.7 Materials and Measurements

3.7.1 Anthropometry

3.7.1.1 Height

The height of the child was obtained by measuring the interval between the top of the head and the flat surface where the feet rested to the nearest centimetre on a height measuring scale.

3.7.1.2 Weight

The weight was obtained by the child wearing a gown and standing on a scientific electronic scale (SECA Model 87432), calibrated and set at zero reading, and the readings were done to nearest gram.

3.7.1.3 Head Circumference

Head circumference was measured to the nearest centimetres with a tape measure placed over the eyebrows, above the tops of the ears and to the occiput of the child.

3.7.2 Virological and Immunological data

The diagnosis of the HIV status of the children was done with HIV-PCR testing in some children, and ELISA test for HIV 1 and 2, and by WHO Clinical Staging of the disease in some others. The CD4 counts and the viral load levels, where available, were extracted from records of the children in the clinic.

3.7.3 Methods of Assessment

3.7.3.1 Gross Motor Function Classification System (GMFCS)

The GMFCS is a system designed for the measurement and classification of the motor function of a child which are based primarily on the truncal and lower limb movements. It is not a diagnostic tool, but provides a standard scale by which assessment can be conducted. It is used to determine the motor function or ability of a child through the assessment of the extent to which a child can perform or exhibit natural movements with or without assistance. It is a 5-point classification system that assesses the mobility and truncal control by the child. It can be used for children from 2 to 18 years of age (15). GMFCS was developed by a team of researchers in

Canada and is available at the CanChild website (www.canchild.ca), where access and use are permitted. The various levels of classification are attached as Annexure 2.

3.7.3.2 Manual Ability Classification System (MACS)

Manual Ability Classification System (MACS) assesses the motor function of the child's hands. MACS is a 5-level classification system that can be used for children in the age group of 4 years to 14 years. This classification system measures grossly, what a child can do with both hands (16).

The various levels of classification are shown below.

MACS levels

Level I	Objects are handled easily and successfully.
Level II	Handles most objects but with some reduced quality and/or speed.
Level III	Handles objects with difficulty – the child will need help to prepare and/or modify activities.
Level IV	Handles a limited selection of easily managed objects and always requires some help from others.
Level V	The child is not able to handle objects or to complete even simple actions with their hands.

3.8 Procedure

Each child was examined by the researcher. The informed consent was obtained from the parent or care-taker of the child prior to commencement of examination. The relevant biodata and immunization history, CD4 counts and percentages and viral loads results were extracted from the reviewed health passport and file of the child. Similarly, the treatment records were also retrieved from the files.

A general medical examination was conducted and the anthropometric measurements - height, weight and head circumferences were obtained and recorded in the data capture sheet. The parent or mother was respectfully requested to provide responses to the questions in the survey questionnaire.

Detailed neurological examination was not performed due to the scope of the research. However, the gross motor examination was conducted in addition to the general examination. The tone was tested by assessing the degree of resistance with passive movement of the joints. The reflexes were assessed by observing the movement elicited with a tendon hammer, taped over the relevant tendons. The power or strength was assessed by asking the child to squeeze the examiner's finger, and by extension and flexion of the elbow and knee joints and, movement against gravity.

The gross motor function (GMF) of the child was obtained by observing level of effort or assistance required for locomotion and the level was recorded. The children's ability to walk was assessed by asking the children to climb a flight of stairs in the hospital up to the second floor of the building and observing how they executed the task and what assistance, if any, was necessary to complete the task.

The MACS was deducted in part from the parent or care-givers' report on the child's use of the hands to accomplish tasks and activities of daily living. The assessment of the ability to use the hands in daily living was obtained by the description of the activities which the care-giver provided. The information provided by the care-giver was supplemented by direct observation of the child handling and manipulating objects. The corresponding MACS level was recorded for the child.

3.8.1 Assessment of Development

Children who are functioning at least 25% below their chronological or adjusted age in one or more of the following areas, namely, cognitive development, physical development (including fine motor, gross motor, vision, and hearing), communication development, social or emotional development, and adaptive development are regarded as having developmental delays. These delays could be progressive, static or plateau, or they may have regression, where previously acquired milestones are lost (10).

In our cohort, the developmental status of each child was assessed subjectively through information provided by the caretakers in response to questions posed by the researcher. Caretakers were asked to provide information on the development of the child and to state any delays in achieving any of the milestones. They were also asked to describe any loss of previously acquired developmental milestones such as speech, behaviour or motor activities like crawling, or walking. Children who had delayed development or stagnation in one or more milestone were identified through the caregivers' description. This was supplemented by the informal screening conducted by the researcher through direct observation of the children and subsequent examination of each child (22, 59). The researcher's assessment of the developmental milestones had limitations as these children were already grown up and no standardized tools were used because this was outside the scope of this research (22).

Each assessment took about 30-45 minutes to complete.

3.9 Data analysis

The 60 children (28 males; 32 females) recruited for the studies were age 6-12 years old. Data were collected from hospital records, health passports, discussions and interview with caregivers as well as through the testing of the children. Descriptive statistics were used to analyze the data. Chi square was used to compare groups where necessary. The results were presented in tables,

figures and charts. The frequencies, means, median, standard deviations and p-values which was set at $p=0.05$ as significant level.

3.9.1 Handling of missing data

The main challenge was encountered with the serum viral load values, CD4 absolute counts and the CD4 percentage values. The missing data were never tested for in some of the children because (1) the variables are not mandatory tests in children according to the local health policy; (2) some children were diagnosed through WHO criteria for Stages 3 and 4 before commencement of ART; (3) and some of the initial diagnoses were made at centres without facilities for these laboratory test. As a result of these factors, the data were not available at the time of commencement of therapy. The available data were analyzed and reported. Imputation or deletion of the subjects was not considered appropriate in this study in accounting for the unavailable data.

WHO EpiInfo Version 7 and Microsoft Excel version 2010 were employed in data analysis.

CHAPTER FOUR: RESULTS

The result of the research will be presented in this chapter. The data of the 60 children enrolled in the study will be presented as well as the result of the assessment done. Descriptive statistics were used to analyze the data and will be shown in tables with frequencies and percentages, or means median, ranges, standard deviations, Z-scores and p-values calculated. Regression analysis was done to establish relationships between variables. A p-value less than 0.05 was regarded as significant.

4.0 Study Population

4.1 Children demographic data

The information was obtained from the questionnaire and results are shown in Table 4.1 below. Of the 60 children enrolled in the study, 28(46.67%) were males and 32 (53.33%) were females. The mean age of all the children was 9.73 years (S.D = 2.024) while the mean age of the males was 8.5 years and females 9.2 years. The median age at the time of diagnosis was 12 months, with a range of 1 to 73 and a SD of 16.11months.

The mean weight of the children was 23.88kg with a median of 22.5kg and SD of 5.46. The mean height of the children was 123.4cm with a median of 124cm and SD of 12.6. The mean

head circumference was 52.85cm with a median of 53cm. The variance was 2.537 while the SD is 1.5933.

The median CD4 count of the 42 children who had a CD4 assay done at diagnosis was 908 with a range of 112-1155 and the median CD4% for 49 children was 27.5% with a range of 10.2-51%. Of the 26 who had viral load tests at the time of diagnosis, the median count was 26204 HIV RNA copies per millilitre cube of blood with a range of 40-3984000 HIV RNA copies per millilitre.

Table 4.1 Characteristics of the study population

Variable	Characteristics
Sex	
Male [N%]	28(46.67%)
Female[N%]	32(53.33%)
CD4 Count N	42
Median [Range]	908(112-1155)
Mean CD4 percentage N	49
Median (Range)	25.7[10.2-51]
Viral Load (HIV RNA copies/mL)	26
Median[Range]	26204[40-3984000]
Age at Onset of treatment(months)	60
Median[Range]	21.5[1-111]
Age at diagnosis (months) N	60
Median[Range]	12[1-73]
Mean Height (centimetres)	123.46
Mean Head Circumference(cm)	52.80
Weight (kg) N	60
Median[Range]	22.5[16.85-41.65]
Weight-for-Age; N	60
Mean Z-score (SD)	-1.694(0.9471)
Weight for Height N	60
Z-score (SD)	-1.355(1.213)
Height-for-Age ; N	60
Mean Z-score (SD)	-1.5547(1.60)

The children had mean Z-scores as follows: WHZ -1.931[SD: 0.758]; HFA: -1.5547[SD: 1.60] and WFA:-1.694[SD: 0.9471] while the BMIZ was -2.0[SD: 0.8516].

Table 4.2 shows the breakdown of some of the characteristics of the cohort by gender. Weight, height and head circumferences and the Z-scores of the children are shown in this table.

Table 4.2: Characteristics of children by gender

Variable	Male	Female	P-value
Mean Height (centimetres)	123.46	127.71	0.0623
Mean Head Circumference (cm)	52.80	52.89	0.8331
Mean Weight (kg)	23.54	24.25	0.6214
Weight for Age Z-score	-1.5875	-1.790	0.5754
Weight for Height Z-score	-1.0135	-1.122	0.083
Height for Age Z-score	-1.6707	-1.45	0.097

By gender, the weight of the children had a mean of 23.54kg (males) and 24.25kg (females); median weight was 22.4kg (males) and 24.45kg (females). The mean height of the population was 125.6cm (males: 123.46 cm; females: 127.71cm) and a median of 124cm (males: 122.55cm; females: 127cm) and SD of 12.38cm.

Analysis of the children's heights, weights and head circumferences percentiles was done and compared with the normal global population of children in their age group. Table 4.3 below shows their performances by percentile.

Table 4.3: Weight and height percentile distribution of the children

Percentile	Weight (kg)	Height(cm)	Head Circumference(cm)
< 3	21 [35.4%]	21 [35.4%]	3 [5.1%]
=>3 - < 5	10 [16.6%]	6 [10.1%]	2 [3.4%]
=>5 - < 95	29 [49.1%]	29 [49.1%]	49 [81.6%]
= > 95 - < 97	0 [0%]	1 [1.6%]	0 [0%]
=>97	0 [0%]	0 [0%]	6 [10.0%]

The children in our study performed poorly in relation to their weights and heights with 35% scoring below the 3rd percentile (<-3SD) in both domains, 16.6% between 3 and 5 percentile(< -2SD) for weight, 10% between 3 and 5 percentile (<-2 SD) for the height and 49% within the normal percentile (5-95%) of the norm for height and weight. On the head circumference, 81% scored within the normal range (5-95%) while about 5% each were at the extremes of +3 SD and -3 SD.

Table 4.4: Z-scores: WAZ, WHZ and HFZ for the cohort

Index	<-2SD	<-2 - +2 SD	>+2SD
WFA	31(51.6%)	29(49.4%)	0 (0%)
HFA	29(49.4%)	31(51.6%)	0(0%)
WFH	28(46.6%)	32(53.4%)	0(0%)

The individual Z-scores of the WFA, HFA and WFH for the children are displayed in Table 4.4. It shows that about 50% of children had Z-scores of less than 2 SD while 50% were in the normal range in both WFA and HFA. Fifty-three percent (53.4%) had a Z-score within the global norm of WFH, while 46.6% were below 2 SD.

Table 4.5: Age distribution of children at diagnosis

Age at diagnosis(months)	Frequency	Percentage (%)
0-6	19	31.67
7-12	11	18.33
13-18	8	13.33
19-24	7	10.00
25-30	2	5.0
31-36	4	6.67
37-42	5	8.33
43-48	1	1.67
49- above	2	3.33

Table 4.5 shows that majority (49%) of the children were diagnosed within the first year of life and by 24 months, over two-third of the diagnoses were confirmed. The early diagnosis of majority of the cohort is in line with the PMTCT programme embarked upon by the Health Department.

Table 4.6: Age distribution of children at intervention

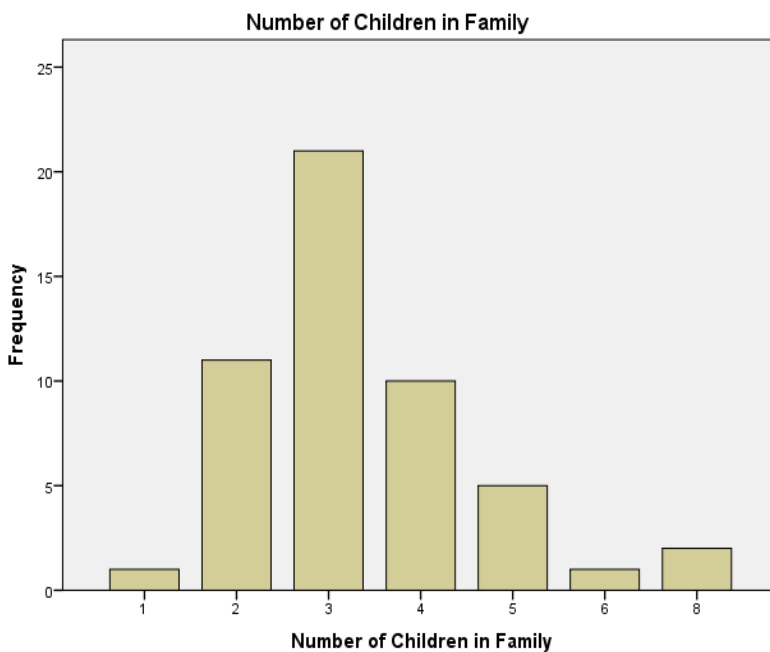
Age at intervention(months)	Frequency	Percentage (%)
0-6	15	25.00
7-12	11	18.33
13-18	9	15.00
19-24	10	16.66
25-30	3	5.00
31-36	4	6.67
37-42	4	6.67
43-48	1	1.67
49-54	3	5.00
55-60	1	1.67
61+	6	10.00

Similarly, over 75% of the diagnosed cases were placed on ART within the same period of 24 months of age as shown in Table 4.6 above. All the children had Apgar scores of above 8 at 10 minutes. They were all fully immunized and all immunizations schedules were up to date as noted in the health passports.

4.2 Socio-economic parameters

The mean number of children in a household was 3.5 with a median of 3 and range of 1-8. Of the 60 children, 30% had access to flush toilets, 16% used pit latrines and 54% used the bush. This reflects the challenging socioeconomic disposition of the children and care-givers.

Figure 4.1. Bar chart of number of children in a family



4.3 Caregivers' profile

4.3.1 Care-giver category

Table 4.7 shows the profile of the care-givers. Forty-two care-givers (70%) were biological mothers of the children; 7 (11.67%) were the fathers; 6 (10%) were close female relatives, while 5 (8.33%) were matrons at orphanages.

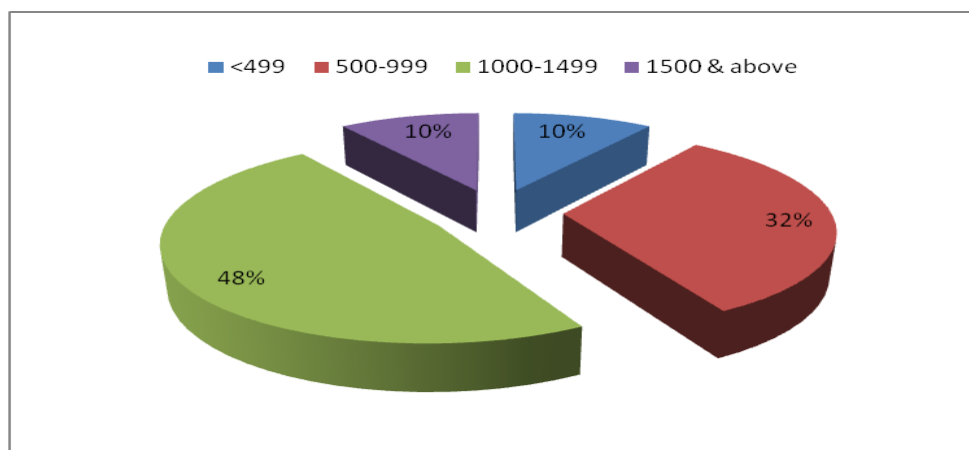
Table 4.7: Categories of Care –givers

Care-giver	Percentage
Mother	70
Father	11.67
Relatives	10
Orphanage Matron	8.33

Table 4.8: Income levels of Care-givers

Income(NS\$)	Percentage
None	0
< 499	10
500 -999	32
1000-1499	48
1500 & above	10

Figure 4.2 Pie chart of income distribution of caregivers (Namibian Dollars)



All caretakers earned monthly income as indicated in Table 4.8. Figure 4.2 illustrates the distribution of the monthly income of the care -givers. Five percent (5%) earned below N\$500; 16% earned between N\$500-N\$999, 24% earned between N\$1000-1499, and 5% earned N\$1500 and above. One United State dollar (US\$) is equivalent to 15 Namibian Dollars (N\$). The 5 children in the orphanage were cared for by the matrons.

4.3.2 Educational Profile of Care-givers

Tale 4.9 shows the educational levels of the care-givers. The profile of the indicates that 10.91% of caretakers had no formal education, 47.27 % attended primary school, while 41.82% acquired secondary education. None of them had tertiary education.

Table 4.9 Educational profile of care-givers

Level of education	Percentage
None	10.9
Primary school	47.2
Secondary school	41.8
Tertiary level	0

4.4 HIV profile of the children

All the children were included in the study on the basis of prior diagnosis of HIV infection. 61.7% were diagnosed using HIV PCR, 31.7% were diagnosed with HIV ELISA test and 6.7% of the diagnosis was made using the WHO Clinical criteria.

Table 4.10 HIV Profile of children

	Male	Female	P-value
Mean CD4 Count	1301	1243	0.7924
Mean CD4 percentage	27.75	28.35	0.8770
Mean Viral Load (HIV RNA copies/mL)	77348	623130	0.445
Age(months) at Onset of treatment	20.4	25	0.0039
Median Age at diagnosis (months)	9.5	16.5	0.1479

Table 4.10 shows the profile of the children. The mean CD4 count and viral load at diagnosis were 1257 and 392,222 HIV RNA copies/mL respectively. Mean CD4 percentage was 27.87 with a median of 25.7 and SD of 10.1. When compared by gender, the mean CD4 for males was 1301, and females was 1234.6 with a non-significant p-value of 0.7924. The mean age at time of treatment is 27.9 months with a median of 21.5 months, a range of 1-111 months and a standard deviation of 25.9. Males had a mean age at onset of treatment of 20.4, median of 15, and SD of 17.4 while for the females, it was: mean 25 months, median 30 months, SD 30. Tests of

population difference with ANOVA yielded a P-value of 0.0306, Bartlett's test, P-value of 0.0039 and with Mann-Whitney Wilcoxon test, P-value 0.0458 ($p < 0.05$). This shows a significant difference between the male and female children in the age at onset of therapy with ARV.

4.4.1 Adherence to ART

Fifty-eight (96.55%) children were compliant with their medications, while 2 (3.45%) were not compliant with the appointments and medication scheduling, citing logistic reasons for missed appointments, and hence, missed the treatments. This variable was verified by records of attendance at the clinic and pharmacy; physical inspection of the medication containers and verbal engagement with caretaker on how treatment was taken by the child. All the caretakers consented to the administration of ART to their wards after counselling by health personnel at the clinic.

4.5 Motor Dysfunction Assessment

4.5.1 Gross Motor Function Classification scores

The score of GMFCS indicated that 94.9% of children were normal and had no need for assistance or had reduced ability or speed to perform normal functions. About five percent (5.1%) scored at GMFCS Level II. They are able to walk and climb stair cases holding onto rails

but could not engage in long distance walk, running, or jumping. This was the highest level of disability recorded in the cohort. They were all males.

4.5.2 Manual Ability Classification scores

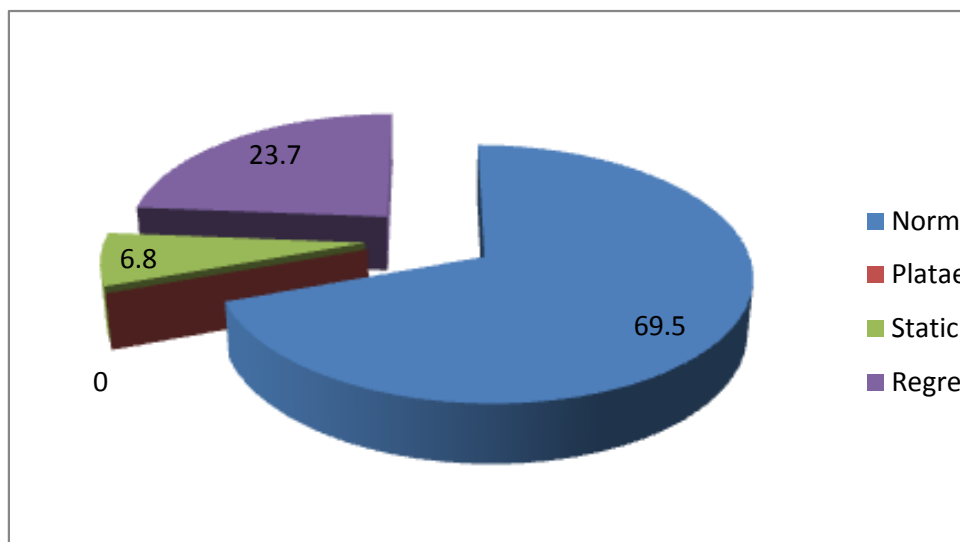
Ninety three percent of the children had normal hand function. In other words, they required no assistance in handling objects and performing activities. Seven percent (7%) of the children had a score of Level II in the MACS. They handled some objects and performed some activities with reduced speed or quality. All of them were males.

4.6 Other Neurological Findings

4.6.1 Developmental Status

Through interviews and examination of the children by the researcher, the development of the children was assessed. The result is displayed in the pie chart below.

Figure 4.3: Pie Chart showing distribution of developmental status of children

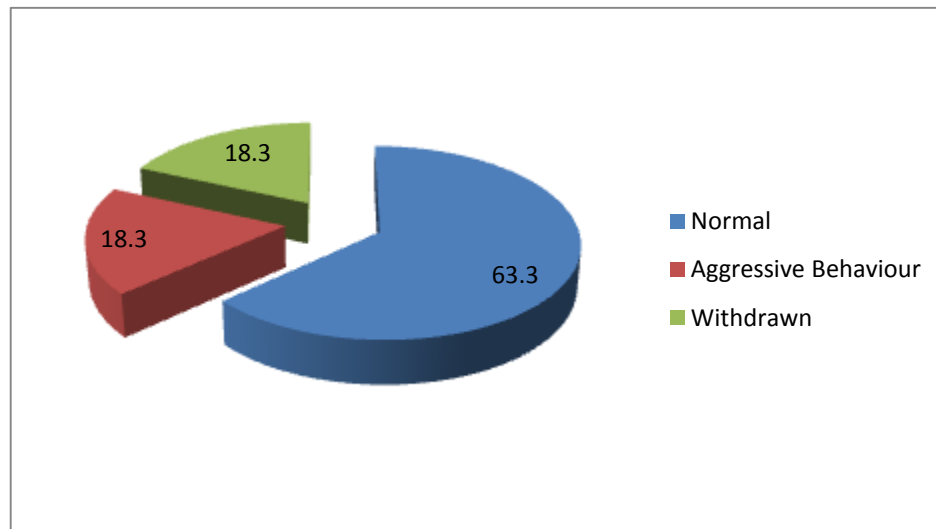


Sixty-nine and a half percent (69.5%) showed normal developmental status, 23.7% showed some regression while 6.8 % displayed features of static delay in development. None expressed any features of plateau in their development.

4.6.2 Behavioural Problems

Behavioural problems were observed in some of the children by the caregivers. Sixty three percent (63.3%) of the children were reported to have normal behaviour while 36.7% exhibited behavioural problems. Eighteen percent (18.3%) of the children were reported to be withdrawn and depressive while 18.33% were reported to be aggressive in their behaviour. These findings were not explored further in this study. The pie chart (Figure 4.4) illustrates the distribution of the children.

Figure 4.4 Pie Chart of the distribution of behavioural Status of children



4.6.3 Intellectual Outcomes

HIV-infected children are at risk for poor intellectual development and performances (56). Impaired cognitive development may manifest with poor intellectual abilities. Intellectual disability is characterized by significantly impaired intellectual and adaptive functioning . A battery of intellectual assessment tools including determination of the Intelligence Quotient (IQ) levels assist with diagnosis. This research did not involve the use of these tools. However, the school attendance and performance reports may be predictors of the extent of intellectual challenge a child may have at school (80). Dropping grades, frequent school absences, school phobia, failed grades and school-teacher reports assist in evaluating the intellectual ability of the child. Our cohort exhibited significant level of intellectual challenge as 48% of them were

unable to attain the appropriate academic level for their age. Table 4.12 shows the distribution of the cohort with regard to school work.

Table 4.12: Distribution of the cohort with regard to school

School Status	Females	Males	Total Number
Appropriate grade	17	14	31
Lower grades	10	7	17
Special schools	3	4	7
Drop outs	2	3	5
Total	32	28	60

Of those in the appropriate grades, care-giver reports indicate that nearly a quarter of them struggle to do well at school. The main complaint by care-givers was that the children were restless and failed to pay attention at school according to the school teachers.

4.7 Co-morbidity

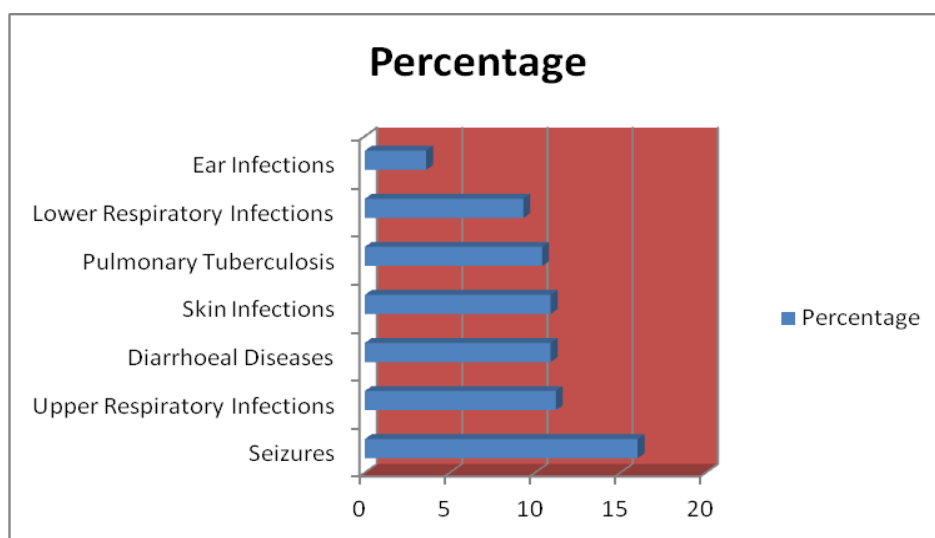
Fifty-six per cent of the children had co-morbidities. Table 4.11 below shows the distribution of co-morbidities in the cohort.

Table 4.11: Distribution of co-morbidity amongst the children

Co-morbidity	Percentage
Seizures	16
Upper Respiratory Infections	11.2
Diarrhoeal Diseases	10.9
Skin Infections	10.9
Pulmonary Tuberculosis	10.4
Lower Respiratory Infections	9.3
Ear Infections	3.6

Sixteen percent (16%) of children had grand mal epilepsy. Other co-morbidities described in this study include upper respiratory infections 11.21%, diarrhoeal diseases accounted for 10.91% of co-morbidities; skin infections 10.91%, pulmonary tuberculosis 10.4%, lower respiratory infections (pneumonias) account for 9.3% and ear infections 3.64% .

Figure 5: Bar chart of the distribution of co-morbidities



These morbidities occurred at various stages in the HIV disease. About eight percent (8.3%) had macrocephaly (male: 3.3%, female 5%). None were diagnosed with brain tumour. Due to limited resources, routine brain imaging was not done, and of the four children where brain imaging (CT scan) was done, one child had brain atrophy.

Regression tests were applied to ascertain any associations between the variables in this research. There is a weak and non-significant association between the age at diagnosis and the behavioural problems reported in the children (Correlation coefficient =0.03, p-value= 0.1863). Linear and multivariate regression tests did not show any associations between age at diagnosis and motor functions, seizures, co-morbidities and developmental outcomes of the children.

Early intervention (ART) reduces the extent of motor function disorders (10). A positive correlation exists between time of start of intervention (ART) and motor function outcomes in the HIV-infected children. Regression studies in our cohort showed weak but significant association between age at intervention (ART) and neurodevelopmental outcomes (correlation coefficient= 0.39, p-value =0.04782), seizures (coefficient. = 0.28; p-value =0.0354), but not with behavioural problems (correlation coefficient = 0.119; p=0.08821).

A positive association and a significant correlation between the serum viral RNA load and the presence of seizures in the children (correlation coefficient = 0.31; P = 0.00327) on the one hand, and between serum viral RNA load and neurodevelopmental delays among the children

(correlation coefficient= 0.4; p-value = 0.00159) on the other hand were also demonstrated. This indicates that high serum HIV RNA load was a predictor of adverse neurodevelopmental outcomes and co-morbidities in HIV-infected school-age children.

A linear regression computation of the relationship between CD4 cell count and the motor functions showed a correlation (correlation coefficient: -0.17; p-value <0.0001), supporting research reports (10). The linear regression test also showed that CD4 at diagnosis was related to the outcome of behavioural problems in the children as well (coefficient= -0.22; P-value = 0.004912), but did not identify a positive correlation or association between serum CD4 count and the co-morbidities and seizures in the children.

The median age at the time of commencement of treatment was 20.5 months (males) and 35 months (female) with a statistically significant P-value of 0.0039. Regression analysis showed a positive correlation (Coefficient = 0.11; P-value = 0.0136) between seizures and motor dysfunctions. Thus, HIV-infected children who had seizures were at risk of having neurological dysfunctions. On the other hand, there was no significant relationship (Correlation coefficient = 0.00; P-value = 0.6411) between seizures and the behavioural problems experienced by the children in our study.

CHAPTER FIVE : DISCUSSION

The study results will be discussed in this section. Challenges and limitations of the study will be described. Recommendations for further studies will be made.

5.1 Motor dysfunction

The risk of abnormal motor development increases in childhood HIV infection (10), and is associated with HIV encephalopathy (9). Gross and fine motor developments are both affected, with gross motor development more severely affected. Early infection in utero leads to a fast and early onset of neurotoxic and neuropathic effects of HIV on the immature developing brain (7, 10). Research reports indicate that up to 49% of HIV-infected children of school-going age may have motor dysfunction (10). The status of the children in my study was evaluated using GMFCS from levels I to V, which describes increasing levels of functional mobility limitations and difficulty to accomplish tasks and MACS (I – V) which describes hand coordination. Motor dysfunction was present in 12% of our cohort. This is less than the motor dysfunction prevalence (18%) from various aetiologies in the general population of children of similar age (76 78), suggesting less motor dysfunction in our study group compared to the general population. Similarly, our result differs from research reports at a specialized orthopaedic setting where 42% of their cohort had a GMFCS score of levels II and III (81). The limitation of the use of GMFCS and MACS instead of standardized screening tools may account for the relatively low prevalence in our cohort. Research utilizing standardized tools to measure motor dysfunction is needed to verify the extent of motor dysfunction in our setting.

The early (mean age: 13months) introduction of ART and the MTCT programmes may play a role in the low level of motor dysfunction in our cohort. Secondly, the policy of starting all under 15 year old HIV positive children on ART may have altered the severity of motor deficit. Research supports this position; even with conflicting research reports, Ruel D, et al indicate that early commencement of ART may be recommended as soon as infection is detected, irrespective of the CD4 count and viral RNA levels to prevent irreversible impairment of neurodevelopment at critical stages (10). In our study, the findings may suggest that early initiation of ART played a role in the reduction of the level of motor dysfunction in the cohort, but further research is needed to validate this observation in our setting.

5.2 Developmental status

HIV-infected children have significant cognitive, motor and language impairment (7, 10). HIV damage to the brain usually predates diagnosis and irreversible damages may be inflicted on the immature CNS, resulting in static, plateau or progressive encephalopathy (9, 82). The assessment of the developmental status of our cohort was done through physician assessment and caregiver observation and history. The study of developmental delay is best carried out with standardized testing tools due to limitations of the physician assessment (10, 22).

Our cohort displayed normal development (69.7%), regression (23.7%), static delay (6.8%) and plateau, zero percent, thus reporting levels lower than other studies. The differences could be due to the effects of early onset of ART in our cohort (7), and the differences in the methodology employed in the various studies may affect the findings. Early onset of ART reduces the incidence of developmental delay, but there is evidence that even after early viral suppression, children may display adverse neurologic outcome later in life (6, 7, 82). This has implications for the future of these children. Evidence of late onset adverse effects should be anticipated by clinicians and considered in the management of the children, and guide patient and parental counselling.

5.3 Co-morbidities

HIV-infected children are at risk of developing co-morbidities resulting from direct effect of the HIV, infections due to compromised immunity or as complications of therapy (83). Upper respiratory infections, anaemia, tuberculosis and dermatological diseases are among the common co-morbidities reported in research. Moreira-Silva et al reported co-morbidities in 67% of children in their series (83). Another study found no difference in the rate of co-morbidities between HIV infected and the HIV uninfected children. They however stated that the severity of the morbidities appeared worse in the HIV-infected children (83, 84).

Our study identified co-morbidities in 56% of children. Common conditions reported were upper respiratory infections (11.21%), diarrhoeal diseases (10.9%), skin infections (10.91%), pulmonary tuberculosis (10.4%), pneumonias (9.3%) and ear infections 3.64%. Research reports indicate similar morbidity trends in the general community amongst children of school going age where respiratory infections, diarrhoeal diseases, and pneumonias accounted for 17-34% of morbidity and mortality worldwide (85).

Sixteen percent of HIV-infected children in our study had grand mal type of seizures more than once. Other studies report prevalence of 7.6-20 % amongst HIV-infected children (86, 87). One study did not report any case of seizures in their series (81). The causes vary and include opportunistic infections, focal brain atrophy, space-occupying lesions, and the direct effect of HIV encephalitis (87). Introduction of HAART has reduced the incidence and severity of co-morbidities, and early commencement of ART improves the outcome. So, HIV-infected children could enjoy better health with fewer clinic and hospital visits. In resource-constrained settings, the cost-saving implications are quite significant.

5.4 Research objectives

This study set out to ascertain and describe the relationship between motor dysfunction observed in the cohort with various variables in the population including age of diagnosis, CD4 plasma level, serum viral RNA level and compliance or adherence to treatment schedules.

5.4.1 Motor dysfunction and age at diagnosis

The study attempted to identify relationships between the age at diagnosis and motor dysfunction. HIV-infected younger infants and children (<30months) have been observed to consistently exhibit features of motor impairment that include muscle weakness, poor head control, gait abnormalities, poor motor coordination, increased or reduced tones and abnormal reflexes(88). These manifestations are different to what is observed among the school-age children. Vertically HIV-infected school-age children tend to display more of gross motor dysfunctions in the lower extremities such as in running speed and display of agility (10, 88).

This is in line with findings in our research: 5.1% were scored GMFCS Level II. They were able to walk and climb stair cases holding unto rails but could not engage in long distance walk, running or jumping. However, there was no statistical correlation between the age at diagnosis of HIV infection in a child and the motor functions (GMFCS: $p=0.658$; MACS: $p=0.461$). This research finding suggests that the age at diagnosis of HIV is not a predictor of the extent of motor dysfunction in HIV-infected school-age children. The loss of motor function is less evident in older children but still subtle strength and fine-motor impairments are documented (15, 6) in line with the result in our research.

5.4.2 Motor dysfunction and HIV Viral Load

The HIV RNA level is a surrogate measure of disease severity in HIV-infected children. High levels are known to correlate with more severe disease conditions. The HIV RNA level is employed in monitoring response to ART (89, 90). Research indicates that a high viral load level is predictive of severe neurologic disease in HIV-infected children, and suppressing the HIV RNA level may reduce the incidence of adverse neurologic outcome (89).

One study reports a mixed result where the global cohort did not display any correlation between the level of HIV RNA and the motor performance of the children. However, a subset of children in that study with HIV RNA levels above the median performed worse than those with HIV RNA levels below the median in subsets of manual dexterity, speed/agility and upper limb coordination (10). Our study demonstrated a significant correlation between the HIV RNA levels and extent of motor dysfunction ($p < 0.0001$), supporting findings in previous researches (10, 8).

5.4.3 Motor dysfunction and CD4 cell Count

Poor neurodevelopmental outcomes are associated with HIV infection in children (7). Low CD4 cell counts and high HIV plasma RNA levels in HIV-infected children are indicators of negative neurodevelopmental outcome. Children develop more acute and severe forms of neurodevelopmental delays in relation to low CD4 cell counts (10). Research indicates that even

with CD4 cell counts that are above the WHO recommended threshold for initiation of therapy, HIV-infected children suffer adverse neurodevelopmental outcomes (10). Our study found 6.7% of the cohort had CD4 plasma levels below the norm. There was a significant correlation between motor dysfunction and CD4 lymphocyte plasma levels ($p < 0.001$). This agrees with findings in other studies where adverse motor dysfunctions are associated with low CD4 lymphocyte levels (19, 63). The finding of low CD4 lymphocyte level in 6.7% of the children and a significant p -value ($p < 0.0001$) support research reports that motor delays and deficits can occur in the absence of advanced disease in HIV-infected children (10,63). The finding suggests great value in the practice by Ministry of Health and Social Services (MOHSS) to initiate ART in all HIV-infected children irrespective of the stage of disease advancement or CD4 level, thus minimizing adverse neurodevelopmental outcomes.

5.4.4 Motor dysfunction and Treatment Compliance

Treatment compliance may be defined as the extent to which a patient takes a medication in the way intended by a health care provider. Antiretroviral adherence/compliance is a strong predictor of disease outcome in HIV management, second only to CD4 lymphocyte counts. Poor compliance with ART has adverse effect on disease management in HIV-infected children (90, 91).

ART adherence rates over a long period of time vary by approximately between 50-75 %, (90) but research has reported levels of up to 98% (92,93). The initial goal of ART is full and durable viral suppression culminating in the reduction of HIV-related morbidity and mortality. Adequate viral suppression allows for maximal reconstitution or maintenance of immune function and minimizes the emergence of drug-resistant virus (92). Failure to achieve this goal leads to adverse neurologic outcome for the HIV-infected child.

Our study shows a compliance level of 96%. Compliance was monitored through directly observed treatment, pill count, pharmacy refill appointments and patient self-report. Research supports these means of adherence measure. Other methods include computerized cap that records frequency of cap opening , and biological markers (serum drug levels and surrogate markers like serum lactate level), both of which are not routinely available in our setting due to cost constraints (92,93). Further suggested measures to improve adherence include providing medicine organizers to care-givers, visual medication schedules and reminder devices such as alarm clocks (93).

Logistic and access burdens, including distance to health facility, facility layout, staff attitude and burdensome childhood ART regimes are themes that need review to improve adherence to ART(94). The pivotal role of adherence to ART in reduction of disease burden makes a case for continued patient and caregiver education towards improving adherence levels.

5.5 Behavioural complications

HIV-infected children are at risk of developing behavioural problems (95). The HIV invades the brain cells at an early age leading to disruption of cognitive and behavioural domains. Joska KA et al suggest that HIV integration into the frontal cortex and connecting structures of the CNS may be possible mechanisms for specific behavioural manifestations (96). Behavioural problems could arise from social and emotional tensions that complicate the HIV infection, diagnosis, disclosure and treatment, especially with adolescent children (95).

The adolescents and school-age HIV-infected children struggle with dealing with their diagnosis, acceptance of their status, coping with the daily burden of medications and the stigma attached to their HIV-positive status in the society. All these tend to raise their levels of neuropsychological stress. Behavioural problems are known to improve with HAART (97). The results of our study shows 36.6% had behavioural problems. Other researchers reported incidences of up to 86% (97,98). The higher incidence in other researches could be due to differences in methodology. Most of the other researches were set in neuropsychology clinics that see more children with neuropsychological challenges.

Behavioural problems involve a wide spectrum of events and conditions, including but not limited to attention deficit disorders, mood and conduct disorders. Behavioural problems could present as aggression or depression. Our research found an equal presentation (18.6%) of

aggressive and depressive conditions reported by care givers. In line with other studies there was no gender differences ($p=0.445$) (94). This high level of behavioural problems reported has implication for management of the patients, and may suggest the need for a multidisciplinary and holistic approach. In particular, mental health of the children should be recognized as a serious health challenge and be addressed earlier on in their management.

5.6 Nutrition

Nutrition is essential for neurodevelopment of a child and for the support of the increased energy and mental demands of the school-age children. Both macro-and the micro-nutrients are crucial in the process. Poor nutrition increases the challenge on the neurodevelopmental processes in a growing child, leading to negative outcomes (67). Childhood HIV infection, as an independent modifiable risk factor for poor nutritional outcomes, contributes substantially to negative nutritional outcomes in children (70). HIV-infected children experience a simultaneous impairment of weight and height in HIV-associated growth impairment resulting in low nutritional indices and poor growth.

The percentiles of the variables (weight, height, BMI and head circumference) are better indices for assessing the nutritional status of the children because each child is compared to the norm. Percentiles from 5-95% are considered normal while less than 5% is low and above 95% is regarded as above the norm. Weight-for-height (WHZ) measures current and acute nutritional or

health conditions, height-for-age (HAZ) measures chronic nutritional situations that may lead to stunting, while weight-for-age (WAZ) score could depict a combination of acute and chronic nutritional or health challenges. Normal range of Z-scores is between -2 and +2 standard deviation (SD) of the mean (72).

The children in our study performed poorly in relation to their weights and heights with 35% scoring below the 3rd percentile ($<-3SD$) in both domains, 15.3% between 3 and 5 percentile ($<-2SD$) for weight, 10% between 3 and 5 percentile ($<-2SD$) for the height and 49% within the normal percentile (5-95) of the norm for height and weight. On the head circumference, 81% scored within the normal range (5-95%) while about 5% each were at the extremes of -3 SD and +3 SD. The results are consistent with findings in other researches (19). Low WAZ is positively associated with adverse cognitive and motor development of children. Linear growth failure precedes poor neurodevelopmental outcome in HIV- infected children (19, 22,70).

Other researchers reported improvement in the nutritional status of HIV-infected children following the initiation of ART, but suggested that ART may not be the sole contributory factor as poverty, access to healthcare services and education impact on overall development of the child (19, 22). Research findings support suggestions that early commencement of ART improves the nutritional outcome of HIV-infected children, especially the improvement in WAZ (98). Further research is necessary to confirm this suggestion in our setting as it has implication on the daily management and early childhood developmental outcomes amongst these children.

5.7 Limitations of the study

There was inadequate documentation on some of the patient data files, so all the necessary information could not be retrieved in some cases.

Lack of routine testing for HIV surrogate markers like absolute CD4 count, CD4 percentage and viral load resulted in all the participants not being assessed in all necessary parameters.

This was a cross-sectional study with no control subjects. The lack of controls was a limitation to the study.

GMFCS and MACS are primarily designed for motor ability assessment studies. Applying them alone in this study limited the scope of parameters and domains that could be investigated.

The lack of use of standardized tools to measure behavioural problems, and development in this study compared to other studies is a limitation to our study.

5.8 Recommendations for further researches

A case-controlled study should be done to determine the extent of the neurological deficits in HIV-infected children at various age groups up to the adolescent to determine the neurodevelopmental challenges these children experience towards adolescence.

More studies are needed to determine the effects of HIV infection on the overall neurodevelopment of the HIV-exposed and infected children employing multiple test batteries to accommodate the various facets of the impact of HIV on child neurodevelopment. This will provide direction in planning a multidisciplinary approach to improve management of these children.

Study to determine the effect of early initiation of ART amongst HIV-positive children should be conducted in our setting .This will establish the benefits of early ART in the neurocognitive development of the children and shape policy decisions.

Study to establish the knowledge, attitude and practices of care-givers towards care of children living with the HIV/AIDS in order to formulate policies and targeted intervention to improve the home-care of the children.

The study utilizing standardized tools to measure behaviour and development of children is highly recommended.

CHAPTER SIX: CONCLUSION

This cross-sectional study examined the extent and severity of motor dysfunction among 60 school-age children infected with HIV, using the GMFCS and the MACS at a referral paediatric unit in a hospital. There was a 5.1% prevalence of gross motor dysfunction of level II in the GMFCS and 7% prevalence of gross motor dysfunction of level II in the MACS scales, both of which are lower than the expected levels in the general community. The nutritional status of the children was poor with 35% below the 3rd percentile in weight and height. This result is similar to globally reported findings where significant numbers of HIV-infected children were malnourished.

Significant correlation was established between the levels of CD4 serum lymphocyte count on the one hand ($p < 0.0001$), and the serum HIV RNA viral load on the other hand ($p < 0.0001$) with the presence of motor dysfunction. Our research suggests that HIV-infected children with low CD4 serum levels and high serum HIV viral RNA levels were more likely to display motor dysfunction. This is globally corroborated in other studies.

There was no significant correlation between motor dysfunctions and adherence to ART in our study. This finding differs from literatures reports which suggest that adherence to ART is a strong predictor of HIV complications. Better compliance results in better disease outcome, thus reducing HIV complications in the process.

As the PMTCT and ART continue to be widely available, more HIV-exposed infected and uninfected children will be surviving to school age. There is need to identify the neurodevelopmental impairments early and to initiate treatment strategies that will minimize and where possible, reverse the deficits. Home care-givers should be empowered to be effective components of the multi-disciplinary team to tackle the complex impairments that the children may exhibit.

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APPENDIX I



R14/49 Dr Goodluck Nwagboso

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M151115

NAME: Dr Goodluck Nwagboso
(Principal Investigator)

DEPARTMENT: Paediatrics and Child Health
Katutura State Hospital, Windhoek, Namibia

PROJECT TITLE: The Prevalence and Severity of Motor Dysfunction
Amongst HIV-Infected Children Aged 6 - 12 Years in
a Paediatric Unit of A Referral Centre in Namibia

DATE CONSIDERED: 27/11/2015

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Lorna Jacklin

APPROVED BY:

A handwritten signature in black ink, appearing to read 'P. Cleaton-Jones'.

Professor P. Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 24/06/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year.

Principal Investigator Signature _____

Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix II

Gross Motor Function Classification System

GMFCS – E & R (Expanded and Revised)

(Excerpt for 6-12 years)

BETWEEN 6TH AND 12TH BIRTHDAY

Level I: Children walk at home, school, outdoors, and in the community. Children are able to walk up and down curbs without physical assistance and stairs without the use of a railing. Children perform gross motor skills such as running and jumping but speed, balance, and coordination are limited. Children may participate in physical activities and sports depending on personal choices and environmental factors.

Level II: Children walk in most settings. Children may experience difficulty walking long distances and balancing on uneven terrain, inclines, in crowded areas, confined spaces or when carrying objects. Children walk up and down stairs holding onto a railing or with physical assistance if there is no railing. Outdoors and in the community, children may walk with physical assistance, a hand-held mobility device, or use wheeled mobility when traveling long distances. Children have at best only minimal ability to perform gross motor skills such as running and jumping. Limitations in performance of gross motor skills may necessitate adaptations to enable participation in physical activities and sports.

Level III: Children walk using a hand-held mobility device in most indoor settings. When seated, children may require a seat belt for pelvic alignment and balance. Sit-to-stand and floor-to-stand transfers require physical assistance of a person or support surface. When traveling long distances, children use some form of wheeled mobility. Children may walk up and down stairs holding onto a railing with supervision or physical assistance. Limitations in walking may necessitate adaptations to enable participation in physical activities and sports including self-propelling a manual wheelchair or powered mobility.

Level IV: Children use methods of mobility that require physical assistance or powered mobility in most settings. Children require adaptive seating for trunk and pelvic control and physical assistance for most transfers. At home, children use floor mobility (roll, creep, or crawl), walk short distances with physical assistance, or use powered mobility. When positioned, children may use a body support walker at home or school. At school, outdoors, and in the community, children are transported in a manual wheelchair or use powered mobility. Limitations in mobility necessitate adaptations to enable participation in physical activities and sports, including physical assistance and/or powered mobility.

Level V: Children are transported in a manual wheelchair in all settings. Children are limited in their ability to maintain antigravity head and trunk postures and control arm and leg movements. Assistive technology is used to improve head alignment, seating, standing, and and/or mobility but limitations are not fully compensated by equipment. Transfers require complete physical assistance of an adult. At home, children may move short distances on the floor or may be carried by an adult. Children may achieve self mobility using powered mobility with extensive adaptations for seating and control access. Limitations in mobility necessitate adaptations to enable participation in physical activities and sports including physical assistance and using powered mobility.

Appendix III

Neurological complications of Paediatric HIV infection

Questionnaire (to be completed by researcher)

Serial No. _____

TO COMPLETE THE FOLLOWING INFORMATION ON THE CHILD ASSESSED.

1. Age (years) ----- 2. Gender: M, F 3. Number of children in family _____
4. Weight (kg) ---- 5. Height (cm)..... 6. Head Circumference (cm).....
7. Apgar Score (at 10 minutes) _____
- 8 Immunization History: Complete ☐ Incomplete ☐
9. Household Demography:
 - 9a. Average total Monthly Income (N\$) : <500 ☐ 500-999 ☐ 1000 -1499 ☐ >1500 ☐
 - 9b .Availability of Amenities (please tick) – Flush toilet; pit latrines; bush
 - 9c. Highest level of parental/caregiver formal education: None; Primary Level; Secondary Level; Tertiary Level.
10. Age at diagnosis of HIV (months).....
11. Method of diagnosis (tick one):
 - a) HIV PCR b) ELIZA c) WHO clinical criteria
12. Viral load (VL) at diagnosis.....
13. a] CD4 level at diagnosis..... b] CD4 percentage.....
- 14 Motor System (Mobility) Assessment (GMFCS) – to tick the score
 - I ☐ II ☐ III ☐ IV ☐ V ☐
- 15 Hand Coordination Assessment (MACS) – to tick the score
 - I ☐ II ☐ III ☐ IV ☐ V ☐
- 16 Co-Infections identified (Please tick):
 - i. Bacterial meningitis ii. Viral Meningitis

- iii. TB Meningitis iv. Opportunistic Infections – specify.....

17. Other Neurologic Findings Reported (tick):

- a. Developmental Status: [Normal] [Regression] [Plateau] [Static delays]
b. Behavioural problems: [Normal] [Withdrawn] [Hyperactive]
d. Acquired microcephaly: [Present] [Absent] Any other- Specify.....
e. Seizures : [Yes] [No] If yes, specify type.....

18 Brain Tumours (tick)

[Primary Lymphoma] [Kaposi's sarcoma] [Others] – Specify.....

18 Treatments

Is the child on HAART? [Yes] [No]

If yes, when was treatment started? Compliant : YES ☐O ☐

If not on treatment, tick reason(s):

- a) Does not meet treatment criteria (e.g.CD4 value)
b) Unaware of treatment
c) Drugs unavailable
d) Parent/patient declined treatment
e) Any other - specify.....

19 **Radio-Imaging (MRI & CT Scan) Reports**

Results of CT scan & MRI Brain:

[Intracranial Haemorrhage] [Space Occupying Lesions] [Intracranial oedema]

[Ring enhancing effects] [Infarcts] [Brain Atrophy]

Others – specify.....

20 **Other comments about the patient:.....**

.....