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A COMPARISON OF THE CLINICAL PRESENTATION OF HIV INFECTED CHILDREN WITH SPASTIC DIPLEGIA TO HIV UNINFECTED CHILDREN WITH SPASTIC DIPLEGIA IN A SOUTH AFRICAN SETTING

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ABSTRACT

The aim of this study was to determine if there are similarities and/or differences with regards to function, tone and strength between children with spastic diplegia as a result of CP and HIV encephalopathy as the prevalence of HIV infected children with diplegia has increased since the advent of HAART.

Participants with spastic diplegia (GMFCS I to IV) between the ages of four and sixteen were consecutively selected at two state hospitals and two private practices in Johannesburg. Thirty three HIV infected and thirty one HIV uninfected participants were assessed using a Gross Motor Function Measure 66 (GMFM-66), Functional Mobility Scale (FMS), Modified Ashworth Scale for tone, and a hand-held dynamometer for strength.

There were no statistically significant differences between the two groups for function, strength and tone. When the groups were separated into functional (GMFCS I and II) and non-functional groups (GMFCS III and IV), there were no statistically significant differences between the HIV infected and HIV uninfected participants for function (functional group p=0.52, non-functional group p=0.74), tone and strength. There was a clinically important difference found for the GMFM-66 in the functional group in favour of the HIV infected participants. There was a trend for the HIV infected functional participants to be weaker and have milder tone compared to their HIV uninfected counterparts while the non-functional HIV infected participants tended to have milder tone and be stronger than their HIV uninfected counterparts.

In conclusion, the HIV infected group presented similarly to the HIV uninfected group. The lack of gait analysis and a small sample size once the initial group was stratified, are limitations of this study. Further research is required with larger sample sizes to verify the results of this study.

DECLARATION

I, **Tasvi Naik, Student number 9704491p**, declare that this dissertation is my unaided work, with the exception of those works indicated in the reference citation and acknowledgements. It is being submitted in complete fulfilment of the requirements of the degree of Master of Science (Physiotherapy) at the University of the Witwatersrand. It has not been submitted before for any other degree or examination in any university.

Signed on this day in Johannesburg

Student Signature_____ **Date**_____22 November 2016_____

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Table of Contents

ABSTRACT ii

DECLARATION iii

ACKNOWLEDGMENTS iv

LIST OF ABBREVIATIONS xi

LIST OF FIGURES xiii

LIST OF TABLES xiv

CHAPTER 1 - INTRODUCTION TO THE STUDY 1

1.1 Introduction 1

1.2 Problem Statement 2

1.3 Research Question 3

1.4 Aim of the study 3

1.5 Objectives of the study 3

1.6 Significance of the study 3

1.7 Conclusion 4

CHAPTER 2- LITERATURE REVIEW 5

2.1 Introduction 5

2.2 Cerebral Palsy 5

2.2.1 Definition 5

2.2.2. Prevalence 6

2.2.3 Aetiology and Risk Factors 6

2.2.4 Clinical features of CP 7

2.2.5 Classification of CP 8

2.2.6 Gross Motor Function Classification Scale (GMFCS) 8

2.3 Spastic Diplegia 12
2.3.1 Gait pattern in spastic diplegia 13
2.3.2 Muscle strength and spasticity in spastic diplegia 14
2.4 HIV 18
2.4.1 Prevalence of children infected with HIV in South Africa 18
2.4.2 Vertical Transmission of HIV 19
2.4.3 Effect of highly active anti retroviral therapy (HAART) on HIV 19
2.4.4 Viral Load 22
2.5 HIV Encephalopathy (HIVE) 23
2.5.1 Definition 23
2.5.2 Pathogenesis of HIVE 24
2.5.3 Presentation of HIVE 26
2.5.4 HIVE and spastic diplegia 31
2.5.5 Effect of HAART on HIVE 33
2.6 Outcome measures and measuring devices 36
2.6.1 Gross Motor Function Measure (GMFM) 36
2.6.2 Functional Mobility Scale (FMS) 38
2.6.3 Modified Ashworth Scale (MAS) 39
2.6.4 Muscle strength and hand held dynamometry 40
2.6.5 Normative muscle strength data 42
2.7 Conclusion 44
CHAPTER 3- METHODOLOGY 45
3.1. Study Design 45
3.2 Ethical Clearance 45

3.2.1 Permission to conduct research 45
3.2.2. Ethical Considerations 45
3.3 Location 46
3.4 Study Population 46
3.4.1 Sample Size 46
3.4.2 Inclusion Criteria 46
3.4.3 Exclusion Criteria 47
3.5 Outcome Measures and Measurement Devices 47
3.5.1 The Gross Motor Function Measure (GMFM) 47
3.5.2 Functional Mobility Scale 47
3.5.3 The Modified Ashworth Scale 48
3.5.4 Hand Held Dynamometer 48
3.5.5. Viral Load 49
3.5.6 Anthropometric measurements 49
3.6 PROCEDURE 49
3.6.1 Recruitment 49
3.6.2 Medical History 50
3.6.3 Measurements 50
3.7 Statistical analyses 52
3.7.1 Descriptive and inferential statistics 52
3.7.2 Correlation statistics 53
3.8 Conclusion 53
CHAPTER 4 - RESEARCH RESULTS 54
4.1 Introduction 54

4.2 Descriptive and inferential statistics 54
4.2.1. Gender demographic 54
4.2.2 Age Demographic 55
4.2.3 GMFCS distribution 56
4.2.4 Demographic information 57
4.2.5 HIV infected group demographics 58
4.2.6 Anthropometric data 59
4.2.7 GMFM 62
4.2.8 Functional Mobility Scale 65
4.2.9 Muscle Tone 66
4.2.10 Muscle strength 70
4.6 Summary of results 73
4.6.1 Results of comparison of HIV infected and HIV uninfected groups 73
4.6.2 Results of comparison of HIV infected and HIV uninfected, functional groups 74
4.6.3 Results of comparison of HIV infected and uninfected, non functional groups 74
CHAPTER 5 - DISCUSSION 76
5.1 Introduction 76
5.2 Demographic data 76
5.2.1 General 76
5.2.2 HIV 78
5.3 Anthropometric data 79
5.3.1 Height and weight compared to normative data 79
5.3.2 Height and weight and viral load 80
5.4 Function 80

5.4.1 GMFM 80

5.4.2 Functional Mobility Scale 82

5.5 Impairments 83

5.5.1 Muscle Tone 83

5.5.2 Muscle strength 85

5.5.3 Muscle strength compared to normative data 86

5.7 Limitations of the study 88

5.8 Clinical Implications of the study 89

5.9 Research implications of the study 89

CHAPTER 6 - CONCLUSION 91

REFERENCES 93

APPENDICES 105

Appendix 1 105

Appendix 2 106

Appendix 3 107

Appendix 4 108

Appendix 5 110

Appendix 6 111

Appendix 7 112

Appendix 8 113

Appendix 9 115

Appendix 10 117

Appendix 11 118

Appendix 12 GMFM Score Sheet 120

Appendix 13 The Functional Mobility Scale 123

Appendix 14 The Gross Motor Curves 124

Appendix 15 South African Antiretroviral Treatment Guidelines for Children 2015 125

Appendix 16 Correlation Analyses 126

Appendix 17 Turnitin Originality Report 128

LIST OF ABBREVIATIONS

3DGA	Three dimensional gait analysis
ART	Antiretroviral therapy
BAZ	BMI for age z score
BMI	Body Mass Index
BSID II	Bayley Scales of Infant Development Second edition
CDC	Centre for Disease Control
CHBAH	Chris Hani Baragwanath Academic Hospital
CHER	Children with early antiretroviral therapy
CNS	Central nervous system
CP	Cerebral Palsy
FMS	Functional Mobility Scale
GMAE	Gross Motor Ability Estimator
GMDS	Griffiths Mental Developmental Scale
GMFCS E&R	Gross Motor Function Classification System Expanded & Revised
GMFCS	Gross Motor Function Classification System
GMFM	Gross Motor Function Measure
HAART	Highly Active Antiretroviral Therapy
HAZ	Height for age z-score
HHD	Hand held dynamometer
HIV	Human Immunodeficiency Virus
HIVE	HIV Encephalopathy
ICC	Intraclass co-efficient
ICF	International Classification of Functioning Disability and Health
LBM	Lean body mass

LSEN	Learners with special educational needs
MAS	Modified Ashworth Scale
MCID	Minimum Clinically Important Difference
MTS	Modified Tardieu Scale
NNRTI	Non- neucleoside reverse transcriptase inhibitors
NRTI	Neucleoside reverse transcriptase inhibitors
PI	Protease Inhibitors
PMTCT	Prevention of mother to child transmission
PVL	Periventricular Leukomalacia
RMMCH	Rahima Moosa Mother and Child Hospital
ROM	Range of Motion
USA	United States of America
VL	Viral load
WAZ	Weight for age z-score
WHO	World Health Organisation

LIST OF FIGURES

Chapter 3

Figure 3.1 Summary of the recruitment process ……..... 49

Chapter 4

Figure 4.1 Gender Demographic of HIV infected and uninfected groups ……. 54

Figure 4.2 GMFCS distribution for HIV infected and uninfected groups ……... 56

Figure 4.3 FMS frequency for non-functional HIV infected and uninfected groups ……..... 64

Figure 4.4 FMS frequency for functional HIV infected and uninfected groups … 65

LIST OF TABLES

Chapter 2

Table 2.1	Gross Motor Function Classification Scale (E & R) ……..…….	10
Table 2.2	Expected GMFM scores for each GMFCS level ……...…….	11
Table 2.3	Sagittal gait patterns in spastic diplegia ……..	14
Table 2.4	Comparison of three studies investigating normal muscle strength values in children …….	43

Chapter 3

Table 3.1	Modified Ashworth Scale ……..	47

Chapter 4

Table 4.1	Age demographic information for HIV infected and uninfected groups ….	54
Table 4.2	Age demographic information for HIV infected and uninfected, functional and non-functional groups …….	55
Table 4.3	GMFCS distribution for HIV infected and uninfected functional and non-functional groups …….	56
Table 4.4	Demographic information for HIV infected and uninfected groups …….	56
Table 4.5	Viral load and initiation of HAART in HIV infected group ..……...	58
Table 4.6	Comparison of z scores for HIV infected and uninfected groups.....	59
Table 4.7	Comparison of z scores for HIV infected and uninfected, functional and non-functional groups …..……..	60
Table 4.8	GMFM scores for HIV infected and uninfected groups ……..	61
Table 4.9	GMFM scores for HIV infected and uninfected, functional and non-functional groups ……..	62
Table 4.10	Percentiles of each GMFCS level using mean age and mean GMFM score ……	63
Table 4.11	P values of comparative MAS scores of HIV infected and uninfected, functional and non-functional groups……..	66
Table 4.12	Average frequencies expressed as percentages for spasticity across two sides in functional group……..…….	67
Table 4.13	Average frequencies expressed as percentages for spasticity across two	68

sides in non-functional group……..…….

Table 4.14 Muscle strength scores for HIV infected and uninfected groups …… 69

Table 4.15 Muscle strength scores for HIV infected and uninfected, functional and non-functional groups …….. 71

CHAPTER 1 - INTRODUCTION TO THE STUDY

1.1 Introduction

Cerebral Palsy (CP) is a well-recognised neurodevelopmental condition beginning early in infancy and continuing into adulthood (Rosenbaum et al, 2007). Permanent injury to the developing brain precipitates abnormal postures and movement pattern that affect activity and participation. It primarily affects motor function but disturbances of sensation, perception, cognition, communication, and behaviour can accompany the motor deficit (Rosenbaum et al, 2007).

Spastic diplegia is the term used to describe children with CP with mainly motor deficits, like muscle weakness and spasticity, in the lower limbs. It is associated with periventricular leukomalacia (PVL) as a result of prematurity (Bottcher, 2010). These children usually walk independently and have a distinct gait pattern that has been identified by Rodda et al (2004). There has been much research in the field of CP with specific attention to muscle strengthening, natural progression into adolescence, the impact of impairments on function and quality of life in children with spastic diplegia (Jaspers et al 2013; Calley et al 2012; Ferland et al, 2012; Kim and Park, 2011; Nyström Eek et al, 2011; Ross and Engsburg, 2007; Bell et al, 2002).

Globally, an estimated 36.7 (34-39.8) million people were living with HIV in December 2015. Sub- Saharan Africa accounts for 69% of the people living with HIV worldwide as well as 90% of the children infected with the virus (UNAIDS, 2015). In South Africa, there has been an increase in HIV prevalence from 5.5 to seven million people from 2008 to 2015. This is attributed to an increase in people accessing highly active antiretroviral therapy (HAART) and a corresponding increase in the life expectancy of people living with HIV. The prevalence of children under the age of fifteen living with HIV in South Africa has decreased from 300 000 in 2012 to 240 000 in 2015. According to 2015 statistics, 73% of infected children in South Africa are receiving HAART. Globally, 49% of children infected with HIV were accessing HAART in 2015 which has increased from 21% in 2010 (UNAIDS, 2015).

Early invasion of the central nervous system (CNS) by the virus affects the developing foetal and infant brain. This results in the most common primary HIV-related CNS complication: HIV encephalopathy (Whitehead et al, 2014; Langerak et al, 2013; Hilburn et al, 2010). Children who develop HIV encephalopathy usually present within the first two years of life (Hilburn et al, 2010) and have significant delays in motor, cognitive and language areas (Bailieu and Potterton, 2008; Hilburn et al, 2010; Donald et al, 2014a; 2014b).

The introduction of HAART has improved the survival and prolonged the quality of life of HIV-Infected children (Hilburn et al, 2010; van Rie et al, 2009). HAART may inhibit or delay HIV dissemination in the CNS. Several studies have shown that there has been a decline in the incidence of HIV encephalopathy since the increase in the use of HAART (Whitehead et al, 2014; van Rie et al, 2009). However, it does not reverse the damage that has already occurred (Smith et al, 2008). Therefore it allows for increased survival, meaning that a greater number of children are reaching school-going age but often with severe developmental delay (Potterton et al, 2016; Hilburn et al, 2010).

One of the residual impairments of HIV encephalopathy is diplegia (Donald et al, 2015; Langerak et al, 2014; Govender et al, 2011). Langerak et al, (2014) assessed children with spastic diplegia as a result of HIV encephalopathy in order to present a first description of gait and physical status. Their results showed two distinct patterns of gait which could not be classified in the typical spastic diplegic CP gait that was described by Rodda et al, (2004).

Children with diplegia as a result of CP or HIV encephalopathy have different pathogenesis but present with similar motor deficits, indicative of an upper motor neuron lesion. However, due to the paucity of literature in the field of spastic diplegia as a result of HIVE, it is unclear whether these groups have similar impairments, activity limitations and if their disability will follow the same progression as that of children with CP.

1.2 Problem Statement

In the South African as well as worldwide context, there are limited studies which have investigated and compared the clinical presentation of children presenting with spastic diplegia as a result of HIVE in comparison to HIV uninfected children with diplegia. Therefore it is uncertain if HIV infected children with diplegia have the same clinical

presentation in terms of impairments and function as children with diplegia who are HIV uninfected.

1.3 Research Question

Do HIV infected children with diplegia have a similar clinical presentation to HIV uninfected children with diplegia across GMFCS levels I-IV?

1.4 Aim of the study

To aim of this study was to determine whether the clinical presentation of HIV infected children with diplegia is similar to that of HIV uninfected children with diplegia with regards to gross motor function, muscle strength and tone in a South African setting.

1.5 Objectives of the study

1. To compare measured anthropometric and demographic data of the two groups
2. To determine and compare the functional status of children with diplegia in the HIV-infected and uninfected groups, across GMFCS levels I-IV according to the GMFM-66 and FMS assessments
3. To determine the spasticity of the subjects using the Modified Ashworth Scale and compare the results of the HIV infected and uninfected groups
4. To determine and compare the muscles strength of the HIV infected and HIV uninfected participants using a hand held dynamometer

1.6 Significance of the study

This study will provide insight into the clinical presentation of HIV infected and non-infected children with diplegia. The information obtained from this study will help clinicians better understand the clinical picture of spastic diplegia as a result of HIV. This will guide health professionals in making more informed, evidence-based decisions with regard to neurological and orthopaedic management as well as rehabilitation of these children. This study will begin to fill some of the gaps that are evident in this field and will form the base upon which future research can be conducted.

1.7 Conclusion

Neurodevelopmental delay in terms of motor, cognitive and language impairment as a result of HIVE has been well documented. With the advent of HAART, HIV infected children are surviving but with this comes an increase in co-morbid complications that are not life-threatening but still have an adverse effect on activity and participation. Spastic diplegia is a known presentation of HIVE but has a different pathogenesis to spastic diplegia as a result of CP. It is important to determine if HIV infected children with diplegia present similarly to HIV uninfected children with diplegia in a South African setting.

CHAPTER 2- LITERATURE REVIEW

2.1 Introduction

This literature review will serve to provide an overview of three areas. Firstly, the definition and global incidence of cerebral palsy will be described and the clinical picture of spastic diplegia will be further elaborated on. Secondly, it will serve to describe the incidence and prevalence of HIV and HIVE in children in South Africa. HIVE will be discussed in terms of the definition, clinical picture as well as the effect of HAART on HIVE. Lastly, an overview of outcome measures used in this study, to assess impairments, activity and participation in children with diplegia will be presented.

Literature dating from 1996 to present was searched using PubMed, Cinahl and Google Scholar search engines. Articles were also physically sourced from the Health Sciences library at the University of the Witwatersrand. The following key words were used when searching: cerebral palsy, spastic diplegia, HIV in children, muscle strength and adverse effects of HIV encephalopathy.

2.2 Cerebral Palsy

2.2.1 Definition

Cerebral Palsy (CP) is a well-recognised neurodevelopmental condition which begins in early childhood and persists through the child's life. There have been many definitions of CP through the years. However, these definitions have not given sufficient importance to the non-motor neurodevelopmental disabilities of performance and behaviour that often accompany CP. They also didn't take into account the musculoskeletal difficulties that often occur with advancing age (Rosenbaum et al, 2007). Therefore Rosenbaum et al (2007), proposed a new definition which would acknowledge these issues.

"Cerebral Palsy describes a group of permanent disorders of the development of movement and postures causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy and by secondary musculoskeletal problems" (Rosenbaum et al, 2007, pg 9). According to the annotations that have accompanied this definition, it was noted that the motor impairments manifest very early in childhood

development, usually before 18 months of age. Other neurodevelopmental and functional difficulties may become more evident later on. With regards to the term ‘fetal’ or ‘infant’ brain, there is no specified upper age limit, although the first two to three years of life are most important in the timing of the disturbances affecting the developing brain (Rosenbaum et al, 2007). This definition is more consistent with the biopsychosocial model of health as embodied in the WHO International Classification of Functioning, Disability and Health (ICF).

2.2.2. Prevalence

The global incidence of cerebral palsy is between two to three per 1000 live births (Tedla, 2014; Tugui and Antonescu, 2013). This has been consistent over the last fifty years due to the increasing survival of premature infants (Tugui and Antonescu, 2013). According to a systematic review of CP in the African context, the prevalence is between two to ten per 1000 children in community-based samples (Donald et al, 2014a).

2.2.3 Aetiology and Risk Factors

According to the latest definition, CP results from injury to the developing brain. This can occur prenatally, perinatally and postnatally (Rosenbaum et al, 2007; Krigger, 2006).

Prenatally acquired CP occurs from largely unknown causes (Krigger, 2006). Intra-uterine infection is the best known risk factor in this group. The risk of CP increases in very low-birth weight infants with a history of prenatal sepsis. CP is more prevalent among low birth weight infants in comparison to normal birth weight infants. Periventricular leukomalacia is one of the main causes of CP in pre-term infants (Odding et al, 2006).

Risk factors for perinatally acquired CP include birth asphyxia, neonatal convulsions, jaundice and infection, and instrument-assisted delivery. The risk of developing CP increases with multiple pregnancies. The prevalence of CP in single pregnancies is 2.3 per 1000 births, 112.6 per 1000 births in twins and 44.8 per 1000 births in triplets (Odding et al, 2006).

Postnatal causes account for 10 to 20% of all cases of CP. Brain damage can be caused by bacterial meningitis, encephalitis, hyperbilirubinaemia, trauma and abuse (Krigger et al, 2006).

In the African context, the most common reported risk factors were birth asphyxia, kernicterus and neonatal sepsis. Prematurity was only identified as a major cause in two of the sixteen studies reviewed (Donald et al, 2014a).

2.2.4 Clinical features of CP

Impairments as a result of CP result in activity limitation as well as participation restriction. These musculoskeletal impairments include spasticity, contractures, abnormal bone growth, poor balance, weakness and poor selectivity of movement (Kim and Park, 2011; Krigger et al, 2006; Odding et al, 2006).

When growth parameters of CP children were assessed and compared to normally developing gender and age-matched peers, children with spastic quadriplegia showed a statistically significant decrease in height, weight and head circumference. Children with spastic diplegia also had decreased growth parameters compared to the control group but were not statistically significant. In this study, weight was found to be the only growth parameter to predict gross motor abilities (Ibrahim and Hawamdeh, 2007). Poor growth and malnutrition are common amongst children with CP. However, those who have marked increase in spasticity and are inactive are also at risk of developing obesity. -Poor growth can be attributed to poor nutritional intake or impaired oro-motor control and swallowing. Non-nutritional factors like immobility and inactivity may also be contributing factors. This increases the risk for sub-optimal growth as there is decreased mechanical stress placed on the bone therefore decreased bone growth (Bell et al, 2010).

Children with CP are also known to have decreased physical fitness and other impairments like cognitive and intellectual impairments, epilepsy, visual and hearing impairments, speech impairments and difficulties with feeding (Odding et al, 2006; Krigger et al, 2006). Epilepsy was the most common reported co-morbidity of CP in Africa which is consistent with developed countries (Donald et al, 2014a). Approximately one third of school-going children with CP in a developed country experience behavioural difficulties. These range from peer problems (55.3%) and hyperactivity (30.3%) to emotional problems (40.8%). These were found to be unrelated to socio-economic, physical or cognitive characteristics, hence an additional cause of stress for the child and family (Brossard-Racine et al, 2012).

A thorough physical and radiological examination is necessary when making the diagnosis of CP. Almost seventy percent of children with spastic CP have abnormal MRI findings.

Radiological abnormalities can include brain malformations, cortical lesions and abnormalities of the peri-ventricular white matter (Odding et al, 2006).

2.2.5 Classification of CP

Classification of CP is done according to the type of movement disorder and the anatomical distribution of the abnormal movements.Abnormal movements can be divided into two groups namely: spasticity and dyskinetic. Spasticity is the more frequent disorder affecting 60%-80% of children with CP (Tugui and Antonescu, 2013; Bottcher, 2010; Krigger, 2006).

Spasticity has been defined in various ways. These include: muscle hypertonia, velocity-dependent stretch to passive movement, stiffness in a muscle during active movement and increased deep tendon reflexes (Krigger, 2006; Ross and Engsburg, 2002). Spasticity is the result of a lesion or injury to the pyramidal tract (Tugui and Antonescu, 2013).

Dyskinetic, athetoid and ataxic types of CP form the minority of cases. Athetoid and dyskinetic features include writhing type involuntary movements and fluctuating tone, while ataxic children with CP have problems with balance and coordination as a result of a lesion to the extra-pyramidal tracts (Tugui and Antonescu, 2013; Krigger, 2006).

Classification of CP can also be done according to the anatomical distribution of the motor deficit. Therefore classifications can include monoplegia (one limb affected), hemiplegia (one half of the body affected), diplegia (lower limbs more affected than upper limbs) and quadriplegia (all four limbs affected) (Tedla, 2014; Tugui and Antonescu, 2013).

2.2.6 Gross Motor Function Classification Scale (GMFCS)

Classification of CP traditionally looked at the condition from an impairment level. In this setting, mild, moderate and severe were the terms used to describe the severity of the motor impairment, while classification was based on the predominant area of the body that was affected. For example, spastic diplegia was the term used to describe a child with CP with predominant motor deficits in the lower limbs. Rosenbaum et al (2007) suggested that this manner of classification is not reliable as there is little uniformity between clinicians.

The Gross Motor Function Classification System (GMFCS) was developed by Palisano et al (1997) to provide a standard classification system that could be understood by both clinicians and parents of children with CP under the age of 12 years. Initially it consisted of five levels of functional abilities across four age bands. The age bands were designed to

account for age-related differences in gross motor function. The five levels were determined through a process evaluating elements of motor function. The CanChild Centre for Childhood Disability Research has been responsible for the development of the Gross Motor Function Measure (GMFM) as well as the GMFCS in order to help clinicians have a better understanding of gross motor function in children with CP. The GMFM is the gold standard outcome measure used by healthcare professionals to measure gross motor function in children with CP (Russell et al, 2000).

In order to establish validity and reliability of the GMFCS, a nominal group and Delphi survey consensus was used by Palisano et al, (1997). Seventy-seven children were classified by 51 therapists. The GMFCS has been found to have good inter-rater reliability (kappa of 0.75) (Palisano et al, 1997) and a high correlation (ICC -0.91) to the GMFM (Rosenbaum et al, 2014; Palisano et al, 2008). This indicates that there is an inverse relationship between these measures because higher numbered GMFCS levels represent children with lower function whereas a higher GMFM score indicates higher function (Palisano et al, 2000). The GMFCS has been shown to have content validity with an agreement of 80% predictive validity (positive of 0.74 and negative of 0.90), high inter-rater reliability (kappa of 0.75) and has evidence of stability over time (Rosenbaum et al, 2014; Palisano et al, 2008; Beckung et al, 2007; Palisano et al, 2000; Palisano et al, 1997).

The GMFCS was expanded and revised (GMFCS E&R) in 2008 to coincide with the ICF framework of activity and participation and to include an additional age band of 12 to 18 years. This was necessary to account for growth related changes that may affect function during puberty. Again, Palisano et al (2008) used a nominal group technique as well as Delphi survey to determine the content validity. Through this process the GMFCS-E&R was found to have content validity with an agreement of 80%. In revising this system, statements were reworded to distinguish between methods of mobility so as to have clear definitions of each level (Rosenbaum et al, 2014; Palisano et al 2008).

The GMFCS E&R consists of five ordinal levels. Each level describes the child's ability in sitting and walking and the need for assistive devices such as walkers and wheelchairs (See Table 2.1). The distance between the levels is not considered to be equal nor is it assumed that children with CP are equally distributed across the five levels (Beckung et al, 2007; Palisano et al, 2000). In order to differentiate between levels, one needs to evaluate the need for assistive mobility devices, as well as assistive technology, rather than quality of movement (Beckung et al, 2007; Palisano et al, 2000). Currently, it includes a

description of the child's ability at each level across different age levels. This was done to include age appropriate activities and participation. The age bands are: 1) less than two years, 2) two to four years, 3) four to six years, 4) six to twelve years and 5) twelve to eighteen years (Rosenbaum et al, 2014; Palisano et al 2008).

Not only is it a stand-alone measure that can be used by parents and professionals without the need for training (Rosenbaum et al, 2007), it is also a reliable tool and has become the principal way to describe motor disability for children with CP (Rosenbaum et al, 2014; Palisano et al 2008; Palisano et al, 1997).

Table 2.1 Gross Motor Function Classification System (E&R) (Palisano et al, 2008)

Level I	Walks without restrictions, limitations in more advanced gross motor skills
Level II	Walks without restrictions, limitations walking outdoors and in community
Level III	Walks with assistance of mobility device, limitations walking outdoors and in community
Level IV	Self mobility with limitations. Children are transported or use power mobility outdoors and in the community
Level V	Self mobility is severely limited even with the use of assistive technology

Impairments, behaviour and environmental factors can determine gross motor function outcome. Primary impairments of poor postural stability followed by the distribution of involvement, decreased quality of movement and spasticity (β=0.52-0.68) together with secondary impairments of muscle strength, decreased range of movement and decreased endurance (β=0.25-0.26) have a significant impact on function in all classifications of CP. Adaptive behaviour was also found to be a significant determinant of function in children with GMFCS level III to V (Bartlett et al, 2014). Using a path model analysis, Kim and Park (2011) showed that spasticity has a significant negative effect, while strength had a significant positive effect on gross motor function. However, Ostenjø et al (2004) found a complex relationship between spasticity, range of movement (ROM), selective motor control and gross motor function. Children with GMFCS I and II had decreased spasticity, fewer deviations in ROM and better selective dorsiflexion compared to children with GMFCS III and IV. In this way they indirectly affect overall activity and participation of children with CP (Kim and Park, 2011; Ostenjø et al, 2004).

In order to enhance the interpretation of the GMFM and the GMFCS, the researchers at the CanChild Centre developed the Gross Motor Function Curves (Appendix 14). The curves assist in determining if a child's gross motor function is in line with the expectation for children of the same age and GMFCS level. Data was transformed into age-90 values, which is the age by which children are expected to attain ninety percent of their motor potential. The expected scores for each level and the age at which the child is expected to achieve it are shown in Table 2.2 (Rosenbaum et al, 2002). These curves have been further elaborated on to improve their clinical use. Hanna et al (2008) created reference curves for each GMFCS level from the third to the ninety-seventh percentile. Beckung et al (2007) used these curves to predict gross motor outcomes in children with CP up to the age of fifteen while Hanna et al (2009) evaluated the stability and decline of the curves as children with various GMFCS levels moved into adolescence and adulthood.

Table 2.2 Expected GMFM scores for each GMFCS level (Rosenbaum et al, 2002)

GMFCS Level	GMFM-66 Limit (50% range)	Age-90 (years) (50% range)
I	87.7 (80.1-92.8)	4.8 (4.4-5.8)
II	68.4 (59.6-76.1)	4.4 (3.3-5.8)
III	54.3 (48.5-60.0)	3.7 (2.5-5.5)
IV	40.4 (35.6-45.4)	3.5 (3.5)
V	22.3 (16.6-29.2)	2.7

Beckung et al (2007) analysed the progression of gross motor development in children with CP over a four year period for all five GMFCS levels. Children with GMFCS level I and II were able to reach 90% of the maximum GMFM score at a median of five years. GMFCS III children reached 80% of the GMFM by the age of seven years. Children at GMFCS IV and V were only able to reach 30 and 20% of the GMFM score by age five and seven years respectively. Children with diplegia were the majority in GMFCS II and III groups. Overall, for all CP subtypes, there was a gross motor plateau at the age of six to seven years which was consistent with Rosenbaum et al (2002).

The gross motor function of 657 children with CP who were followed into adolescence and adulthood in order to determine the stability or decline of function. Children at GMFCS I and II showed no decline into adolescence. Children at level III peaked at 7 years

11months, while children at GMFCS IV and V peaked at 6 years11 months. These three levels showed a decline in GMFM score by 4.7, 7.8 and 6.4 points as they moved from adolescence to adulthood. This decline is seen to be significant and provides evidence that children at levels III, IV and V are at a greater risk of losing function. This may be attributed to increase in energy cost, increased contracture and deformity and increase stiffness (Hanna et al, 2009).

The natural progression in children with CP as they move from childhood into adolescence and adulthood is one of plateau then decline as they get older. The Gross Motor Function Curves have been found to be valid and reliable and are useful in being able to predict gross motor function according to GMFCS level in children with CP (Hanna et al, 2009; Beckung et al, 2007).

2.3 Spastic Diplegia

Children with spastic diplegia were traditionally identified as children whose lower limbs were more affected than their upper limbs. It is associated with periventricular leukomalacia (PVL) as a result of prematurity (Bottcher, 2010).

Periventricular leukomalacia results in dilatation of the ventricles and reduction of the white matter. The disruption of the motor tracts results in motor deficits. It is also thought that the white matter tracts connecting the prefrontal and posterior brain region may be affected. This will affect other brain functions like information processing and cognitive function. Executive function is the last cognitive area to mature and this occurs well into adolescence. It is defined as “the ability to control impulses, anticipate consequences, establish goals, plan, monitor results and use feedback and they are thought to regulate both immediate behaviour and planning towards long-term goals.” (Bottcher et al, 2010, pg 42). Children with diplegia may present with specific cognitive impairments in visual perception, attention, speech and language and executive function which results in learning difficulties. This can affect the child’s participation in school and make him or her more prone to behavioural problems (Bottcher, 2010; Bottcher et al, 2010). This together with the primary motor and postural disabilities can limit a child’s activity, restrict participation and negatively impact on quality of life.

When quality of life was assessed in ambulant children with CP, lower limb spasticity, severe gait pathology and slow gait speed played an important role in the domains of social well being, impact of disability and pain (Jaspers et al, 2013). Similarly when activity

and participation in relation to quality of life, was compared to that of age-matched typically developing children, children with CP experienced lower levels of participation across community life, personal levels of care and recreation, as well as lower quality of life with respect to function. This was mainly due to their physical restrictions which affected function and mobility (Calley et al, 2012).

Motor disability is regarded as the primary manifestation of CP. These restrictions of function and mobility can be due to trunk weakness, poor balance and intellectual impairment (Tedla, 2014). Muscle weakness is an important and well-documented characteristic of children with diplegia (Tedla, 2014; Nyström et al, 2008; Ross and Engsburg, 2007; Wiley and Damiano, 1998). Children with spastic diplegia can usually walk independently and have a distinct gait pattern (Rodda et al, 2004). These impairments will be discussed further.

2.3.1 Gait pattern in spastic diplegia

Rodda et al (2004) analysed the gait of 187 children with diplegia in order to provide a description of the typical diplegic gait patterns. Their classification of gait was based on the position of the ankle followed by that of the knee, hip and pelvis and was demonstrated to be reliable (kappa of 0.74). They identified five different patterns namely: true equinus, jump gait, apparent equinus, crouch and asymmetrical gait. Table 2.3 summarises the components of each pattern. Not described in the table, is the mild gait in which the subjects mainly presented with in-toeing but other kinematics at the hip, knee and ankle fell within the normal range. Younger children presented most commonly with true equinus and jump gait pattern whereas apparent equinus and crouch were more commonly seen in older children. This suggests that there may be a natural gait progression as children get older (Rodda et al, 2004).

The natural progression of gait in children with CP is due to increasing growth and age. Bell et al (2002) evaluated this progression over time using three-dimensional kinematics, temporal and stride parameters, as well as clinical examination measures in children with CP who had not had any orthopaedic intervention. Two assessments were completed four years apart. They had a small sample of 28 children of which 19 were classified as diplegic. Their results indicated that gait function decreased with respect to stride measures, range of motion and kinematic parameters over a four year period. Factors contributing to this decline included increasing body weight, the ratio of body weight to

strength, development of contractures and compliance with physiotherapy (Bell et al, 2002).

There is a positive correlation between gait and muscle strength. Improving muscle strength in the lower limbs can positively improve gait function (Nyström Eek et al, 2011; Nyström Eek et al, 2008; Ross and Engsburg, 2007).

Table 2.3 Sagittal Gait patterns in Spastic Diplegia (Rodda et al, 2004)

	Ankle	**Knee**	**Hip**	**Pelvis**	
True Equinus	Equinus	Extends fully	Extends fully	Neutral or anterior tilt	Younger children
Jump Gait	Equinus	Flexed in early stance and extend in late stance	Flexed in early stance and extend in late stance	Neutral or anterior tilt	Younger children
Apparent Equinus	Normal range	Flexed through stance	Flexed through stance	Neutral or anterior tilt	
Crouch Gait	Increased dorsiflexion	Flexed through stance	Flexed through stance	Normal or posteriorly tilted	
Asymmetric Gait	Subjects' two lower limbs are classified as belonging to two different groups.				

2.3.2 Muscle strength and spasticity in spastic diplegia

Muscle weakness and spasticity are known impairments of CP (Ferland et al, 2012; Ross and Engsburg, 2007; Ross and Engsburg, 2002). It is well documented that compared to their typically developing peers, children with CP have less strength in their affected areas (Dekkers et al, 2014; Thompson et al, 2011; Wiley and Damiano; 1998).

Lower limb strength profiles for spastic CP were documented by Wiley and Damiano in 1998. A hand-held dynamometer was used to assess the strength of lower limb muscles in 30 ambulatory children with spastic diplegia and hemiplegia as well as 16 age-matched typically developing children. The age range was between five and twelve years old. Eight muscle groups were assessed using the break test. The force value for each muscle group was normalised for body weight for better comparison across age groups and recorded as Newtons per kilogram (N/kg). This study provided evidence that children with CP were

significantly weaker than age-matched typically developing children and that weakness was more prevalent distally compared to proximally (Wiley and Damiano, 1998).

Ross and Engsburg have conducted several studies to investigate muscle strength in children with CP. In 2000, Engsburg et al investigated the relationship between hip spasticity and strength in spastic diplegia. Forty-four children with CP as well as typically developing children were assessed. Their results showed that hip adductor tone was significantly higher and hip strength measures were significantly lower in children with CP. In 2002, Ross and Engsburg investigated the relationship between spasticity and strength in individuals with spastic diplegia. These results were compared to results of 50 individuals without disability. Spasticity was assessed at the ankle plantar flexors and the knee flexors while strength was assessed at the knee flexors and extensors and ankle plantar and dorsiflexors. Results from this study were clinically significant. It showed that spasticity was not related to strength and could not be the cause for muscle weakness that was found in children with spastic diplegia. They concluded that muscle weakness was a significant impairment in these individuals as it was present in all subjects while spasticity was not. There was no significant correlation between the amount of spasticity in a muscle group to the amount of strength in agonist and antagonist groups. Their results supported previous literature in that spasticity was more prevalent distally than proximally in children with spastic diplegia. In 2007, they investigated the relationship between spasticity, strength, gait and the GMFM-66 in children with spastic diplegia. Their results showed that strength correlated significantly to function ($r=0.83$) and gait speed as compared to spasticity ($r=0.27$). A KinCom dynamometer was used in all the above studies to measure strength and spasticity (Ross and Engsburg, 2007; Ross and Engsburg, 2002; Engsburg et al, 2000).

Similarly Nyström et al have conducted several studies to investigate the impact of muscle strength and training on gait in children with CP. In the first study, they investigated the effect of strength training on gait function. The muscle strength of sixteen children with GMFCS level I and II were assessed pre and post intervention. Muscle weakness was most pronounced at the ankle followed by the hip (Nyström et al, 2008). Their results showed that muscle strengthening program has a positive effect on muscle strength as well as gait. In 2011, they elaborated on this relationship between gait and muscle strength but focused on gait kinematics. Twenty children with CP were compared to twenty typically developing children with regards to muscle strength and gait kinetics. All the lower limb

muscles were found to be weaker and the gait moment and power at the ankle was significantly lower in children with CP. There was a significant correlation between the muscle strength of six out of eight muscle groups and ankle generating power. This highlighted the importance of the plantar flexors during gait and more importantly that overall muscle strength in the lower limb is vital for the plantar flexors to generate the power required during gait. In both the above studies a myometer was used to assess muscle strength using the 'make test' method. All force values were recorded as torque (Nm) and then normalised for body weight (Nyström Eek et al, 2011; Nyström Eek et al, 2008).

Evidence of plantar and dorsiflexor weakness in children with CP as a result of an inability to produce the desired torque as well as inability to maximally activate the muscle was found by Elder et al (2003). Furthermore, these investigators determined that the cross-sectional area of the gastro-soleus muscle was much smaller in children with CP compared to normally developing counterparts (Elder, 2003).

Muscle strength is important for achieving function other than walking. This relationship between strength and function was assessed in two studies. In the first study lower limb strength in fifty ambulant children with CP was assessed using the 'make' test. Muscle strength was recorded as torque. In addition to muscle strength being weaker than the control group, the researchers also found an inverse relationship between strength and increasing GMFCS levels. The greatest reduction in strength from GMFCS I (independent walkers) to GMFCS III (walking with assistive device) was in the hip abductors (61%) and knee extensors (30%) (Thompson et al, 2011). The second study assessed strength in relation to overall locomotor function by using the Six Minute Walk Test, 10-meter Shuttle Run Test and Timed Up and Down Stairs Test. Hip flexor and ankle plantar flexor strength were associated with walking (47.8%) and stair climbing (32.9%) while hip abductors was associated with running (43.5%) (Ferland et al, 2012).

Muscle strengthening in children with CP has been studied to understand its effect on function. A randomised controlled trial in which a twelve week progressive resistance training program was administered to children in the intervention group while the control group received ongoing therapy showed that a strengthening program had a positive effect on muscle strength but this was not carried over into an improvement in mobility (Scholtes et al, 2008). This was supported by another study that sought to determine if a strengthening program would impact on daily physical activity like number of steps taken

and time spent sitting or lying in children with CP. The results of this study showed that an improvement in strength did not translate into an improvement in physical activity (Bania et al, 2016). The authors have suggested that strengthening needs to be context-specific rather than generalised strengthening to have a positive impact on activity and function.

A randomised controlled trial was conducted to determine the effect of a six week strengthening program on balance in children with diplegia. The experimental group received a specific strengthening program for lower limb and trunk muscles as well as conventional therapy while the control group received only conventional therapy. There were significant improvements in the experimental group for strength, balance and GMFM as compared to the control group (Tedla, 2014).

The above studies indicate that there is a correlation between muscle strength, gait and function in children with spastic diplegia but there is no consensus as to which muscle groups are consistently weak. In addition it has been shown that strengthening programs alone, do not improve function and activity.

Only one study was found which suggested that muscle strength could be an important factor in standing in children with CP. Lidbeck et al (2015), using 3D analysis, assessed the muscle strength of hip flexors, knee extensors, ankle plantar and dorsiflexors as well as standing posture. Muscle strength was assessed in a seated position but was analysed with respect to both the child's ability to stand and in the seated posture. Children standing with support presented with a more flexed posture but the same strength in the hips and ankle muscles as children standing without support. Hence, they have suggested that the sensory system deficits may also be a determining factor for standing. Further research is required in this regard (Lidbeck et al, 2015).

To summarise, the above studies have shown that muscle strength and spasticity have an impact on standing and walking (Lidbeck et al, 2015; Ferland et al, 2012). Spasticity increases from proximal to distal in children with spastic diplegia (Ross and Engsburg, 2002) but did not account for the greatest variance in gross motor function or gait (Ross and Engsburg, 2007). Muscle strength in children with CP has been found to be consistently weaker than typically developing children (Thompson et al, 2011; Wiley and Damiano, 1998). It is highly correlated to function and moderately to gait (Ross and Engsburg, 2007). Kim and Park (2011) found that strength and spasticity together accounted for 48.8% of the variance and are the causal factors in gross motor function. The results of this study must be interpreted with caution as there was a skewness

towards GMFCS level V. However, Ross and Engsburg (2002) found that there was no significant relationship between spasticity and strength at the knee and ankle in children with spastic diplegia GMFCS I and II. Muscle strengthening programs have proved to have a positive effect on strength (Bania et al, 2016; Tedla et al, 2014; Nyström et al, 2008; Scholtes et al, 2008) but not necessarily on function (Bania et al, 2016; Scholtes et al, 2008). Therefore we can see that there is a complex relationship between spasticity, strength, selective motor control and function in children with CP.

In conclusion, children with spastic diplegia as a result of CP have varying degrees of musculoskeletal impairments and cognitive impairments which lead to activity limitations and participation restrictions as compared to typically developing children of the same age.

Spastic diplegia as a result of HIV will be explored in the next section.

2.4 HIV

2.4.1 Prevalence of children infected with HIV in South Africa

Globally 3.2 to 3.4 million children are estimated to be living with HIV. Sub –Saharan Africa is home to 90% of HIV infected children (Kukoyi et al, 2016; Donald et al, 2015; Vreeman et al, 2015).

In South Africa the number of HIV infected children below the age of 14 has gone from 1900 in 1990, to peaking at 380 000 in 2008 and then decreasing to 240 000 in 2015 (UNAIDS, 2015). This decline may be attributed to the improved prevention of mother to child transmission (PMTCT) in South Africa which began in 2001. In the USA, the PMTCT programme has reduced the rate of vertical transmission to 2% (Donald et al, 2015; Vreeman et al, 2015; van Rie et al, 2007). According to UNAIDS Fact sheet (2015), since 2010, there has been a 66% reduction in the number of new infections in children in the Eastern and Southern African region while 59% of adult women in this region were accessing HAART in 2015 (UNAIDS, 2015).

Presently, in South Africa the PMTCT programme involves: initiation of anti-retroviral therapy during pregnancy in HIV infected women, all infants are tested at 6 weeks and prophylaxis is given to all HIV exposed infants. Access and adherence to PMTCT can be challenging in resource-limited settings (Donald et al, 2015).

2.4.2 Vertical Transmission of HIV

Children are mainly infected by HIV through mother to child transmission or vertical transmission which may occur in utero (less than 10%), at the time of delivery (10-20%) or from breast milk (10-20%) (Hilburn et al, 2010). Twenty five to forty percent of HIV infection in children is as a result of mother-to-child transmission (Hilburn et al, 2010). High maternal viral load has been associated with an increased risk of mother-to-child transmission (Hilburn et al, 2010; Mirpuri and Jain, 2010). One of the issues affecting mother-to-child transmission is the maternal side effects of HAART. Mirpuri and Jain (2010) have reviewed several studies which had conflicting results on whether HAART increased the risk of prematurity. However, they noted that initiation of HAART prior to pregnancy or in the first trimester was more strongly associated to pre-term delivery as compared to if it was initiated in the second or third trimester (Mirpuri and Jain, 2010). Furthermore, elective caesarean sections are recommended when the maternal viral load is greater than 1000 copies per ml. This is done to reduce the rate of mother to child transmission but it also increases the rate of prematurity in neonates (Mirpuri and Jain, 2010).

2.4.3 Effect of highly active anti retroviral therapy (HAART) on HIV

HIV drugs are classified into three main categories namely: 1) neucleoside or neucleotide reverse transcriptase inhibitors (NRTI's), 2) non-neucleotide reverse transcriptase inhibitors (NNRTI's) and 3) protease inhibitors (PI's). NRTI's and NNRTI's block viral replication while PI's prevent cleavage of viral proteins (Donovan et al, 2013). HAART is defined as the use of a combination of three drugs from at least two different classes of HIV drugs (Patel et al, 2008). The combination of drugs depends on the patient's previous exposure and resistance to HAART, age, tolerability and other co-existing illnesses (Donovan et al, 2013).

The introduction of HAART has improved the survival and prolonged the quality of life of HIV infected children (Hilburn et al, 2010; van Rie et al, 2009). HAART became available in developed countries such as the USA in 1996. Patel et al, (2008) conducted a study in the USA where they investigated the long-term effectiveness of HAART in children over a period of 10 years. The study included 1236 children who were part of the Paediatric AIDS Clinical Trials Group. Subjects were observed from 1996 (pre-HAART) to 2006. At each visit the data in the following categories were collected: sociodemographic characteristics, antiretroviral therapies and laboratory measurements. During this period 70% of

participants had initiated HAART. They concluded that HAART use amongst children and adolescents was associated with significant lower mortality compared with non-HAART regimens. They suggested that HAART be used as first line therapy for children (Patel et al, 2008). In the USA mortality of HIV infected children has decreased by 90% since the introduction of HAART (Vreeman et al, 2015). However, this is not the same in resource-limited settings where less than 25% of HIV infected children are receiving HAART (Kukoyi et al, 2016; Vreeman et al, 2015).

The ideal time to initiate HAART in infants was investigated as part of the Children with Early Antiretroviral Therapy (CHER) trial in South Africa. Three hundred and seventy seven infants were enrolled and randomised into three groups namely, the deferred group or one of two early therapy groups. The deferred group only received treatment if the CD4 count dropped to below 20% or clinical criteria were met. The early therapy group was divided into two arms: one in which therapy was administered early (at a median age of 7.4 weeks) but limited to 40 weeks and one in which it was administered early but limited to 96 weeks. Mortality was consistently higher in the deferred group. Their results also showed that HAART initiated at a median of seven weeks reduced early mortality from sixteen to four percent. This study provided strong evidence for early initiation of HAART in infants irrespective of CD4 count or clinical staging (Violari et al, 2008).

In South Africa, the HAART regimen was instituted in 2004. Initially, Centre for Disease Control (CDC) criteria, were being used for administration of medication. This meant that infants and children had to either have a CD4 count lower than 15% or have an incident of opportunistic illness to begin the treatment. Thereafter at the end of 2010, treatment was being given to infants under the age of one year irrespective of disease stage (Potterton et al, 2013). A large study of over 3000 participants in sub-Saharan Africa, showed that from 2005 to 2010 that the number of children initiating HAART had increased and that the age of initiation had decreased but the number of children initiating HAART with severe disease had remained high (Davies et al, 2013). The authors stated that even though the number of children accessing HAART had increased, improvement was still required in the field of early diagnosis and treatment. In 2013, the WHO guidelines stated that HAART should be initiated for all children under the age of five years regardless of clinical stage, with only older children needing to meet the immunological criteria (Donald et al, 2015; Vreeman et al, 2015) and this WHO recommendation has been further revised in 2015, which states that HAART should be administered to all children less than ten years as well as adolescents between the age of 10 and 19 years irrespective of stage of disease or

CD4 count. Once these guidelines are being followed in resource-limited settings, the number of children on HAART will sharply increase (Kukoyi, 2016).

In South Africa, the three stages of HAART treatment involve the first, second and third line regime (Appendix 15). All infants under the age of three or less than 10 kg use a combination of Abacavir (ABC), Lamividine (3TC) and Lopinavir or Ritonavir (LPV/r). Alternatively, LPV/r can be replaced with Efavirenz (EFV) (Department of Health 2015). Failure of this combination will cause the patient to move on to the second regime of drugs which include ABC, 3TC, LPV or Stavudine (D4T) in place of ABC (Department of Health 2015).

Growth failure was a hallmark sign of disease progression and an independent risk factor for death (Arpadi, 2005). However, the initiation of HAART not only decreases mortality but has also improves growth parameters in HIV infected children. In the pre-HAART era, HIV infected children were shown to have significantly lower weight and height for age compared to normally developing children (Shead et al, 2010) and progressive stunting was more common than wasting (Arpadi, 2005). This was attributed to persistent infection, protein breakdown and malnutrition (Shead et al, 2010).

In a longitudinal study to investigate the effect of HAART on growth in South Africa, Feinstein et al (2012) assessed 2399 children between 2004 and 2008. Measurements were taken at treatment initiation and again two years later. At baseline, 71% presented with growth failure. At two year follow up, 81% and 64% had attained normal weight and height respectively. Younger children and children with less severe growth failure were more likely to have catch-up growth after HAART initiation. This was supported by Sutcliffe et al (2011) and Weigel et al (2010) who investigated the effect of HAART on growth in children in sub-Saharan Africa. In both studies baseline scores showed HIV infected children were significantly underweight and stunted compared to age-matched peers. HAART resulted in significant improvement in these growth parameters but they did not reach normal growth after two years of treatment. Unlike Feinstein et al (2012), Weigel et al (2010), found that the severely undernourished and stunted children benefitted the most from HAART with regards to catch-up growth. A high viral load was initially associated with poor growth in children and infants with HIV however no association was found between the two once HAART was initiated (Arpadi, 2005).

Although HAART has been shown to improve mortality, it also has adverse effects. The interaction between the virus, HAART and inflammation can lead to various multi-organ

metabolic conditions (Donald et al, 2014b; Stanley and Grinspoon, 2012). NRTI's are associated with peripheral neuropathy and lipodystophy as a result of mithochondrial dysfunction. PI's are associated with dyslipidemia, osteoposrosis and impaired glucose homeostasis (Arpadi et al, 2013; Schiller 2004). Changes in lipid and glucose metabolism are prevalent in older children, adolescents as well as 20-80% of adults receiving HAART (Arpadi et al, 2013; Schiller 2004). Fat redistribution results in lipoatrophy peripherally and lipohypertrophy centrally around the trunk. This together with insulin resistance increases the risk for cardiovascular abnormalities which in turn can result in a sedentary lifestyle (Miller et al, 2010; Schiller, 2004). Cardiovascular disease is the leading cause of mortality among HIV infected adults in developed countries (Somarriba et al, 2013). There is also a high risk for cardiovascular abnormalities in children and adolescents but the extent to which it impacts morbidity and mortality is unclear (Miller et al, 2010).

Other organ systems that can be affected adversely are gastrointestinal e.g. nausea and vomiting; musculoskeletal e.g. osteopaenia; neurologic e.g. peripheral neuropathy; renal e.g. nephrotoxicity; dermatological and haematological. These side effects are reported in 50% of adult patients and are responsible for poor compliance with treatment regimens (Donald et al, 2014b; Schiller 2004).

2.4.4 Viral Load

Viral load (VL) is defined as the number of viral particles (HIV virus) present in the bloodstream of the organism. It is used to monitor the effectiveness of antiretroviral therapy, detect treatment failure and guide changes in treatment regimens. Optimal viral load should be below the level of detection as it indicates effective viral suppression (Rutherford et al, 2014).

The definition of virological treatment failure, as defined by WHO, is plasma viral load levels above 1000 copies/ml. This should be based on two viral load measurements after three months of HAART. The rate of treatment failure in HIV infected children in sub-Saharan Africa is between 13 to 44%. Therefore regular VL monitoring is important to determine the effectiveness of first line HAART management in children (Kukoyi et al, 2016).

2.5 HIV Encephalopathy (HIVE)

Vertical transmission leads to an increased risk of irreversible brain damage, intracerebral calcifications, microcephaly and developmental and cognitive impairment (Walker et al, 2013; Hilburn et al, 2010). This form of HIV-associated neurological disease in children is known as HIV encephalopathy (HIVE).

2.5.1 Definition

Early invasion of the CNS by the virus affects the developing brain and results in the most common HIV related CNS complication - HIV encephalopathy (Donald et al, 2015, Vreeman et al; 2015). HIVE was included as an AIDS-defining illness in children in 1987 (Patel et al, 2009; Smith et al, 2008). It is described as the failure to attain or a loss of a previously attained motor or cognitive milestone (Hilburn et al, 2010) and is often evident before there are any other significant signs of immunosuppression (van Rie et al, 2007).

The WHO (2007) defines HIV encephalopathy as follows: "at least one of the following progressing over at least two months in the absence of another illness:-

1. Failure to attain, or loss of, developmental milestones or loss of intellectual ability
2. Progressive impaired brain growth demonstrated by stagnation of head circumference
3. Acquired symmetric motor deficit accompanied by two or more of the following paresis, pathological reflexes, ataxia, gait disturbances" (WHO, 2007, pg 39)

Brain computed tomography scan or magnetic resonance imaging should be performed to exclude other causes (WHO, 2007).

"The CDC criteria for HIVE require at least one of the following to be present for the past two months in the absence of another illness:

1. Loss of previously acquired skill
2. Significant drop in cognitive test scores general to the borderline/delayed range, with functional deficits
3. Cognitive test scores in the borderline/delayed range , with functional deficits (and no history of significant drop or previous testing available)

4. Significantly abnormal neurological exam with functional deficits (i.e. significant tone, reflexes, cerebellar, gait or movement abnormalities)
5. Significant improvement in cognitive test scores over approximately a six month period associated with new treatment when baseline scores are in the borderline to delayed range, with or without significant brain imaging or neurologic abnormalities" (Walker et al, 2013, pg e863).

There are three sub-types of encephalopathy, namely: 1) subacute-progressive, 2) plateau encephalopathy and 3) static encephalopathy (Hilburn et al, 2010). Progressive encephalopathy is associated with neurodevelopmental and intellectual regression (Donald et al 2015; Hilburn et al, 2010; van Rie et al, 2007) and can be characterised by microcephaly (Smith et al, 2008). These children are stable for prolonged periods of time until they present with a gradual loss of previously obtained milestones. Plateau encephalopathy depicts a pattern whereby children do not progress nor do they show deterioration in their development for prolonged periods of time. Children who have been vertically infected usually present with static encephalopathy. In these cases there is no deterioration of attained milestones but they do have significantly delayed developmental and motor milestones (Donald et al, 2015; Hilburn et al, 2010). The prevalence of HIVE in South Africa has been documented between 13 and 35% (Smith et al 2008) and can increase to 20-60% in untreated children (Donald et al, 2014a).

2.5.2 Pathogenesis of HIVE

The developing brain is more susceptible to early and more severe invasion of HIV compared to adults (Donald et al, 2015). HIV is able to enter the central nervous system (CNS) during pregnancy and this, results in damage to the developing brain (Whitehead et al, 2014). HIV invades the central nervous system via infected monocytes and macrophages that are able to cross the blood-brain barrier. HIV can also infect astrocytes and this is thought to be significant in paediatric HIVE as they are more susceptible to infection (Crowell et al, 2014; Hilburn et al, 2010; van Rie et al, 2007). Neuronal damage can occur due to an inflammatory response and these changes are associated with disruption of synapse formation which is closely correlated to neurocognitive deficits (Crowell et al, 2014). The most vulnerable areas in the brain include the white matter, basal ganglia and cells around the blood vessels. Radiological findings have shown cortical atrophy and basal ganglia calcification and white matter lesions (Govender et al, 2011; van Rie et al, 2007).

Abnormalities found in the white matter in children under the age of three months, are indicative of early CNS invasion. Furthermore, subtle white matter abnormalities indicate a combination of diffuse myelin loss, astroglial proliferation and an infiltration of monocytes and macrophages (Donald et al, 2015). Magnetic Resonance Imaging (MRI) scans were taken of 44 children who were part of the CHER trial and suspected of having neurological complications. Thirty-four participants were from the early HAART initiation group. The mean age at which the scans were taken was 31.9 months. A review of the scans showed that 50% of the children referred had white matter signal abnormalities in the frontal and parietal lobes. No correlation was found between these radiological findings and the developmental scores or viral load. This suggests that brain lesions can occur early and initiation of HAART at eight weeks of age may still be too late to prevent HIV from penetrating the CNS (Ackerman et al, 2014).

HIV is neurotropic. There is rapid replication of the virus in the central nervous system which leads to early manifestation of severe physical and neurocognitive signs and symptoms. This neurological manifestation can occur before any other signs of immunosuppression that are associated with HIV (Donald et al, 2014b; Walker et al, 2013; Smith et al, 2008).

Risk factors associated with HIVE include maternal and child immune status, high plasma viral load in infancy, high circulating monocytes, timing of infection, route of transmission and availability of early treatment (Donald et al, 2015; Hilburn et al,2010; van Rie et al, 2007). The risk of developing HIVE is also higher if the maternal viral load at the time of delivery is high and if children have a high plasma viral load in infancy (van Rie et al, 2007).

HIV infected children are also predisposed to opportunistic infections that affect the CNS such as meningitis. As a result, neurological manifestations of HIV may be complex (Donald et al, 2014b; Smith et al, 2008). In resource-limited settings, environmental factors contribute towards neurocognitive development. Poverty, malnutrition, altered family dynamics, poor maternal education, drug and alcohol abuse and prolonged illnesses will negatively impact both motor and cognitive development in children infected with HIV (Donald et al, 2015; Hilburn et al, 2010; van Rie et al, 2007).

2.5.3 Presentation of HIVE

A major feature of encephalopathy is neurodevelopmental delay. These delays are seen in cognitive deficits like: impairment of memory, visual-spatial integration, executive function, language and speech deficits and general gross and fine motor deficits (Donald et al, 2015; Vreeman et al, 2015; Whitehead et al, 2014; Hutchings and Potterton, 2013; Potterton et al, 2013; Govender et al, 2011; Potterton et al, 2010; Shead et al, 2010; van Rie et al, 2009; Bailieu and Potterton, 2008). In South Africa various studies have been conducted to determine the extent of delay and the effect of HAART on neurodevelopmental delay. These will be presented chronologically from infancy to adolescence.

2.5.3.1 Neurodevelopmental delay in infancy

The roll-out of HAART began in 2004 in South Africa. As discussed previously during this period, children only received treatment if they had a CD4 count of less than 15% or an incident of opportunistic illness. The percentage of motor, cognitive and language delay in infants who did not receive HAART and were severely immunocompromised was 97.5% for motor and cognitive delay and 82.5% for language delay (Bailieu and Potterton, 2008). All infants were assessed using the Bayley Scales for Infant Development second edition (BSID II) and motor delay was the most severely affected. Shead et al (2010) investigated the extent of delay in institutionalised infants whose family circumstances were not conducive to their well-being. These subjects were not on HAART and results were compared to HIV uninfected infants that were also institutionalised. Similar to the previous study, the HIV infected group were significantly delayed in motor and cognitive areas compared to the HIV uninfected group and motor delay was more severe. In this study both groups showed a delay in mental development which could have been a result of inadequate mental stimulation as a result of poor living circumstances (Shead et al, 2010). Children in institutional care had a better motor performance than those in foster care when assessed using the Peabody Development Motor Scale, but in both places children with HIV performed worse than HIV uninfected children. In this study, all HIV infected children were receiving treatment and after six months showed improvement. This was attributed to stimulation provided by volunteers at these institutions (Jelsma et al, 2011).

With increasing access to HAART, the results from the CHER trial in South Africa showed that early initiation of treatment (< eight weeks) had better morbidity and mortality outcomes than deferred initiation. As a continuation of this trial, Laughton et al (2012) assessed the neurodevelopmental outcomes using the Griffiths Mental Developmental

Scales (GMDS) in infants receiving early HAART (< three months) and deferred HAART (> three months). Infants receiving early treatment scored better than those who received deferred treatment. The early treatment group had better scores for speech and hearing and eye-hand coordination. When compared to HIV uninfected children, the early treatment group scored similarly except in the locomotor scale. The authors provided strong evidence for the benefits of early treatment on neurodevelopmental outcome (Laughton et al, 2012).

In order to determine whether these benefits had a sustained effect over time, the development of infants on treatment needs to be assessed longitudinally. Twenty-seven HIV infected infants and 29 HIV exposed but uninfected infants were assessed using the BSID III prior to initiating HAART, at three months and again at six months. All HIV infected subjects were on a HAART regimen. The results for cognitive development showed that thirty percent of HIV infected infants had delay at baseline but by the second visit there were no significant differences between the groups. In terms of language, 45% had delay and the HIV infected infants performed worse than the HIV uninfected infants. Forty percent of HIV infected infants had motor delay by the second assessment and this increased from 29.6% at baseline. The authors postulated that there may be residual effects of the virus on muscle growth and strength (Whitehead et al, 2014). A similar study conducted in Zimbabwe, also found that HIV infected infants presented with 64.29% cognitive, 60.71% language and 53.57% motor delay compared to HIV uninfected exposed infants. This study had a larger sample size of sixty HIV infected and thirty-two HIV uninfected but exposed infants (Hutchings and Potterton, 2013).

The above studies have shown that cognitive, motor and language delays in infancy have decreased since HAART exposure has increased in South Africa, but they are still prevalent. Therefore it can be assumed that these problems may persist as the child moves forward into the school going phase. The next section will discuss the delays that children may experience in this phase.

2.5.3.2 Neurodevelopmental delay in pre-school and school-going children

Three studies have focussed on the neurodevelopment preschool age children between three and six years old in Africa and South Africa (Potterton et al, 2016; Lowick et al, 2012; van Rie et al, 2009). During this stage there is substantial amount of cognitive, language and speech development. Children refine their gross motor skills and start developing fine

motor co-ordination (CDC, 2016). Delays in this age group can have a negative impact on play and participation.

The two more recent studies conducted in South Africa, evaluated the development of HIV infected pre-school children using the GMDS as an outcome tool. In both studies children had access to early HAART and were medically stable. The subjects showed good virological control and HIV management. Lowick et al (2012) compared HIV infected subjects to HIV uninfected subjects from the same community and Potterton et al (2016) only assessed HIV infected children. Both studies found HIV infected children were delayed in all facets of cognitive performance. Lowick et al (2012) found that ninety percent of the infected group had severe cognitive delay with 46.7% showing signs of mental handicap. The percentage of delay was better (55.8%) in the study done by Potterton et al (2016) and this could be as a result of early ARV initiation in this group of children. However, despite early initiation there was still prevalence of delay. Hearing and speech were the most affected in both studies. These results were similar to an earlier study conducted in the Democratic Republic of Congo. The authors used the BSID II, the Peabody Developmental Motor Scale (2nd edition) and the Snijders-Oomen Nonverbal Intelligence Test as outcome measures. After a year of HIV treatment motor scores improved but cognitive scores didn't improve as significantly compared with baseline data. The motor improvement was attributed to improved general health and access to nutritional programs. The lack of cognitive gain was attributed to negative living environment, poverty and illness of the parent (van Rie et al, 2009).

As compared to infants who showed more severe motor delay, pre-school children appear to show more cognitive delay. Pre-school children with delay are then expected to enter into the formal school system where greater demand will be placed on them both physically and cognitively.

Visual and auditory performance, attention, visual-spatial processing, problem solving, planning, manual dexterity and speed and agility were assessed in HIV infected and uninfected children over the age of six years in Uganda. All HIV infected participants were not receiving treatment but had CD4 counts over 15% or greater than 350cells/µL. This study was done to evaluate the neurocognitive function of school-aged children. HIV infected children scored significantly lower in visual modules, attention, processing and problem solving as well as motor function. The authors postulated that these significant motor and cognitive deficits could be prevented or reversed with early initiation of

treatment (Ruel et al, 2012). These results are supported by Smith et al (2008) who assessed the neurocognitive function of the first children who accessed HAART treatment in 2002 and 2003. Deficits in cognitive, motor and language areas persisted after six months of treatment. They also advocated for early HAART initiation (Smith et al, 2008).

Walker et al (2013) assessed the neurocognitive function of HIV infected children with the diagnosis of HIVE compared to those without HIVE in Jamaica, which is also regarded as a developing country. A small sample of fifteen subjects per group with a mean age of 8.7 and nine years respectively, were assessed using tests that measured intelligence, visual and auditory memory, attention and fine motor coordination. Children with HIVE presented with the following: delayed milestones, hyperreflexia, spasticity, microcephaly, quadruparesis, diplegia, poor behaviour, milestone regression and poor learning. Other neurological abnormalities such as learning deficits, delayed milestone, isolated hyperreflexia and isolated leukencephelopathy were found in non-encephelopathic children. Children with HIVE performed significantly worse in all areas tested. Their prevalence of HIVE was 23.3% (Walker et al, 2013).

Besides motor and cognitive delays, behavioural problems may also be a concern in this population of children which could negatively impact learning. The Abberant Behaviour Checklist was completed by parents as part of study to determine the extent of neurological conditions affecting HIV infected children. Parents of 39 out of 63 children reported behaviour problems which ranged from hyperactivity (20%), psychosomatic (28%), conduct (10%) and anxiety (8%). The authors postulated that this could be as a direct result of the virus on the frontal cortex and basal ganglia (Govender et al, 2011).

HIV infected children experience motor, cognitive and language delays from infancy through to school going age. Behavioural problems start becoming more prevalent during the school going years. Furthermore, those presenting with HIVE perform worse in these areas compared to children without HIVE. These deficits are not reversed with HAART indicating that there may have been irreversible CNS damage early on, ongoing neuronal injury due to inflammation, neurotoxic effects of HAART or poor CNS penetration leading to ongoing viral replication (Crowell et al, 2014; Smith et al, 2008). Children with HIV have a greater survival rate and thus it is necessary to also understand how these delays impact them in their teenage years.

2.5.3.3 Neurodevelopmental delay in adolescence

Adolescence is regarded as a period when individuals learn to be more independent and start to develop their own identity. Their ability to think abstractly and refine their cognitive abilities improves during this time. The brain doesn't grow in size during this time but matures through increased myelination and organisation of the frontal lobes. This area is important for cognition and executive function. As with infancy, this maturation is influenced by genetic and environmental factors (Laughton et al, 2013). This is also a time for rapid physical growth and pubertal development. HIV infected adolescents have delayed entrance into puberty (Vreeman et al, 2015) and have to deal with stigma that may be associated with slow growth compared to peers (Lowenthal et al, 2014).

A child born in 2004 or 2005 would be twelve or thirteen in 2016 and just entering adolescence. Due to the variation of treatment policies when these children were born there is a great variability in the amount of HAART exposure that they have had. Some may have started treatment early if they fulfilled the CDC criteria at the time, some may have started after the diagnosis of HIVE and some may have been initially ARV naïve.

One review article highlighted the neurodevelopmental concern of HIV infected adolescents. There was a paucity of literature with regard to this age group (10-25 years) in developing countries. The author cautioned against assuming that results from studies conducted in the developed world can be applied to developing countries due to differences in treatment policies, economy and environment. A review of literature globally showed that HIV infected children and adolescents performed poorly in cognitive assessments and in specific executive function tasks like memory and attention compared to HIV uninfected counterparts. Language and hearing were was also poor thereby affecting literacy and academic success. Learning deficits result in 27-33% of children and adolescents needing special education, 51% having repeated at least one grade and 15% having repeated two or more grades. Pre-existing motor difficulties continue to pose challenges into adolescence (Laughton et al, 2013).

Studies from the USA report 25% prevalence of psychiatric problems in HIV infected children and adolescents. This was highly correlated to negative coping skills and poor neuropsychological functioning. In resource-limited settings the prevalence of attention deficit hyperactivity disorder was 28.6%, anxiety 24.3% and depression 25%. There were a limited number of studies in this setting but Efivarenz was associated attention and hyperactivity problems in children with HIV (Donald et al, 2014b).

These behavioural problems have an impact on compliance with HAART and risk-taking behaviours like promiscuity and drug abuse (Laughton et al, 2013). Furthermore, HIV infected adolescents are also at higher risk for psychosocial issues as they may have to deal with death of parents or siblings and may be responsible for running the household themselves (Lowenthal et al, 2014). The authors concluded that the impact of HIV on adolescents is complex and not well understood. Therefore there is a need for further research in this area especially in developing countries where HIV is more prevalent.

All evidence presented shows that infants, children and adolescents with HIVE perform poorly with regards to cognitive, language and hearing, behavioural and motor functions. They also present with significant neurodevelopmental delay compared to HIV uninfected peers. These delays remain despite children having early access to treatment. As children get older, there is a greater association with more subtle and specific cognitive impairment as well behavioural and psychological problems (Donald et al, 2014b) and this has a profound impact on learning and scholastic achievement. This suggests that CNS damage has occurred early on despite participants having good viral control (Donald et al, 2015). A comprehensive neurodevelopmental and behavioural assessment needs to be carried out to accurately detect delays (Govender et al, 2011). Unfortunately, in resource-limited settings, HIVE remains a frequently undiagnosed problem in clinical practice (Donald et al, 2015; Govender et al, 2011).

2.5.4 HIVE and spastic diplegia

Neurological signs like abnormal rigidity of limbs and abnormal postural tone are not very different from what is observed in children with CP (Tardieu, 1998; Mintz, 1996). At the Red Cross Children's Hospital in South Africa, HIVE is the most common primary neurological disorder of HIV infected children. Donald et al (2015), set out to determine the descriptive profile as well as the challenges of management of children attending the HIV-Neurology clinic. Their study included 87 children, between the ages of two and nine who fulfilled the criteria for HIVE. Each participant underwent a medical and physical examination. Their findings indicated that 80% of the children had delayed walking, 75% delayed speech, 48% presented with microcephaly and 63% presented with spastic diplegia. There was no statistical difference in the age of commencement of HAART and children with and without microcephaly. However, this was approaching significance ($p=0.06$) in those with and without diplegia (Donald et al, 2015).

Similarly Govender et al (2011) assessed 78 HIV infected children with a mean age of five years at the Groote Schuur and Red Cross Children's Hospitals in South Africa. Subjects underwent a general and neurological examination. In their study 59% of subjects had abnormalities on neurological examination. These included HIVE, global pyramidal tract signs, cerebrovascular events, diplegia, quadraparesis, proximal weakness, distal weakness and epilepsy. HIVE was statistically more common (p=0.012) in patients that did not receive antiretroviral therapy (Govender et al, 2011).

Diplegia is a known classification of CP and is also one of the residual impairments of HIV encephalopathy (Donald, 2015; Langerak et al, 2014; Govender, 2011). In order to differentiate between the two Langerak et al, (2014) assessed children with spastic diplegia as a result of HIV encephalopathy in order to present a first description of gait and physical status. Fourteen children between the age of four and ten years old with a diagnosis of HIVE and diplegia were assessed. Demographic, medical, socio-economic and anthropometric information was collected. In addition to this, children were classified according to the GMFCS and Functional Mobility Scale (FMS). Gait was analysed using Three-dimensional Gait Analysis (3DGA) and body function parameters of muscle strength, tone, selective motor control and contractures were also assessed. Their results showed two distinct patterns of gait which could not be classified in the typical spastic diplegic CP gait that was described by Rodda et al, (2004). Group one walked with a gait pattern close to the pattern of a typically developed person, they had mainly increased plantarflexor tone and showed a decrease in muscle strength. Group two had a more pathological gait pattern. This was mainly noted with persistent knee flexion and ankle plantarflexion through the gait cycle. Their tone increased from proximal to distal and was higher than group one while muscle strength was significantly lower than group one. HAART initiation was significantly earlier in group one (6.7months) compared to group two (11.2 months). Limitations of this study include a small sample size as well as the lack of a comparative control group. The authors have suggested that diplegia as a result of HIVE may be underreported and they recommend that further studies are required to understand the underlying pathology and natural progression of this condition (Langerak et al, 2014).

These studies suggest that HIVE may result in a presentation similar to that of CP diplegics but to date there are no studies that have documented the similarities and differences in their presentations.

2.5.5 Effect of HAART on HIVE

HAART needs to cross the blood-brain-barrier in order to inhibit or delay HIV replication in the CNS. Antiretroviral medications are given a score based on its ability to effectively penetrate the CNS. High CNS penetrating drugs like zidovudine and nevirapine have a score of four. These regimens were associated with a 41% reduction in the incidence of HIVE (Patel et al, 2009). Several studies have shown that there has been a decline in the incidence of HIV encephalopathy since the increased use of HAART (Whitehead et al, 2014; Patel et al, 2009; van Rie et al, 2009).

In the USA, HAART has decreased prevalence of HIVE from 35-50% to less than 2% (Donald et al, 2015; Vreeman et al, 2015). Viral suppression before the age of five years was associated with positive neurocognitive outcomes in school-going children. Further studies are required to determine if these benefits persist through adolescence (Crowell et al, 2015). Early initiation of HAART results in improved neurodevelopmental outcomes compared to deferred initiation (Whitehead, 2014; Laughton et al, 2012). However in developing countries prior to 2010, HAART initiation is often delayed beyond infancy as it was only initiated if the CD4 count was below 15% or if there was evidence of an opportunistic illness, therefore HIVE still remains a frequent problem (Donald et al, 2015).

HAART improves some of the neurological sequelae of HIVE, however, it does not reverse the damage that has already occurred (Vreeman et al, 2015; Laughton et al, 2013; Walker et al, 2013; Govender et al, 2011; Smith et al, 2008). Neurological, behavioural and cognitive deficits may still persist (Govender et al, 2011; Smith et al, 2008; van Rie et al, 2007). Many studies in both resource limited as well as resource rich settings have advocated for early HAART initiation in order to minimise neurodevelopmental consequences (Whitehead et al, 2013; Laughton et al, 2012; van Rie et al, 2009; Patel et al, 2009; Smith et al; 2008). Early HAART initiation before three months of age is associated with a more favourable neurological outcome (Donald et al, 2014b). One also needs to consider the impact the environment, access to resources, the effect of opportunistic infections, nutrition and poverty can have on the child's neurodevelopment (Donald et al, 2015; Donald et al, 2014b; Laughton et al, 2013; van Rie et al, 2009; Smith et al, 2008).

In a review of the physical and psychological effects of HIV infection and treatment on HIV infected children, Vreeman et al (2015) noted that the potential neurotoxic effects of HAART on the developing foetus in utero are unclear although acquisition of HIV in utero

is associated with more severe neurocognitive function (Crowell et al, 2014). Medication that has high CNS penetrating qualities may be able to control HIV replication in the CNS but it may also increase the risk for neurotoxicity. The mechanism by which this occurs is through metabolic derangement associated with the medication, mitochondrial toxicity associated with NRTI's and proteosomal dysfunction associated with PI's (Crowell et al, 2014). Currently the benefits of good CNS viral control must be weighed up against the effect of neurotoxicity. There is a strong need for research to investigate neurotoxic effects of HAART as well as to investigate if its benefits will continue into adolescence and adulthood (Vreeman et al, 2015).

2.5.6 Muscle Strength in HIV

During the acute phase of HIV, there is a loss of muscle protein (Hsu et al, 2005). Impaired muscle strength in children with HIV has been described in several studies where gross motor development is impaired or delayed (Langerak et al, 2014; Govender et al, 2011; Miller et al, 2010).

In children normal muscle strength is required to play and explore the environment and therefore enhance normal development. Skeletal muscle represents 50-54% of lean body mass (LBM). A combination of malnutrition and abnormal endocrine function in HIV affects the body's protein turnover. There is an increased protein demand due to inflammation from the virus and inadequate protein intake and absorption results in a loss of LBM. This is observed as muscle wasting and is associated with decreased muscle strength (Dudgeon et al, 2006; Grinspoon and Mulligan, 2003). Peripheral fat loss and increased central fat redistribution is an adverse effect of HAART. It can result in increased fat in the muscle tissue thereby affecting the force that can be generated by the muscle (Vreeman et al, 2015). This predisposes HIV infected children to increased cardiovascular and metabolic dysfunction which can lead to a sedentary lifestyle (Miller et al, 2010; Grinspoon and Mulligan, 2003).

Many studies have investigated the effect of HIV, HAART and strengthening programmes on strength in adults as compared to very few in children.

Humphries et al (2014) conducted a pilot study to investigate the muscle strength of children, between the age of four and eight years old, infected with HIV. The muscle strength of HIV infected children receiving HAART and not receiving HAART were compared with those of normally developing children. None of the subjects in this study

were diagnosed with HIVE. These results showed that the group not receiving HAART was significantly stronger than the group receiving HAART. Both these groups still displayed a 50% decrease in muscle strength compared to typically developing children. However the group receiving HAART were more severely immunocompromised and qualified for the CDC criteria for HAART initiation. The non-HAART group had not yet met this criteria and therefore they could have been stronger. This study suggests that further testing is required to determine if HAART negatively impacts muscle strength and that a comprehensive values of normative muscle strength in children needs to be established.

Physical fitness, strength and anaerobic power were investigated in HIV infected children and adolescents by Somarriba et al (2013), Ramos et al (2012) and Miller et al (2010).

The first study compared muscle strength, flexibility and cardiorespiratory fitness while the second study compared the muscle strength and anaerobic power of HIV infected children and adolescents to an uninfected control group. Both studies had small sample sizes of 45 and 14 respectively. Somarriba et al (2013) found the HIV infected group to have less cardiorespiratory fitness and strength compared to the healthy control group while Ramos et al (2012) found the HIV infected group to have the same strength as the control group but decreased anaerobic power. Anaerobic power is required to complete daily, recreational or sports tasks efficiently (Ramos et al, 2012). Similar to Humphries et al (2014), Somarriba et al (2013) found that increased duration of HAART and increased body fat independently and negatively impacted on physical fitness. Fat redistribution and mitochondrial toxicity occur with increased exposure to NRTI's and PI's. This impact on mitochondrial function affects energy distribution to skeletal muscle thereby affecting strength and exercise capacity (Somarriba et al, 2013).

Muscle strength, length and cardiorespiratory fitness improved with twenty-four supervised hospital exercise sessions which included aerobic exercises, resistance training and stretching. Of these measures, the greatest improvement was seen in strength. This exercise program also had a positive impact on lean body mass. Only seventeen HIV infected children and adolescents (mean age 15years) participated in this study. They also completed unsupervised home exercise program after completion of the hospital program. Follow-up assessment after seventeen weeks showed that there was no significant change and participants were able to maintain strength and fitness with a home program. This was a pilot, feasibility study and it is recommended that a larger study should be conducted (Miller et al, 2010).

Increasing protein intake as well as muscle strengthening programmes, have been found to be effective in decreasing muscle wasting and improving muscle strength (Miller et al, 2010; Dudgeoun et al, 2006; Grinspoon and Mulligan, 2003).

In summary, HIV infected children who were exposed to the virus during a period of rapid brain development may present with HIVE. They have been and will be exposed to the virus as well as the medication throughout their life and while HIV is no longer a life-threatening illness, the long term complications are more prevalent. Motor, cognitive, behavioural and language deficits may persist and will need to be managed by a multi-disciplinary team to give children the best chance possible for future success and quality of life.

2.6 Outcome measures and measuring devices

Assessment tools were selected to assess body structure and function (muscle strength and tone), activity (gross motor function) and participation (mobility in a community setting) in children with spastic diplegia. This is accordance with the International Classification of disability, functioning and health (ICF) framework which was developed by the WHO for the management of persons with disability. The aim of the ICF is to provide a framework that is internationally recognised and thereby gives health professionals a common language by which to describe patient's disabilities and needs. The framework breaks down the patient's disability into the following components: body structure and function, activity, participation, personal and environmental factors. Body structure and function describes the anatomical parts of the body and physiological body systems. Activity refers to the ability of the individual to execute a task while participation refers to the involvement of the person in life situations (Franki et al, 2012).

2.6.1 Gross Motor Function Measure (GMFM)

The GMFM is the gold standard outcome measure used by healthcare professionals to measure gross motor function in children with CP. It is a criterion- referenced based observational tool that was developed to assess children with CP, from the age of five months to 16 years (Russell et al, 2000). It is widely used by clinicians to measure change over time as well as change related to an intervention (Altoaibi et al, 2014). The first edition of the GMFM was published in 1990.

The GMFM-88 is the original measure testing 88 items over five dimensions. These items are organised in a way which reflects normal developmental milestones (Alotaibi et al, 2014). These dimensions are: a) lying and rolling (17items), b) sitting (20items), c) crawling and kneeling (14items), d) standing (13items) and e) walking, running and jumping (24 items). Observation of these items enables the examiner to have a clear understanding of how much (quantity) the child can do rather than how well (quality) they do it. Each Item is scored on a four-point ordinal scale (zero=does not initiate, one=initiates < 10% of activity, two=partially completes 10 to <100% of activity and three=completes). Any item that the child is unable to or unwilling to do is given a zero rather than unachieved. This does not accurately reflect the child's ability. For each item the child is allowed a maximum of three attempts. Scores for each dimension are calculated, averaged out and converted into a percentage. The difference in points between GMFCS levels differentiates whether a child is able to roll, sit, crawl and walk (Palisano et al, 2000). The limitation of this tool is that it can take long to administer and it has a nominal scale. This means that the there is no set interval between different items on the scale making it difficult to interpret change in the scores (Russell et al, 2000).

In order to improve the interpretability and clinical usefulness of the GMFM, Russell et al (2000) applied the Rasch analysis to the GMFM. This helped to identify 66 items from the original 88 that form a unidimensional, hierachial scale. The advantages of using the GMFM-66 are that it takes less time to administer, items are arranged in the order of difficulty and the conversion from percentage to interval scaling has improved the interpretability of the total score. This provides the clinician with more information which is useful for goal-setting.

The Gross Motor Ability Estimator (GMAE) is a computer program that converts the GMFM-66 individual scores into an interval scoring system. The GMFM-66 has a high test-retest reliability has been found to be a valid (intraclass correlation coefficient=0.99) and is able to detect change after an intervention ($P < .0001$). With the above mentioned properties the GMFM-66 is widely used during clinical research (Russell et al, 2000).

Several systematic reviews of outcome measures in children with CP have been conducted. The GMFM and Paediatric Evaluation of Disability Inventory (PEDI) were found to be valid and reliable with respect to responsiveness to change (Ketelaar et al, 1998), while the GMFM was found to have sound psychometric properties (Harvey et al, 2008). Debuse and Bruce (2011) also reviewed outcome measures for activity for children with

CP. Although they found the GMFM-88 and 66 to be appropriate for this group, they have highlighted a few clinical considerations that need to be taken into account. Firstly, both the GMFM-88 and 66 only examine gross motor function and therefore it should be used in conjunction with other outcome measures to provide a comprehensive assessment of the child's activity and participation. Secondly, they only give an indication of the child's performance in a test environment. It does not account for the child's motor responses in their normal environment. In addition to this, the following considerations need to be made when using the GMFM-66: it has a floor effect in children with poor motor ability and a ceiling effect in children older than five years.

Most recently Alotaibi et al (2014) also reviewed the efficacy of the GMFM-88 and 66 to detect change in gross motor function in children with CP. Twenty one studies fulfilled their inclusion criteria. The studies had a moderate to high methodological quality and covered a wide age range from 10 months to 16 years. They concluded that both these measures were able to detect significant clinical change in gross motor function for children with CP under the age of 17. It may be less sensitive for detecting change in children who are at GMFCS level IV and V compared to GMFCS level II and III. They had similar clinical considerations as Debuse and Bruce (2011) with regard to the ceiling effect and using additional outcome measures to provide a comprehensive assessment.

The minimum clinically important difference (MCID) is the amount of change required for an observable clinical difference (Oeffinger et al, 2008). It is measured using effect sizes i.e. small effect sizes are not noticeable by the human eye, medium effect sizes are large enough to be noticed in normal observation and large effect sizes are obviously observable. MCID's for medium and large effect sizes were established for the Dimension D and E by assessing ambulant children with CP. This means if a change in score exceeds the MCID it is likely that the change is clinically important. The reported MCID, for the GMFM, of a medium effect size is 0.8 and for a large effect size is 1.3. These values are important in assessing change over time (Oeffinger et al, 2008).

2.6.2 Functional Mobility Scale (FMS)

The Functional Mobility Scale (See Appendix 14) was designed to evaluate the mobility of children with CP at different distances. The clinician asks a few questions of the child and parent in order to develop a performance rating. The scale rates the walking ability of the children at three different distances: 5m (at home), 50m (at school) and 500m (in the community). The completion of these distances is rated from one to six, with one indicating

that the distance is attained by the use of a wheelchair or buggy, and six indicating that the subject is independently mobile on all surfaces. The tool also takes into account crawling, and if the distance is not applicable (Graham et al, 2004).

In a systematic review of available outcome measures for children with CP by Harvey et al (2008), the FMS was the only measure that took into consideration the different devices that a child with CP might use as well as looking at the child's mobility in different environments. However, it concluded that further evidence of reliability was required.

Harvey et al, (2010) investigated the reliability of the FMS for children with CP. Forty-four raters assessed 118 CP children with GMFCS levels I-IV. The raters included hospital and community-based physiotherapists as well as orthopaedic surgeons. Results showed that there is good inter-rater reliability of the FMS for children with CP over all three distances with the kappa coefficient being 0.87 for 5m, 0.92 for 50m, and 0.86 for 500m. It was concluded that the FMS can be used by clinicians to assess the mobility of children with CP.

2.6.3 Modified Ashworth Scale (MAS)

The MAS is a 6-point rating scale that is used to assess the resistance of a muscle to passive movement. The original Ashworth scale was a five point scale which rated the amount of tone felt as the limb was moved passively through its full ROM. Modifications were added to give additional information of how soon in the motion and how much during the motion the resistance was felt (Damiano et al, 2002). The MAS is the most frequently used scale in clinical practice to measure spasticity in children with CP and/or adults with an upper motor neuron lesion (Numanoglu & Gunel, 2012; Mutlu et al, 2008). There is a significant correlation between the MAS and GMFM-66 (r=0.64) (Ostenjø et al, 2004). Despite this, the reliability of the scale is questionable.

Numanoglu & Gunel (2012) and Yam and Leung (2006), investigated the intra-observer and the inter-tester reliability of MAS and the Modified Tardieu Scale (MTS) respectively in children with CP. Spasticity of elbow flexors, wrist flexors, hip adductors, hamstrings, gastrocnemius and soleus muscles were evaluated by one assessor using both scales. Intra class coefficient (ICC) was chosen as the test statistic for reliability. Good reliability was defined as ICC greater than or equal to 0.75 in both studies. The intra-observer reliability for MAS did not reach the acceptable ICC level of 0.75, while MTS reached this

level for most muscles. Both the MAS and MTS showed ICC values of less than 0.75. The researchers found that the distinction between the scores is dependent on range of movement (ROM) and this makes interpretation difficult especially in muscles that are shortened. Factors such as emotional state of the child and pain were given as possible explanations for low reliability scores. They concluded that although it is easy to administer and does not require equipment, it is based on subjective decisions and has poor intra-rater and inter-rater reliability. Further studies were recommended to establish reliability (Numanoglu & Gunel, 2012; Yam and Leung, 2006).

The inter and intra-rater reliability of the MAS in children with hypertonia was also investigated by Clopton et al in 2005. Seventeen subjects were initially examined by three to four testers. They were re-tested by the principal examiner within six to eight days. The following muscles were tested: elbow flexors, hip adductors, quadriceps, hamstings, gastrocnemius and soleus. Their results showed that hamstrings had good inter-rater and intra-rater reliability (ICC>0.75), while elbow flexors had only good inter-rater reliability. The gastrocnemius and soleus muscles had the lowest reliability scores. A possible explanation for this could there is a shorter lever arm and there is usually more limited range of movement. Similarly, hip adductors and quadriceps showed low levels of reliability but this could not be explained by the shorter lever arm theory. The decreased attention span of the children was noted as a limitation of the study. They also recommended that the 1+ score be used as a rating for clonus (Clopton et al, 2005).

The reliability of both the Ashworth and the Modified Asworth scale in children with CP was investigated by Mutlu et al in 2008. They assessed 38 spastic diplegic children between GMFCS level I-III. Each child was assessed by three different therapists in two different sessions a week apart. The muscle groups tested were: hip flexors, hip adductors and internal rotators, hamstrings and plantar flexors with the knee extended. Scores were recorded for both the Ashworth scale and the MAS. The results indicated good interrater reliability for hamstrings and adductors and moderate reliability for hip flexors and gatrocnemius. Intra-rater scores ranged from poor to good with hip internal rotators showing the least and hip flexors the most reliability. In this study, MAS had higher intra-rater reliability scores than the Ashworth Scale (Mutlu et al, 2008).

2.6.4 Muscle strength and hand held dynamometry

Isometric muscle strength is indicative of the force produced at a particular muscle length while isokinetic muscle strength indicates the force produced through a controlled

movement (Verschuuren et al, 2008). Clinically, muscle strength is usually assessed isometrically using manual muscle testing or a dynamometer. Manual muscle testing is subjective, uses an ordinal scale and is not sensitive to small or medium muscle strength changes (Verschuren et al, 2008). In order to objectively measure strength one would need to use a device that is shown to be valid and reliable.

Furthermore, isometric muscle testing can be done using the 'break' or the 'make' method. In the 'break' method, a force is gradually applied by the examiner to allow the subject to recruit the maximum number of muscle fibres. In the 'make' method, maximal effort is exerted by the participant against a stationary force. The reliability of using these methods for muscle testing with a hand-held dynamometer (HHD) was assessed in children with CP. The inter-tester reliability results were questionable for both methods. The precision of the break test ranged from 22.2% in the hip to 35.3% for the hip and knee, while the precision of the make test ranged from 16.2% in the hip to 56.2% in the ankle (Vershuren et al, 2008).

Dekkers et al, (2014) systematically reviewed the availability of instruments for the measurement of upper limb strength in CP children. The clinimetric properties of the measuring instruments in each study were assessed. Six different measurement instruments were studied namely,1) manual muscle testing, 2) the Jamar dynamometer, 3) a HHD, 4) an instrument based on muscle strength-torque sensors, 5) a computerised measurement tool using a strain gauge and 6) a modified sphygmometer. The review highlighted the paucity in the literature with regard to upper limb strength testing. None of the instruments were rated as "strong" or "moderate" for their level of evidence. In this study, the MicroFET2 dynamometer was reviewed. The positive characteristics of the HHD are that it is a small, relatively inexpensive, easy-to-use device. It had the property of being able to detect small changes. The assessor may have challenges in being able to appropriately stabilise the patient when using this device. They suggested that standardised HHD procedures should be developed for testing of CP children and that the MicroFET2 dynamometer has the potential to be reliable in measuring upper limb strength (Dekkers et al, 2014).

A recent study by Willemse et al (2013) assessed the reliability of isometric lower extremity testing in CP children. They used a MicroFET HHD to measure isometric strength on two separate occasions. Fourteen children with GMFCS level I-III were assessed. The 'make'

test was used and three trials were measured for each muscle group. The muscle groups assessed were knee extensors and flexors, hip flexors and abductors and ankle plantar flexors. Results showed that averaging scores over two trials is the most efficient approach. Two trials on two separate occasions would also improve the measurement error. The small sample size was a limitation of their study but they were able to provide a design for measurement. They concluded that a HHD is reliable and sensitive to changes in isometric muscle strength in children with CP (Willemse et al, 2013).

This is supported by an earlier study by Crompton et al, (2007) who found HHD testing for hip extensors in prone and ankle plantarflexors was unreliable. They concluded that hand-held dynamometry has acceptable reliability (ICC>0.70) for hip flexors, knee flexors and extensors, ankle dorsiflexors with stabilisation and hip extensors in supine. Their results are valid for spastic diplegic children with GMFCS levels I-III.

HHD has been shown to have good test-retest reliability (Crompton et al, 2007) and fair inter-rater reliability (Vershuren et al, 2008). It is an affordable and portable method for testing muscle strength.

2.6.5 Normative muscle strength data

In order to determine whether muscle strength of children with CP or HIV is weak or strong, we need to compare it to normative data for children of a similar age. There have been very few studies that have investigated normative muscle strength in children namely Beenakker et al. (2001), Nyström Eek et al. (2006) and Macfarlane et al (2008). These studies have been analysed in Table 2.4 below.
The subjects in all the studies were normal typically developing children. All the researchers divided their samples into categories of age and gender. This resulted in the maximum number of children per group to be 18 and the minimum number to be five. Torque was calculated by dividing the strength by the distance of the lever arm. It allows for better comparison over time and between subjects that are growing (Nyström Eek et al, 2006). Macfarlane et al (2008) also provided cut off values for muscle strength. These values can be used to identify muscle weakness in children between the ages of six to eight.

Although these studies all measured muscle strength in typically developing children, there is great variability in the age range, the sample sizes when divided into gender and age groups as well as the methodology. They have all reported an increase in strength with

increasing age weight and height but their predictors for muscle force all differ. It is important to compare the strength of a child to a group of the same gender and age.

Table 2.4 Comparison of three studies investigating muscle strength values in normally developing children

	Beenakker et al 2001	**Nyström Eek et al, 2006**	**Macfarlane et al, 2008**
Age Group	4-16 years	5-15 years	6-8 years
Number of subjects	270	149	154
Device	HHD (CT3001)	HHD	HHD (Micro FET II)
Muscle groups	11 (upper and lower limb)	12 (upper and lower limb)	6 (lower limb)
Muscle Strength Unit measurement	Newton	Newton meter (Torque)	Newton meter and Pounds
Type of Muscle testing	Isometric- Break test	Isometric – Make test	Isometric- Make test
Methodology	Reproducible	Reproducible	Reproducible
Finding related to age, weight and height	Weight was the best predictor of force in boys. Weight and age were the best predictor of force in girls	Strong correlation to age and weight up to the age of 12	Increase in strength with increasing age, weight and height. Height was the strongest predictor in this group.
Findings related to gender	No significant gender differences in 11-13 year old age group	Boys were stronger after the age of 13	No differences between gender
Implications	Individual muscle force values are provided but summed scores may be more useful when determining a pattern of weakness where there is pathology	None noted	Important to have a standardised procedure to minimise compensatory movements
Limitations	None noted	None noted	All measurements were taken by one therapist, therefore caution should be exercised when interpreting the generalisability and

			intra-rater reliability of the values

2.7 Conclusion

Spastic diplegia as a result of CP and as a result of HIVE may result in impairments growth, cognition and motor development. Abnormal muscle tone and decreased strength and poor selective motor control may also be present. These impairments as well as the natural progression are well described in children with CP but there is a paucity of literature with regard to diplegia as a result of HIVE. They both occur as a result of damage to an immature brain but the pathophysiology is different. HAART has resulted in a large number of children with HIVE surviving and reaching adolescence. Therefore it is important to determine the similarities and differences between these two groups as it will assist in guiding future management of HIV infected children with diplegia.

CHAPTER 3- METHODOLOGY

This chapter discusses the methodology that was used to conduct this research

3.1. Study Design

A cross sectional, quantitative study was conducted. A once-off assessment of function, muscle strength and tone was performed on participants by the researcher.

3.2 Ethical Clearance

Application for ethical clearance was made to the Human Research and Ethics Committee (Medical) of the University of the Witwatersrand and approval was granted prior to starting the data collection process. The study ethical clearance number is M140936 (See Appendix 1).

3.2.1 Permission to conduct research

Permission to conduct research was granted by the research board of Rahima Moosa Mother and Child Hospital (RMMCH) and Chris Hani Baragwanath Academic Hospital (CHBAH) respectively (See Appendices 2 and 3). Participants and their parents or care givers were given information sheets with an attached consent and assent form prior to the beginning of the assessment (See Appendices 4 and 5). Written informed consent and assent (for children over the age of six) was obtained from the participant and his or her primary caregiver (See Appendices 6 and 7).

3.2.2. Ethical Considerations

Since this study included human interaction the rights of patient's were considered. This was achieved by emphasizing the Patient's Rights Charter. Informed Consent is a substantial ethical cornerstone of human research. This study fulfilled this criterion by attaching an information sheet and consent form which explained the purpose of the study and as well as a detailed explanation of the research procedure. Parents and/ or caregivers of the subjects were required to complete the consent form as well as the medical questionnaire. Additional information may be obtained from the hospital file. Furthermore, an assent form was given to all participants over the age of six with an explanation of the procedure. Participants over the age of six were required to sign the document as confirmation that they understood the study, and that their decision to

participate was completely autonomous. Parents and participants had the right to withdraw from the study at any stage with no adverse consequences. For parents and participants who did not understand English, the forms and questionnaire were translated by the physiotherapy assistant who spoke the language.

Any materials or information obtained during the study will remain anonymous. Confidentiality will be maintained at all times. This was achieved by excluding the use of any information that would allow the subject to be identified; such as photographic material, subject's name and identification documents. Feedback of the assessment was provided to the therapists working in the clinic, by the researcher. The researchers and any other personnel that had an interaction with a participant in the study conducted themselves in a professional manner. Guidelines, as defined by the Health Professions Council of South Africa, were adhered to during the study.

3.3 Location

This study was conducted at Chris Hani Baragwanath Academic Hospital (CHBAH), Rahima Moosa Mother and Child Hospital (RMMCH) and two private physiotherapy practices in Johannesburg, Gauteng. All assessments were done in the treatment gyms of the respective physiotherapy departments. These sites were chosen as they have a patient base from which subjects could be recruited.

3.4 Study Population

3.4.1 Sample Size

In the absence of other available published data on the functional status of children with HIVE, the central limit theorem was used to calculate a sample size of 30 participants per group. This was a sample of convenience which was obtained consecutively.

3.4.2 Inclusion Criteria

Children were included to participate in the study if:

- They presented with spastic diplegia
- They presented with GMFCS level I-IV

- They were HIV positive or negative and willing to disclose their HIV status
- They were between the age of four to sixteen years
- They were able to follow a two-step instruction

3.4.3 Exclusion Criteria

Children were excluded if:

- They had botulinum toxin injections less than six months prior to testing
- They had orthopaedic surgery less than one year prior to testing
- They presented with diplegia but had an unknown HIV status

3.5 Outcome Measures and Measurement Devices

3.5.1 The Gross Motor Function Measure (GMFM)

The GMFM is a standardised tool which is used to measure the gross motor function of children with CP from childhood to adolescence. This tool is seen as the gold standard for gross motor assessment in this population (Debuse & Brace, 2011). The GMFM-66 was used as it takes less time to administer, has interval scaling for improved interpretability and a computer scoring system compared with the GMFM-88. It has the properties of reliability, validity and responsiveness. It is also widely used for research purposes (Russell et al, 2000). The GMFM-66 measures the quantity of the child's performance on the day rather than the quality.

3.5.2 Functional Mobility Scale

The Functional Mobility Scale (FMS) is used to classify functional mobility in children with CP. It takes into account the range of assistive devices that the child might use as well as their ability in different environments of home, school and community. It is a performance measure of the child's walking ability over 5 meters, 50 meters and 500 meters. This scale has been shown to have good inter-rater children with CP with the kappa coefficient being 0.87 for 5m, 0.92 for 50m, and 0.86 for 500m (Harvey et al, 2010).

3.5.3 The Modified Ashworth Scale

The Modified Ashworth Scale (MAS) was used to measure the spasticity in the lower limbs.

Spasticity is defined as the resistance of a muscle to passive stretch. The MAS is a clinical tool that is used to quantify a patient's spasticity. This is done by applying a passive velocity-dependent stretch and rating the resistance. It is quantified on a 6-point ordinal scale (see Table 3.1) from zero to four. Zero indicates no increase in muscle tone and four indicates that the affected limb is rigid (Mutlu et al, 2008; Clopton et al, 2005).

Table 3.1 Modified Ashworth Scale (Clopton et al, 2005)

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of range of motion when the affected part is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected parts easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected parts rigid in flexion or extension

3.5.4 Hand Held Dynamometer

Lower and upper extremity strength can be measured objectively by using a hand-held dynamometer (HHD). The device contains a force transducer that enables measurement of isometric muscle strength when it is held rigid and perpendicular to the person's body (Willemse et al, 2013). Accurate measurement of strength is important for identifying any impairment of strength. Willemse et al (2013) proposed that a HHD is reliable and sensitive to changes when being used to assess muscle strength in children with CP.

In this study the the MicroFET 2 was used. This dynamometer measures muscle strength as force, measured in Newtons. The minimum force it is able to measure is that of 3.6 N,

the maximum force is that of 660N. Forces are measured in 0.8 N increments. The dynamometer was manufactured by Hoggan Health Industries and certified on February 19th 2007. Isometric muscle strength of upper and lower limb muscles was tested using the 'make test' with a HHD.

3.5.5. Viral Load

Viral load monitoring is recommended as the preferred method to confirm and diagnose treatment failure by WHO (Kukoyi et al, 2016). Viral load information was available for all HIV infected participants in this study, therefore the most recent viral load was obtained. Viral load levels were obtained through the National Health Laboratory Services (NHLS) at CHBH and or through information found in the patients file.

3.5.6 Anthropometric measurements

Height and weight measurements were taken for each child. The weight and height for each participant was converted into a standardised z-score using WHO Anthroplus software. This software is used to facilitate the application of the WHO Reference 2007. The WHO reference 2007 provides a reference for standard height-for-age (HAZ), weight-for-age (WAZ) and BMI-for-age (BAZ) growth parameters for the age group five to nineteen years. The data tables and charts cover the first to the 99th percentile and standard deviations from +3 to -3. WHO Anthroplus software is used to determine the percentile and z-score for each individual. Depending on the child's age the software applies the WHO standards (children under 5) or the WHO reference (5 to 19 years) to determine the scores. A z-score < -2.00 indicates that a child in stunted (HAZ) or underweight (WAZ) while scores beyond +3.00 or -3.00 represents extremes in nutritional status.

3.6 PROCEDURE

3.6.1 Recruitment

A database of children with spastic diplegia was obtained from the physiotherapy departments of CHBH and RMMCH as well as the orthopaedic department of CHBH. All children who met the inclusion criteria were invited either personally or telephonically to participate in the study. Appointments were scheduled for the assessment. Where possible, appointments were made to try to correspond with other clinic appointments. Participants and care-givers were reimbursed a value of R50.00 towards transport costs.

The researcher also attended the orthopaedic and neurology clinic at CHBH from the period March to October 2015 to recruit participants. Children who were attending the clinic and eligible for the study were invited to participate on the same day. Participants were consecutively recruited. The flow diagram below summarises this process.

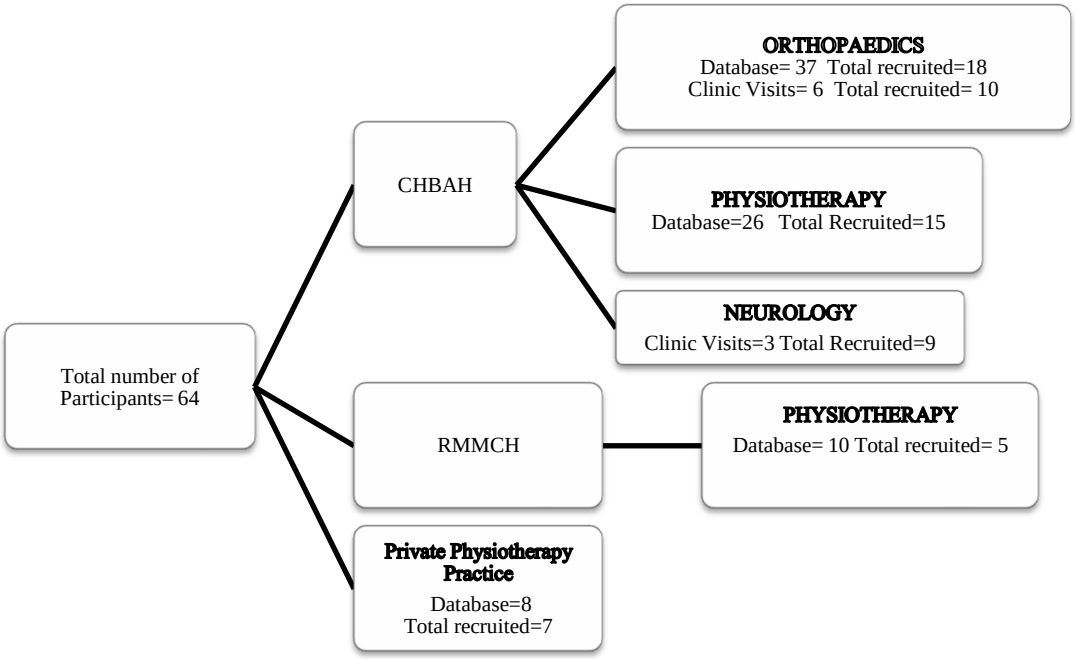


Figure 3.1: Summary of recruitment process

Each participant and care-giver was given an information sheet (Appendix 4 and 5) explaining the purpose of the study, a consent form (Appendix 6) and an assent form (Appendix 7) to complete. All forms were available in English. Verbal translation was provided when required. All participants were given the right to refuse to participate in the study.

3.6.2 Medical History

Parents and/or caregivers were required to complete a questionnaire (Appendix 8) which provided the researcher with information regarding the child's medical history. This included pregnancy and birth history, complications after birth, developmental milestones, medication, additional medical and surgical history, HIV status and management and care with regard to this. Additional information was obtained from the hospital file. The participants were placed into one of two groups based on their HIV status.

3.6.3 Measurements

All measurements as described below were conducted on all participants by the primary researcher. She had 14 years of physiotherapy experience on commencement of this

study and is trained in neurodevelopmental therapy. Willingness of the parent to disclose the HIV status of the participant was one of the inclusion criteria therefore the primary researcher was not blinded to the participants HIV status. All results were recorded on a data collection sheet (Appendix 9).

1. Anthropometric measurements of weight and height were carried out. Participants' height was measured in supine with their feet against the wall. It was measured in centimetres from the wall to the top of the head. Their weight was measured in kilograms using a standing electronic bathroom scale. Height-for-age, weight-for-age and BMI-for-age z scores were calculated using WHO Anthroplus Software.
2. The GMFCS score was determined by the physiotherapist according to the GMFCS guidelines.
3. The FMS was scored for each child according to care-giver report (See Appendix 13).
4. The GMFM-66 was completed according to the guidelines in the user manual (Gross Motor Function Measure (GMFM 88 & GMFM66) User's Manual (2002)). Each child was given three turns to complete an item, as per the instruction manual and scores were recorded on the scoring sheet (Appendix 12). The total score was calculated using the Gross Motor Ability Estimator (GMAE) program. Each dimension score from A to E was converted into a percentage out of a 100.
5. Muscle tone was assessed in supine using the Modified Ashworth scale. The following muscles were assessed bilaterally: hip adductors, hamstrings, soleus and gastrocnemius. Each joint was moved through its passive range of motion 3 times. The passive movements were done at approximately one second per movement through the range in an effort to standardise the procedure. Assessment and measurements were conducted as outlined in Appendix 10.
6. Isometric muscle strength of bilateral upper and lower limb muscles was tested using the MicroFET2 Dynamometer (Hoggan Health Industries Inc, Draper, Utah). It measured strength in pounds and this was then converted to Newtons. For all testing, the 'L' or lower threshold setting was used as it is more sensitive. A 'make test' was performed, in which the HHD was stabilised by the investigator, while the participants were asked to "Push as hard as you can" for 5 seconds against the HHD. All movements were demonstrated to the patients and one or two practice trials were performed to familiarise the participants to the procedure. Two trials were measured for each muscle group. The following muscle groups were assessed

supine: shoulder flexion and abduction, elbow flexion and extension, hip abduction and ankle plantarflexion. Hip flexion, knee flexion and knee extension were assessed in sitting. The average score over two trials was calculated and rounded off to one decimal place for each muscle group. The testing protocol as used by Willemse et al (2013) was followed (see Appendix 11).

3.7 Statistical analyses

The null hypothesis stated that there is no difference between the two groups' clinical presentation in terms of function, tone and strength.

All data collected was analysed in consultation with a statistician using STATA 12 software (Stata Corp, Texas, USA) and STATISTICA Version 12.7.
Significance was set at $p<0.05$ however, for crude analysis, the significance level was also set as $p<0.1$ as the sample size was small. Furthermore, GMFCS classification was condensed into two groups based on the ability of the participants to walk. Therefore, participants of GMFCS level I and II were grouped together and were named the functional group while participants in levels III and IV represent the non-functional group.

3.7.1 Descriptive and inferential statistics

Descriptive statistics were used to summarise collections of data. The demographic information of the HIV infected and uninfected groups were analysed using means, standard deviations, percentages, minimum and maximum values.
The WHO AnthroPlus software for personal computers versions 3.2.2 was used to convert the weight and height measurements into z-scores for all participants. These scores were analysed using student t-tests.

Inferential statistics were used to determine the statistical significance of relationships between the variables, and to statistically contrast these relationships. Normality for continuous variables was assessed using Shapiro-Wilk tests. Data which was not normally distributed was transformed to fit a normal distribution. Student t-tests were performed on normally distributed or transformed data. This test is used where there are two different experimental conditions (the HIV infected and uninfected group as well as the functional and non –functional group). These tests were applied to analysis of GMFM and muscle strength values.

The modified Ashworth scale and FMS represented ordinal data. In order to determine the statistical significance of the relationship of these variables between the two groups, non-parametric Mann-Whitney U tests were used.

3.7.2 Correlation statistics

The Pearson Product Moment-Correlation Coefficient (r) is a correlation between two variables. It is used to determine the degree of relationship between variables. Two-tailed t-tests were employed in order to determine whether or not these relationships are statistically significant.

Pearson correlation analyses were done in order to determine the relationship between viral load and GMFM, strength, weight and height in the HIV infected group as well as between GMFM and age.

3.8 Conclusion

The results obtained will be presented in the following chapter.

CHAPTER 4 - RESEARCH RESULTS

4.1 Introduction

This chapter will present the results of the study. Interpretation and discussion of the results will follow in chapter five.

4.2 Descriptive and inferential statistics

4.2.1. Gender demographic

Figure 4.1 depicts the gender composition of the each group. There was a predominance of males (80.6%) in the HIV uninfected group while there was a more even gender distribution in the HIV infected group (boys=51.5%; girls=48.5 %).

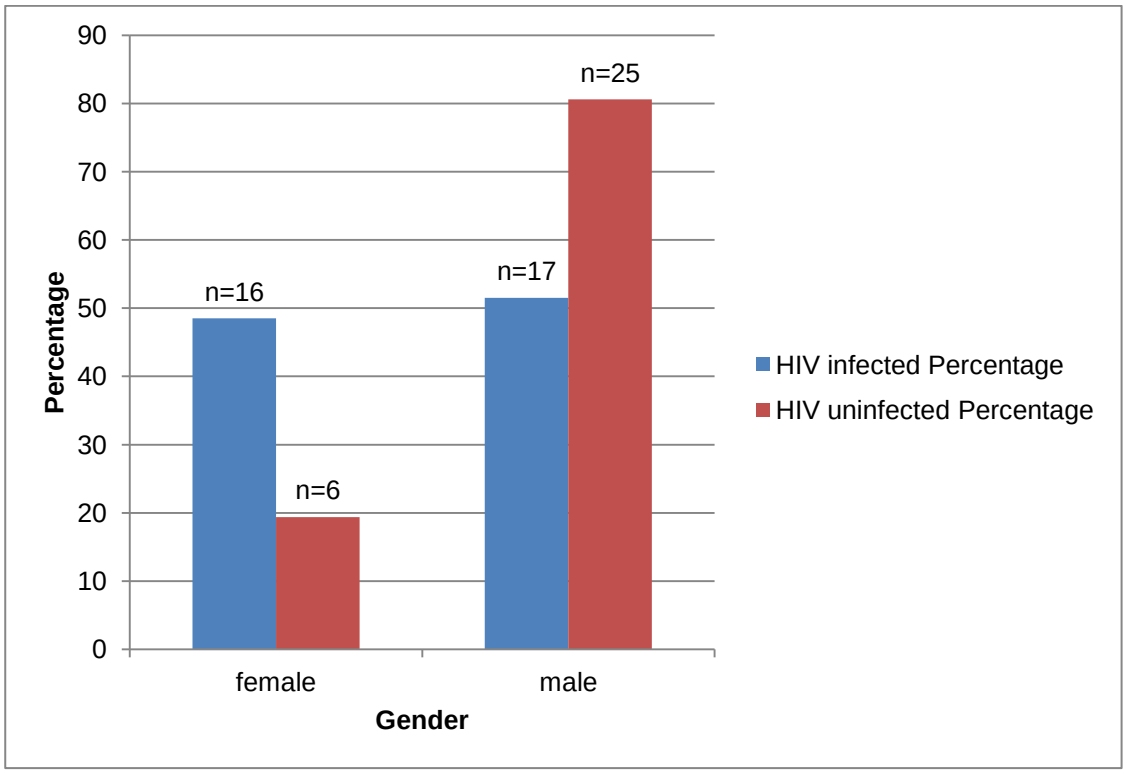


Figure 4.1 Gender Demographic of HIV infected and uninfected groups

4.2.2 Age Demographic

Table 4.1 indicates the age of children in the HIV infected and HIV uninfected groups while Table 4.2 summarises the distribution of the functional (GMFCS I and II) and non-functional (GMFCS III and IV) groups.

Table 4.1: Age demographic information for HIV infected and uninfected groups

	HIV infected n=33			**HIV Uninfected n=31**			
	Mean (SD)	**Minimum**	**Maximum**	**Mean (SD)**	**Minimum**	**Maximum**	**Probability Value (p)**
Age (years)	7.78 (2.57)	4.0	15.0	8.77 (3.26)	4.0	16.0	0.18

The two groups were well matched for age.

Table 4.2: Age demographic information for HIV infected and uninfected, functional and non-functional groups

	Non functional group (n=36)			**Functional Group (n=28)**			
	HIV Infected (n=16)	**HIV Uninfected (n=20)**	**p Value**	**HIV Infected (n=17)**	**HIV Uninfected (n=11)**	**p Value**	Analysis
	Mean (SD)	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**		
Age (years)	8.06 (2.35)	7.8 (3.04)	0.78	7.53 (2.76)	10.55 (3.01)	0.01**	t-test

* Comparison was significant at the 0.1 level

** Comparison was significant at the 0.05 level

When comparing the age of participants in the HIV infected to uninfected group, there is no statistical significance (p=0.18) between the groups. The groups appear evenly matched.

However, there is a statistical significance (p=0.01) in the functional group. The HIV infected functional participants were significantly younger than their uninfected counterparts.

4.2.3 GMFCS distribution

The GMFCS distribution across the HIV infected and uninfected groups is presented in Figure 4.2.

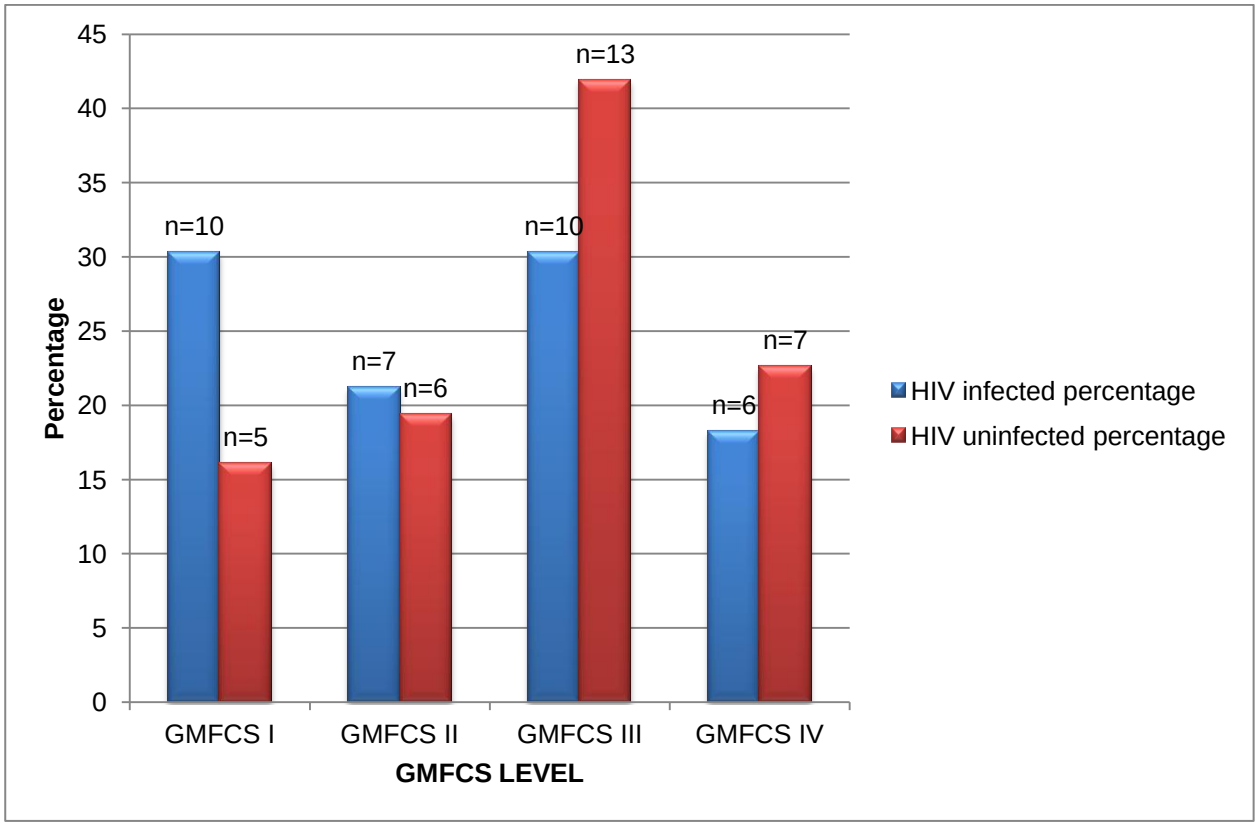


Figure 4.2: GMFCS distribution for HIV infected and uninfected groups

There was an uneven distribution across the four levels. With a Pearsons Chi² analyses, the p value was 0.542, indicating that there was no significant difference between the groups.

For the purposes of crude analyses GMFCS I and II were grouped together (functional group), while levels III and IV were grouped as the non-functional group. Table 4.3 shows the revised distribution of the condensed groups.

Table 4.3 GMFCS distribution for HIV infected and uninfected functional and non-functional groups

		HIV Infected	HIV Uninfected
		n	n
Functional	GMFCS I + II	17	11
Non-Functional	GMFCS III + IV	16	20

The functional group was able to walk either independently or with assistance while the non-functional group was predominantly wheelchair bound. This means that participants in the GMFCS III category were household ambulators only and used a wheelchair for longer distances. Those in the GMFCS IV category were able to crawl around the house but needed a wheelchair for longer distances. Pearsons Chi² test showed no significant difference between the groups (p= 0.196). There is a trend for the HIV uninfected group to be less functional.

4.2.4 Demographic information

Additional demographic information for both groups is presented in Table 4.4. Relevant information from the medical questionnaire that was completed by the parent or caregiver was extracted.

Table 4.4 Demographic information for HIV infected and uninfected groups

	Total n=64			
	HIV Infected		**HIV Uninfected**	
	n	Percentage	n	Percentage
Total per group	33		31	
Botox	19	57.6	18	58.1
Surgery	1	3.0	4	12.9
Medication				
HAART	32	97.0	0	0
Ritalin	2	6.0	6	19.4
Epilim	0	0	3	9.7
Risperdal	0	0	2	6.5
Baclofen	0	0	1	3.0
Birth Complications				
Prematurity	3	9.1	13	41.9
Long labour /anoxia	4	12.1	5	16.1
one of twin	1	3.0	3	9.7
unknown-orphan	5	15.2	0	0
unknown history	4	12.1	0	0

Illness < 1 year				
None	13	39.4	21	67.7
Respiratory	13	39.4	2	6.5
Meningitis	1	3.0	1	3.2
VP shunt	0	0	3	9.7
Fits	2	6.1	2	6.5
Other	0	0	2	6.5
Unknown	4	12.1	0	0
Milestones				
Delayed	33	100	31	100
Loss of milestones	3	9.1	0	0
School History				
Pre school	5	15.2	2	6.5
***LSEN- mainstream	13	39.4	13	42.0
***LSEN special	8	24.2	9	29.0
Mainstream	4	12.1	1	3.2
Stimulation	2	6.1	5	16.1
not in school	1	3.0	1	3.2
repeated grades	3	9.1	8	25.8

***LSEN- refers to schools for learners with special educational needs

Botox was done almost equally across the groups (57.6% and 58.1%). The frequency of prematurity as well as other complications like pre-eclampsia was higher in the HIV uninfected group. Unknown birth history as a result of parents being deceased was only prevalent in the HIV infected group. Illness requiring re-admission into hospital was prevalent in both groups. The most common cause of illness under a year was respiratory complications (39.4 %) in the HIV infected group. All participants had delayed milestones but three participants in the HIV infected group had attained all motor milestones and then lost them at a later age. Ninety seven percent of participants in both groups attended school. The majority of participants in both groups attended a school for learners with special educational needs (LSEN) (63.6% and 71%).

4.2.5 HIV infected group demographics

Table 4.5 provides additional insight into the demographics of the HIV infected group with regard to medication and viral load. Only one participant in this group was not receiving HAART while one participant had defaulted on his medication.

Table 4.5: Viral load and initiation of HAART in HIV infected group

HIV Infected group- Viral Load		
	N	Percentage
Total number of participants	32	97
LTD- <20 copies/ml	12	37.5
20-400	14	43.8
400-1000	2	6.3
>1000	4	12.5
Age of HAART initiation		
birth-6 weeks	5	15.6
6wks - 6 months	10	31.3
6 -12 months	10	31.3
1-2 years	3	9.4
>2 years	3	9.4
Unknown	1	3.0

Thirty two participants were receiving HAART at the time of the assessment. Viral load values ranged from lower than detectable (LTD) to 21658copies/ml.
HAART initiation was most frequent between 6 weeks and 1year (62.6%). Early HAART initiation from birth to 6 weeks was only observed in 15.6% of participants. One participant was being cared for in a home therefore the age of HAART initiation was unknown.

4.2.6 Anthropometric data

4.2.6.1 Anthropometric data to compare HIV infected and uninfected groups to the norm for their age

Tables 4.6 and 4.7 show the comparison of the participant's height-for-age, weight-for-age and BMI-for-age z scores. A two sample student's t test of equal variance was used to compare the groups. There were no height and weight measurements taken for one participant in the HIV infected group therefore 32.
Depending on the age, z scores were calculated using either the WHO standards (0-5years) or the WHO reference (5-19years). For children over the age of 10, weight-for-age is no longer regarded as a good indicator of growth as many children are experiencing puberty. They may appear to have excess weight but in fact they may be just tall. Seven participants were over the age of ten in the non-functional group and similarly there were eleven participants over the age of 10 in the functional group. Therefore, there were no weight-for-age scores for these participants.
Means, standard deviations, minimum and maximum values are included.

Table 4.6: Comparison of z scores for HIV infected and uninfected groups

	HIV Infected 32			HIV Uninfected 31			
	Mean (SD)	**Minimum**	**Maximum**	**Mean (SD)**	**Minimum**	**Maximum**	**Probability Value (p)**
Height-for- age z score	-1.61 (2.02)	-5.07	2.84	-1.75 (1.81)	-5.73	1.59	0.78
Weight-for-age z score	24 -0.67 (1.62)	-3.79	3.31	21 -0.66 (1.62)	-3.66	2.48	1.0
BMI-for-age z score	0.51 1(1.47)	-2.4	0.88	0.03 (1.70)	-3.66	2.86	0.24

There were no significant differences in z scores between the two groups. The weight-for-age and BMI-for-age mean z scores for the HIV infected and HIV uninfected groups lies between negative one and positive one. This indicates that both groups fall within the median percentile for these growth parameters. Mean height-for-age for both groups lies between negative two and negative one. This indicates that they fall in the fifteenth percentile for height, indicating that participants in both groups are shorter than the median for the age group.

Table 4.7: Comparison of z scores for HIV infected and uninfected, functional and non-functional groups

	Non functional group (36)			Functional Group (28)		
	HIV Infected (16)	HIV Uninfected (20)	p Value	HIV Infected (16)	HIV Uninfected (11)	p Value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Height-for- age z score	-2.38 (2.07)	-1.81 (2.10)	0.40	-0.84 (1.89)	-1.63 (1.20)	0.23
Weight-for-age z score	n=13 -0.91 (2.16)	n=16 -0.48 (1.81)	0.56	n=11 -0.39 (1.06)	n=5 -1.26 (0.53)	0.11
BMI-for-age z score	0.76 (1.49)	0.15 (1.81)	0.29	0.26 (1.45)	-0.18 (1.55)	0.46

* Comparison was significant at the 0.1 level

** Comparison was significant at the 0.05 level

In the non- functional group, the mean height-for-age of the HIV infected group and HIV uninfected group fell into the 3rd percentile and the 15th percentile respectively. Weight and BMI-for-age for both groups fell into the 50th percentile. The trend in this group was for the HIV infected participants to be shorter and lighter.

In the functional group the mean z scores fell into the following percentiles: Height-for-age (HIV infected) - 50th percentile, height-for-age (HIV uninfected) - 15th percentile, weight - for-age (HIV infected) - 50th percentile, weight-for-age (HIV uninfected) - 15th percentile, BMI-for-age HIV infected and HIV uninfected - 50th percentile. The HIV infected participants had a tendency to be taller and heavier in this group.

No significant differences were noted in the z scores for weight-for-age, height-for-age or BMI-for age between the HIV infected and HIV uninfected groups. A significant difference (p=0.02) exists between the heights of the functional and non functional HIV infected

group indicating that participants in the non-functional group are significantly shorter than the functional participants.

4.2.6.2 Correlation between viral load and weight and height

The correlation between viral load, weight and height was determined using Pearson's Product Moment-Correlation Coefficient (r) and probability value (p) was calculated using student t-tests to determine if this correlation was true.

There was a moderate correlation between viral load and weight (r=0.38, p=0.03) and height (r=0.36, p=0.04) which was significant.

4.2.7 GMFM

Table 4.8 and 4.9 summarise the means, standard deviations and p values of the GMFM scores for the HIV infected, uninfected, functional and non-functional groups.

Table 4.8 GMFM scores for HIV infected and uninfected groups

	HIV Infected 33			**HIV Uninfected 31**			
	Mean (SD)	**Minimum**	**Maximum**	**Mean (SD)**	**Minimum**	**Maximum**	**Probability Value (p)**
GMFM Total	62.59 (11.07)	44.6	85.2	58.72 (9.89)	46.3	84	0.15
% Dimension A	100.00 (0)	100.00	100.00	100.00 (0)	100.00	100.00	1.0
% Dimension B	98.59 (4.90)	73.3	100	97.50 (5.98)	80	100	0.43
% Dimension C	95.76 (7.14)	70	100	95.70 (5.85)	76.7	100	0.98
% Dimension D	59.35 (28.47)	7.7	97.4	48.97 (28.33)	4.2	92.3	0.15
% Dimension E	48.81 (32.53)	5.5	95.8	37.40 (28.77)	2.8	97.3	0.13

* Comparison was significant at the 0.1 level

** Comparison was significant at the 0.05 level

Table 4.9 GMFM scores for HIV infected and uninfected, functional and non-functional groups

	Non functional group (36)			Functional Group (28)		
	HIV Infected (16)	HIV Uninfected (20)	p Value	HIV Infected (17)	HIV Uninfected (11)	p Value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
GMFM Total	53.13 (5.39)	53.78 (4.76)	0.74	72.22 (6.63)	69.86 (6.20)	0.52
% Dimension A	100 (0)	100 (0)	1.0	100 (0)	100 (0)	1.0
% Dimension B	97.09 (6.83)	96.13 (7.13)	0.82	100 (0)	100 (0)	1.0
% Dimension C	92.91 (9.35)	93.84 (6.43)	0.90	98.44 (2.08)	99.09 (2.16)	0.27
% Dimension D	36.86 (22.70)	32.20 (19.80)	0.60	80.52 (12.49)	79.48 (8.74)	0.54
% Dimension E	19.52 (14.77)	18.95 (14.11)	0.73	76.38 (15.71)	70.08 (15.78)	0.16

* Comparison was significant at the 0.1 level

** Comparison was significant at the 0.05 level

There were no significant differences between groups with regard to GMFM scores. There is a trend for the HIV infected participants to perform better in the functional group and this is most noticeable in Dimension E (walking, running and jumping) where there is a difference in scores of 6.3%.

4.2.7.1 Correlation between GMFM and viral load

No significant correlation was found between viral load and GMFM in the HIV infected group (r=0.18, p=0.3). Correlation statistics were performed using Pearson's Product Moment-Correlation Coefficient (r).

4.2.7.2 Correlation between GMFM and age

No significant correlation was found between age and GMFM in the HIV infected group (r=0.18, p=0.12). However, a moderate correlation which was found to be significant (r=0.66, p=0.03) was found between age and GMFM of the HIV uninfected, functional participants. Correlation statistics were performed using Pearson's Product Moment-Correlation Coefficient (r) and student t-tests were used to determine if it was significant. The results of this analysis can be found in Appendix 16.

4.2.7.3 Comparison of GMFM scores to percentiles of each GMFCS level

Hanna et al (2008) created reference percentiles for each GMFCS level according to their age group. This was used as a reference to determine the percentiles for each HIV infected and uninfected group at each GMFCS level. These results are shown in Table 4.10.

Table 4.10 Percentiles of each GMFCS level using mean age and mean GMFM score

	GMFCS I		**GMFCS II**		**GMFCS III**		**GMFCS IV**	
	HIV Infected	**HIV Uninfected**	**HIV Infected**	**HIV Uninfected**	**HIV Infected**	**HIV Uninfected**	**HIV Infected**	**HIV Uninfected**
Age (years)	7.7	12.2	7.3	9.2	8.3	7.5	7.7	8.3
Mean GMFM	75.1	74.3	66.3	66.2	55.8	55.1	48.6	47.9
Percentile	15-20	10-15	55	40	60-65	60-65	80-85	80-85

The GMFM score for the HIV infected and uninfected participants in the non-functional group fell within the same percentiles while those of the HIV infected participants in the functional fell within a higher percentile compared to the HIV uninfected participants.

4.2.8 Functional Mobility Scale

FMS scores for the groups were compared using Mann-Whitney U tests as the data is ordinal.

There were no significant differences between the HIV infected and HIV uninfected groups as a whole, at 5meters (p=0.18), 50meters (p=0.14) and 500meters (p=0.08). At five hundred meters there is a significance if p<0.1.

Figures 4.3 and 4.4 represent the frequency in the form of percentages for each level in the three categories of the FMS for the functional and non-functional groups.
The FMS evaluates the mobility of children with CP at different distances. Each level of the scale indicates how a participant mobilises at that distance. N represents not applicable; C represents crawling; 1represents use of a wheelchair; 2 indicates that a participant walks with a walking frame; 3 indicates that a participant walks with crutches; 4 indicated that they walk with one or two sticks; 5 indicates that a participant can walk independently over even surfaces while 6 means that they can walk independently over all surfaces. These levels are represented in the figures below.

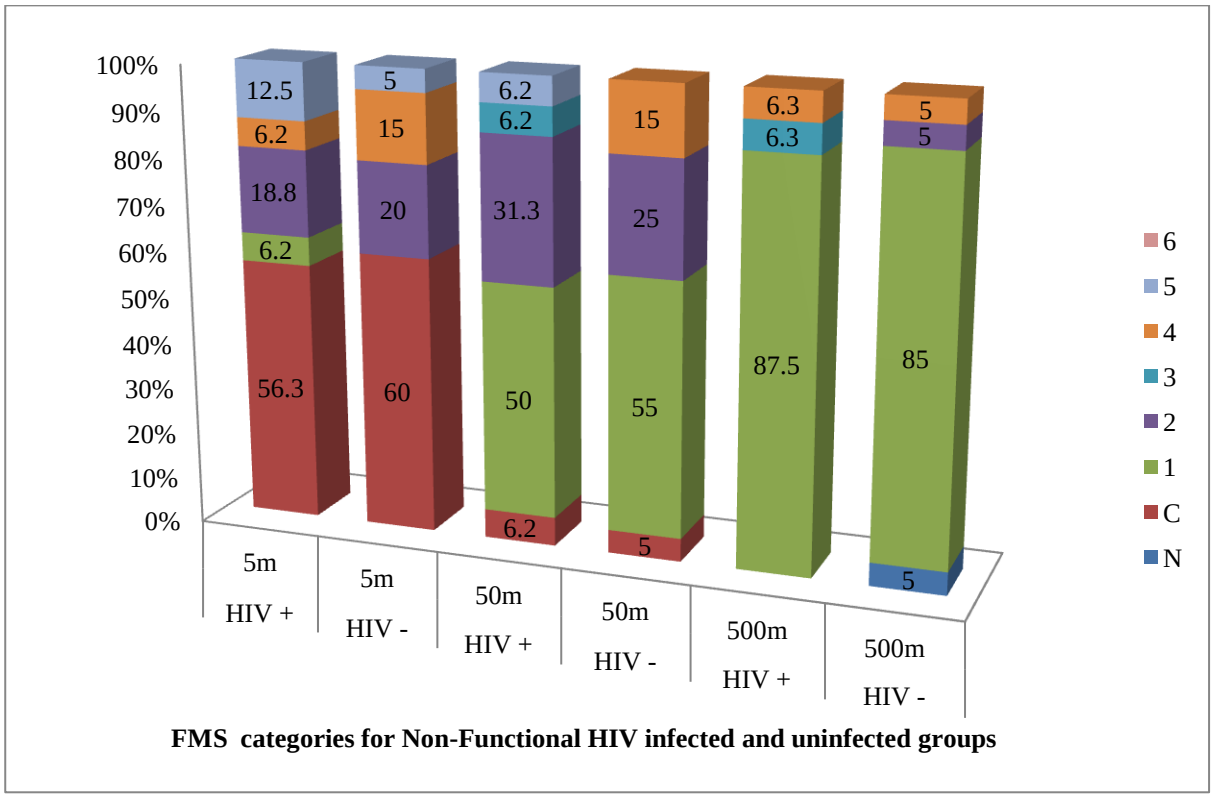


Figure 4.3 FMS frequency for non-functional HIV infected and uninfected groups

There were no significant differences between the non-functional HIV infected and HIV uninfected groups at 5meters (p=0.87), 50meters (p=0.94) and 500meters (p=0.54). The majority of participants in both groups crawl at 5meters and use wheelchairs at 50 and 500 meters.

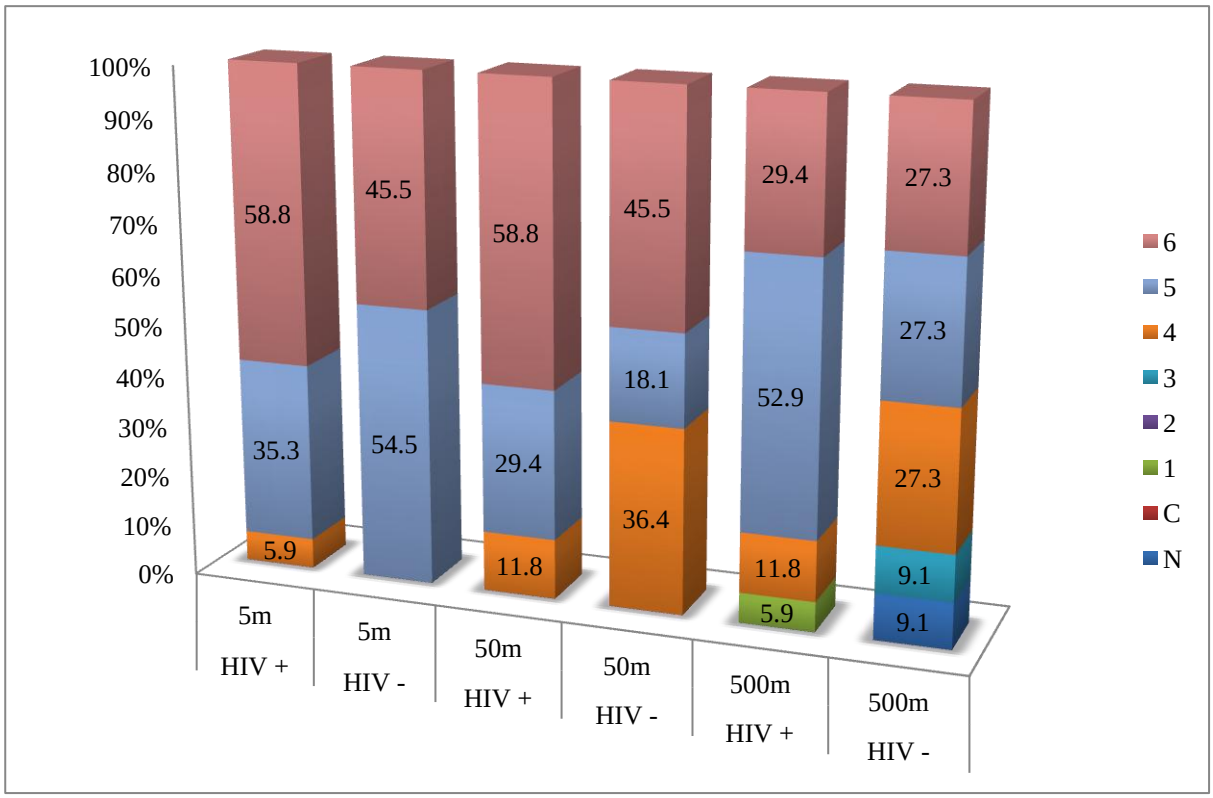


Figure 4.4 FMS frequency for functional HIV infected and uninfected groups

There was no significant difference between the HIV infected and HIV uninfected participants in the functional group at 5meters (p=0.61), 50meters (p=0.29) and 500meters (p=0.30). The majority of the participants were able to walk independently at 5, 50 and 500 meters. There was an increase in the use of an assistive device like a crutch or stick as the distance increased.

4.2.9 Muscle Tone

The scores attained using the MAS were compared using Mann-Whitney U analyses as the data is ordinal. The scale represents different degrees of spasticity that is felt in a muscle group. Table 3.1(pg 47) gives a description of each level of spasticity in this scale.

There is no significant difference in tone when comparing HIV infected to uninfected participants. Similarly there were no significant differences between the HIV infected and HIV uninfected participants in the functional group. Significantly lower right (p=0.03) and

left (p=0.1) adductor tone was found in the HIV infected children who are graded non functional. P values for the comparison of these groups are documented in Table 4.11.

Table 4.11 P values of comparative MAS scores of HIV infected and uninfected, functional and non-functional groups

	Non-functional Group	Functional Group
	p Value	**p Value**
Adductor Left	0.10*	0.98
Adductor Right	0.03**	0.59
Hamstring Left	0.93	0.23
Hamstring Right	1.00	0.90
Gastrocnemius Left	0.97	0.73
Gastrocnemius Right	0.95	0.22
Soleus Left	0.38	0.49
Soleus Right	0.86	0.60

* Comparison was significant at the 0.1 level
** Comparison was significant at the 0.05 level

In order to determine the pattern of spasticity in the functional and non-functional groups, the average percentage of the frequency in each muscle group was calculated across both the left and right side. Furthermore, grade one and one plus was grouped together as mild tone, grade two as moderate tone while grade three and four was grouped together as severe tone.

Table 4.12 and Table 4.13 below summarise these percentages for the functional and non-functional group.

Table 4.12 Average frequencies expressed as percentages for tone across two sides in functional group

	Tone	Adductors	Hamstrings	Gastrocnemius	Soleus
HIV infected (17)	**No Increased tone (0)**	8.9%	0%	5.9%	5.9%
	Mild (1/ 1+)	64.7%	55.9%	55.9%	58.8%
	Moderate (2)	26.5%	41.2%	32.4%	38.3%
	Severe (3/4)	0%	5.9%	8.9%	0%
HIV uninfected (11)	**No Increased tone (0)**	9.1%	0%	9.1%	18.1%
	Mild (1/ 1+)	50%	36.4%	63.7%	72.8%
	Moderate (2)	27.3%	36.4%	31.9%	18.2%
	Severe (3/4)	9.1%	27.2%	0%	0%

The frequency of mild tone accounted for more than 50% of the tone across all muscle groups in the HIV infected participants. The incidence of severe tone was less than 10% and only prevalent in the hamstrings (5.9%) and gastrocnemius (8.9%) muscle groups.

In the HIV uninfected participants, mild tone increased in frequency from proximal to distal while severe tone decreased from proximal to distal. However, almost one third of the group (27.2%) had severe tone in the hamstrings. Overall, both the HIV infected and uninfected groups presented predominantly with mild tone.

Table 4.13 Average frequencies expressed as percentages for tone across two sides in non-functional group

	Spasticity	Adductors	Hamstrings	Gastrocnemius	Soleus
HIV infected (16)	**No Increased tone (0)**	6.3%	0%	0%	0%
	Mild (1/ 1+)	28.2%	34.5%	65.7%	53.2%
	Moderate (2)	40.5%	37.5%	21.9%	37.6%
	Severe (3/4)	15.7%	28.2%	12.5%	9.4%
HIV uninfected (20)	**No Increased tone (0)**	0%	0%	5%	5%
	Mild (1/ 1+)	30%	20%	55%	72.5%
	Moderate (2)	20%	37.5%	35%	27.5%
	Severe (3/4)	55%	42.5%	12.5%	12.5%

In the non-functional group, the HIV infected participants had a predominance of mild tone distally and moderate tone proximally. The greatest frequency of severe tone was observed in the hamstrings (28.2%). The frequency of mild tone increased from proximal to distal.

The non functional HIV uninfected participants had a greater frequency of severe tone proximally in the hip adductors (55%) and hamstrings (42.5%) while the frequency of mild tone was more prevalent in the distal muscle groups. It can be said that the severity of tone decreased from proximal to distal in this group.

4.2.10 Muscle strength

Muscle strength data (mean, standard deviation, minimum and maximum values) for both groups are given in Table 4.14 and 4.15. A two sample student's t test of equal variance was used to compare groups. Values of muscle strength are represented in Newtons (N).

Table 4.14 Muscle strength scores for HIV infected and uninfected groups

	HIV Infected 33			HIV Uninfected 31			
Muscle Group	**Mean (SD)**	**Minimum**	**Maximum**	**Mean (SD)**	**Minimum**	**Maximum**	**Probability Value (p)**
Shoulder Abduction Left	23.04 (8.79)	11.57	46.71	22.31 (10.24)	7.12	54.27	0.76
Shoulder Abduction Right	21.86 (9.21)	7.56	49.38	21.60 (10.11)	5.78	50.71	0.91
Shoulder Forward Flexion Left	22.96 (9.12)	10.68	43.59	23.93 (12.55)	9.79	59.61	0.61
Shoulder Forward Flexion Right	23.28 (8.97)	10.23	43.59	23.69 (12.80)	8.01	58.27	0.88
Elbow Flexion Left	25.62 (10.84)	8.90	44.93	26.62 (14.82)	8.90	67.61	0.76
Elbow Flexion Right	26.04 (11.18)	6.67	51.15	25.25 (15.29)	9.34	77.84	0.81
Elbow Extension Left	25.54 (9.87)	9.34	44.04	25.48 (14.47)	7.12	72.06	0.98
Elbow Extension Right	26.77 (12.60)	4.89	61.83	24.61 (13.75)	8.90	63.16	0.51
Hip Abduction Left	19.49 (8.90)	7.12	44.93	21.55 (12.67)	6.23	71.17	0.45
Hip Abduction Right	21.62 (9.88)	5.34	52.49	21.91 (11.02)	7.12	61.39	0.91
Ankle Plantarflex Left	15.77 (7.65)	4.45	45.82	14.44 (5.56)	8.01	32.47	0.43
Ankle Plantarflex Right	15.56 (6.61)	5.34	33.36	12.81 (4.23)	5.78	28.47	0.05**
Knee Flexion Left	18.06 (6.98)	7.12	33.81	19.29 (13.14)	4.45	68.06	0.64

Knee Flexion Right	19.33 (7.70)	8.45	41.81	19.86 (12.14)	6.23	53.38	0.83
Knee Extension Left	19.80 (10.63)	7.12	52.93	20.42 (11.28)	6.23	53.82	0.82
Knee Extension Right	19.09 (9.26)	5.34	44.93	21.54 (11.37)	5.78	44.93	0.33
Hip Flexion Left	19.80 (9.08)	6.67	37.81	20.72 (11.31)	8.01	58.27	0.72
Hip Flexion Right	19.18 (8.91)	8.45	45.82	20.59 (11.13)	6.23	52.93	0.58

* Comparison was significant at the 0.1 level (2-tailed)

** Comparison was significant at the 0.05 level (2-tailed)

For the most part there is no significant difference between the groups except, that the HIV infected participants have significantly stronger ankle plantarflexors (p=0.05) on the right.

There were no consistent significant differences between the functional and non-functional groups. HIV infected functional participants were significantly stronger in right ankle plantarflexors (p=0.10), but weaker in right knee flexion (p= 0.08) and extension (p=0.10). HIV infected non-functional participants were significantly stronger in right elbow extension (p=0.05) and right knee flexion (p=0.09).

Although there were no significant statistical findings the following trends were observed. In the functional group, the HIV uninfected participants tended to be stronger in all muscle groups except right and left ankle plantar flexion. In the non-functional groups there was a tendency for the HIV infected participants to be stronger in all muscle groups except right knee extension and left hip abduction.

Table 4.15 Muscle strength scores for HIV infected and uninfected, functional and non-functional groups

	Non functional group (36)			Functional Group (28)		
	HIV Infected (16)	HIV Uninfected (20)	p Value	HIV Infected (17)	HIV Uninfected (11)	p Value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Shoulder Abduction Left	22.55 (7.81)	19.44 (10.59)	0.14	23.51 (9.84)	27.54 (7.43)	0.16
Shoulder Abduction Right	20.88 (9.13)	17.97 (7.46)	0.36	22.79 (9.47)	28.19 (11.25)	0.16
Shoulder Flexion Left	22.35 (8.07)	22.04 (12.30)	0.93	23.52 (10.22)	27.38 (12.84)	0.38
Shoulder Flexion Right	21.05 (7.56)	19.44 (9.42)	0.58	25.38 (9.88)	31.42 (14.88)	0.21
Elbow Flexion Left	26.08 (11.29)	21.66 (9.34)	0.25	25.20 (10.73)	35.63 (18.83)	0.20
Elbow Flexion Right	25.72 (11.52)	20.35 (8.50)	0.18	26.35 (11.19)	34.17 (20.71)	0.41
Elbow Ext Left	24.83 (10.44)	21.11 (11.04)	0.31	26.22 (9.57)	33.44 (16.98)	0.16
Elbow Ext Right	26.24 (11.59)	19.46 (8.29)	0.05**	27.26 (13.82)	33.97 (16.95)	0.26
Hip Abduction Left	18.24 (9.14)	18.99 (9.40)	0.85	20.67 (8.78)	26.20 (16.64)	0.30
Hip Abduction Right	18.90 (9.19)	17.79 (7.16)	0.96	24.18 (10.09)	29.40 (13.10)	0.22
Ankle Plantarflex Left	14.26 (5.07)	13.47 (3.73)	0.88	17.19 (9.41)	16.22 (7.80)	0.86

Ankle Plantarflex Right	13.79 (5.74)	12.66 (3.25)	0.76	17.22 (7.10)	13.10 (5.78)	0.10*
Knee Flexion Left	17.54 (6.63)	15.26 (7.86)	0.21	18.55 (7.47)	26.61 (17.58)	0.22
Knee Flexion Right	20.68 (8.78)	16.41 (10.45)	0.09*	18.05 (6.53)	26.12 (12.95)	0.08*
Knee Extension Left	17.65 (11.71)	16.24 (6.93)	0.95	21.82 (9.42)	28.02 (13.85)	0.22
Knee Extension Right	16.82 (9.51)	17.77 (8.24)	0.64	21.22 (8.77)	28.39 (11.75)	0.10*
Hip Flexion Left	16.60 (8.91)	16.24 (5.82)	0.72	22.82 (8.40)	28.87 (14.34)	0.26
Hip Flexion Right	17.18 (8.82)	16.12 (5.88)	0.89	21.06 (8.84)	28.71 (13.92)	0.15

* Comparison was significant at the 0.1 level (2-tailed)
** Comparison was significant at the 0.05 level (2-tailed)

4.2.10.1 Correlation between viral load and muscle strength

Pearson's Product Moment-Correlation Coefficient was used to determine if a relationship existed between viral load and muscle strength in the HIV infected participants. A moderate correlation ($r= 0.35-0.48$) which is significant ($p<0.05$) was found in six muscle groups suggesting that viral load may have an impact on muscle strength in children with HIV. The data of this analysis can be found in Appendix 16.

Since there is no consistency in difference in muscle strength between the groups, regression analysis was not done.

4.6 Summary of results

4.6.1 Results of comparison of HIV infected and HIV uninfected groups

Participants were well matched for age, GMFCS level, weight and height.
The only significant differences between these groups, was for FMS at 500 meters and right ankle plantarflexor strength. The HIV uninfected group performed better in the FMS at 500 meters and had significantly weaker right ankle plantarflexor strength.

When comparing participants in the HIV infected group, the functional participants were significantly taller than the non functional participants. There was a moderate correlation between viral load and weight and height and viral load and six muscle groups for the HIV infected participants.

4.6.2 Results of comparison of HIV infected and HIV uninfected, functional groups

There were no statistically significant differences for GMFCS, weight, GMFM scores, FMS and majority of muscles tested for tone and strength. There was no significant correlation between viral load and GMFM.

The following were found to be statistically significant:

- Functional HIV infected children were younger than HIV uninfected children
- Functional HIV infected children had stronger right ankle plantarflexors but weaker right knee flexors and extensors than functional HIV uninfected children
- A moderate significant correlation was found between age and GMFM scores of the HIV uninfected participants

The following trends were observed:

- The HIV infected participants scored better in the GMFM, particularly in Dimension E where there was a 6.3% difference in scores.
- The HIV infected participants had a predominance of mild tone from proximal to distal.
- Severe hamstring tone was prevalent in almost one third of the HIV uninfected participants compared to less than 10% in the HIV infected participants.
- The HIV infected participants were weaker in all muscle groups except that of ankle plantarflexors compared to the HIV uninfected participants

4.6.3 Results of comparison of HIV infected and uninfected, non functional groups

There were no statistically significant differences for GMFCS, weight, GMFM scores, FMS and majority of muscles tested for tone and strength. There was no significant correlation between viral load and GMFM.

The following were found to be statistically significant:

- Non-functional HIV infected children had less right and left adductor tone compared to HIV uninfected children

- Non-functional HIV infected children had stronger right elbow extensors and right knee flexors than HIV uninfected children

The following trends were observed:

- The HIV infected and HIV uninfected groups had similar GMFM scores in all dimensions
- The HIV infected participants had a greater frequency of mild tone compared to the HIV uninfected participants.
- The HIV uninfected participants presented with severe tone proximally in 50% of cases while the HIV infected group presented with more moderate tone proximally
- The HIV infected participants were stronger than the HIV uninfected participants in all muscle groups.

4.7 Conclusion

The research results presented in this chapter facilitate both a description of the data collected and presentation of the inferential statistics needed to examine the research aims and objectives. Interpretation and discussion of these results will follow in chapter five.

CHAPTER 5 - DISCUSSION

5.1 Introduction

The primary aim of this study was to determine if there are similarities and differences between children with diplegia as a result of CP and HIVE. This chapter serves to interpret and discuss the results of the present study. Clinical implications, limitations of the study and implications for future research will be discussed.

Children of school going age were chosen because HIV infected infants are surviving into adolescence and adulthood but they are living with the complications of HIVE such as diplegia. They are accessing the South African school system and management and rehabilitation of these children is becoming increasingly relevant.

5.2 Demographic data

5.2.1 General

Children from both groups were divided into a functional group (GMFCS I and II), who were independently ambulant and a non-functional group (GMFCS III and IV) who were more limited in self mobility. This was done to be able to compare similar groups of children based on function. The rationale for the stratification is based studies by Palisano et al (2000) and Oeffinger et al (2009). Palisano et al (2000) found that the difference between the GMFM scores between GMFCS level II and III can differ by up to twenty-eight points and in contrast the difference between GMFCS level I and II was only 7.5 points while Oeffinger found that there is a large overlap between GMFCS I and II but no overlap between II and III. This indicates that the attainable gross motor function varies very little between level I and II and that children in level II may take longer to attain their maximum function (Palisano et al, 2000).

In splitting the groups, the sample size of each of the four groups was much smaller which could explain the lack of statistical significance in GMFCS distribution.

Children were well matched for age and gender between the HIV infected and HIV uninfected groups.

There was a higher incidence of prematurity in children with CP (41.9%) compared to those with HIV (9.1%). Prematurity is one of the most common known causes of CP (Odding et al, 2006) however in an African setting it was only identified by two studies as a major cause (Donald et al, 2014a). The use of HAART by the mother prior to pregnancy or in the first trimester may predisposes her to premature delivery (Mirpuri and Jain, 2010) which could account for the three children with HIV that were born prematurely. In resource-rich settings elective caesarean sections are offered to women to reduce the risk of mother-to-child transmission (Mirpuri and Jain, 2010), but is not common practice in the public health setting in South Africa.

In Africa, anoxia was noted as the most common risk factor for CP (Donald et al, 2014a). The incidence of anoxia was similar between the groups. However for the CP group, prematurity was still a more prevalent cause than anoxia.

Five children in the HIV infected group were orphans compared to none in the HIV uninfected group. One was in an institution and four were being cared for by family members. Children with HIV are at greater risk of orphanhood as parents are also affected by the epidemic. They may also have to bear the burden of siblings and other family members being affected. Extended families and institutions provide care for these children (Jelsma et al, 2011; Shead et al, 2010) but will have to cope with the extra burden of disability.

The definitions of both CP and HIVE, state that motor milestones may be delayed (Rosenbaum et al, 2007; WHO, 2007). As per these definitions, motor milestones were delayed in all participants in this study. Furthermore the definition of HIVE also acknowledges the loss of a previously acquired skill (WHO, 2007). This was true for three participants with HIVE whose milestones regressed.

In both groups, the majority of children (63.6% HIV infected and 71% HIV uninfected) were attending a school for children with special educational needs rather than a mainstream school (12.1% HIV infected and 3.3% HIV uninfected). Twenty-five percent of HIV uninfected participants, compared to nine percent of HIV infected participants had repeated a grade. In a review of literature highlighting the concern of HIV in adolescence, it was reported that 51% of children with HIV fail a grade while 27-33% require special education (Laughton et al, 2013). Adverse neurocognitive deficits affects both groups of children and is widely reported. In children with CP this may be as a result of direct injury to the brain which results in white matter tracts being disrupted leading to impaired

processing, attention and executive function and can lead to cognitive and intellectual impairments (Brossard-Racine et al, 2012; Bottcher, 2010). This can lead to children with CP requiring special schooling. Similarly neurocognitive deficits in children with HIV may be as high as 90% (Lowick et al, 2012) and delays can be persistent despite children initiating early treatment (Potterton et al, 2016). Furthermore, children with HIVE have been shown to perform worse in these areas compared to children who do not have the diagnosis of HIVE (Walker et al, 2013). This may be due to irreversible CNS damage early on by the virus or ongoing viral CNS replication as a result of poor penetration of medication into the CNS or neurotoxicity of HAART (Crowell et al, 2014; Smith et al, 2009). Persistent cognitive impairment in the presence of good systemic viral control may indicate that there is inadequate CNS viral suppression due to poor CNS penetration of drugs (Vreeman, 2015). Invasive measures are required to monitor the viral load as well as the penetration of medication in the CNS and is not readily done in children therefore it is difficult to know the exact cause of ongoing neurocognitive deficits (Crowell et al, 2014). Orphanhood and environmental factors such as poverty, illness, malnutrition and negative living environment are known to have an effect on learning and behaviour in both groups of children however socioeconomic status was not assessed as part of this study (Laughton et al, 2013; Jelsma et al, 2011; Shead et al, 2010).

Six percent of HIV infected participants and 19% of uninfected participants in this study were taking Ritalin which is used for attention and hyperactivity. The prevalence of hyperactivity in children with CP was found to be 30% in a developed country. This was not associated with poor socio-economic, physical and cognitive characteristics (Brossard-Racine, 2012). Studies conducted in resource-limited countries have reported hyperactivity to be between 20% and 28% among HIV infected children (Donald et al, 2014b; Govender et al, 2011) which is similar to the findings of this study.

5.2.2 HIV

Seventy eight percent of HIV infected children initiated HAART below the age of one year. Only 16% initiated treatment below the age of six weeks. The CHER study advocated for early initiation of treatment before the age of seven weeks as the morbidity and mortality outcomes are more favourable than if it was deferred (Violari et al, 2008). Children in this study were born between the years of 1999 and 2010. The HAART regimen was instituted in South Africa in 2004 and initially children had to have an incident of an immunocompromised illness or CD4 count less than fifteen percent before HAART was

administered (Donald et al, 2015). In 2010 all infants below the age of one year received treatment irrespective of clinical stage of disease (Potterton et al, 2013). Therefore the majority of children in this study were unlikely to have had treatment from birth and the older children in this study (born between 1999 and 2004) may have been severely immunocompromised before HAART was initiated. This could possibly explain why there is a higher percentage of children initiating HAART between six week and one year. Despite initiation under the age of one year, the children in this study are experiencing both motor and cognitive deficits. This is consistent with participants with diplegia as a result of HIVE who all initiated HAART before the age of one year (Langerak et al, 2013). It also fits in with the trend that early initiation improves mortality but doesn't protect against neurological damage (Potterton et al, 2016; Donald et al, 2015; Laughton et al, 2012; Smith et al, 2009)

Viral load is the number of viral particles in the blood stream and is used to monitor a patient's response to HAART (Rutherford et al, 2014). Virological treatment failure is defined by VL greater than 1000copies/ml based on two consecutive viral load measurements (Kukoyi et al, 2016). In this study, only 12.5% of participants had levels above 1000copies/ ml indicating poor virological control. The viral load for the majority of children fell within 20-1000copies/ml which is indicative of adequate viral suppression. Inadequate viral suppression can lead to drug resistance and this may have negative long term consequences since these drugs are needed from birth (Vreeman, 2015).

5.3 Anthropometric data

5.3.1 Height and weight compared to normative data

There were no significant differences between the groups for weight and height as well as weight-for-age and height-for-age z scores.

The weight-for-age z score fell within the median percentile indicating that children were neither under nor over weight. The mean height-for-age z score for both groups was approaching -2.0 (-1.61 for HIV infected; -1.75 for HIV uninfected) indicating that in both groups participants fell within the fifteenth percentile which shows a trend towards being shorter. On further examination, the mean height-for-age z score of the HIV infected non-functional participants was -2.38. Values below -2.0 indicate severe stunting (WHO reference 5-19years). The non-functional HIV infected children were significantly shorter

than the functional HIV infected counterparts. Growth failure is prevalent in CP and HIV (Hutchings et al, 2013; Feinstein et al, 2012; Bell et al, 2010).

For both groups malnutrition, poor socioeconomic circumstances as well as inactivity could contribute toward decreased height. However, neither nutritional nor socioeconomic status was assessed as part of this study. The non-functional group were mainly wheelchair bound. They may walk for short distances with assistance. Lack of weight bearing through the lower limbs means there is decreased mechanical stress on the bones which in turn leads to poor bone growth and result in stunting (Bell et al, 2002). Bone mineral density in HIV infected children can be reduced due to the virus itself as well as to increased HAART exposure and this may also affect growth in this population (Donald et al, 2014b) Malnutrition is unlikely to be a significant cause in children in this study as their mean weight-for-age z scores fell within normal limits (-0.91).

5.3.2 Height and weight and viral load

Growth failure was one of the hallmarks of HIV infection in children in the pre-HAART era (Shead et al, 2010). Additionally, Arpadi (2005) noted that there was no association between viral load and growth since the initiation of HAART. The HIV infected participants in this study did not show significant signs of growth failure and the majority had adequate viral control. However, a moderate significant correlation between viral load and weight and height was found to be and this should be carefully interpreted. Since majority of the participants in this study had good virological control, there isn't enough variability in the viral load levels to deem this correlation to be meaningful. Furthermore, if there was to be a meaningful correlation, one would expect a negative correlation between these variables. HAART is known to have a positive effect on growth and that normal growth parameters can be attained after two years of treatment (Feinstein et al, 2012; Sutcliffe et al, 2011; Weigel et al; 2010) and this is evident in the participants in this study.

5.4 Function

5.4.1 GMFM

There was no statistically significant difference between the two groups for GMFM. However, the reported minimum clinically important difference (MCID) for the GMFM-66 of a large effect size (0.8) is 1.3 (Oeffinger et al, 2008). The difference in the mean GMFM scores between the HIV infected and HIV uninfected groups was 3.87 which is clinically important. This is largely attributed to the difference of 2.36 in GMFM scores between the

functional HIV infected group and the functional HIV uninfected group which is also clinically important. Within this functional group, the greatest difference in scores (6.3%) was noted in Dimension E which is that of walking, running and jumping. This difference is also clinically important. The difference between the two non-functional groups was 0.65 and is not clinically important

This clinical important difference in the HIV infected functional group could be attributed to the difference in age between the two groups. The HIV infected children were younger than the HIV uninfected and this was shown to be statistically significant (p=0.01). The mean age of the HIV infected group was 7.5years. Children with spastic diplegia at GMFCS I and II attain 90% of their maximum GMFM score between the age of five and seven and thereafter they begin to plateau (Beckung et al, 2007; Rosenbaum et al, 2002). The function of children with GMFCS I and II remains stable from adolescence into adulthood (Hanna et al, 2009). It is possible then, that the HIV uninfected children had already reached a plateau and have a stable function according to the GMFM, while the HIV infected group were still perhaps reaching their peak. The extensive research that has been done on these motor curves and the stability and decline of function, has been done on children with diplegia as a result of CP. Therefore, we need to use them with caution when applying them to the results of the HIV infected participants. Since there are no longitudinal studies to determine the progression of this group of children, we cannot use these curves to prognosticate for the HIV infected group.

Additionally the significance in the difference in age is evident when comparing the percentiles of the GMFM score for the functional groups. The mean GMFM score for HIV infected functional children was between the 15-20th percentile and 55th percentile for GMFCS I and II respectively. This was better than those of the HIV uninfected group whose scores fell with the 10-15th percentile for GMCS I and 40th percentile for GMFCS II. These percentiles measure the relative ability of the participants compared to other children of the same age and GMFCS level (Hanna et al, 2008). A moderate positive correlation was found between age and GMFM scores of the HIV uninfected, functional group. This would mean that as age increases, the GMFM score will increase. The potential for improvement in function is always present and in this group, we also know that they are unlikely to deteriorate as the progress into adulthood (Hanna et al, 2009). Again, even though the functional HIV infected participants in this study are younger and performing better than the HIV uninfected participants, we are unable to predict how they will continue to function over time. In the non-functional group, both the infected and

uninfected groups' scores fell within the same percentile for GMFCS III (60-65th percentile) and GMFCS IV (80-85th percentile).

For the HIV infected participants, no correlation was made between GMFM and viral load and GMFM and age. This could be due to the small sample size or the fact that the majority of participants had good virological control and so there was not enough variation of this variable to make an association.

Strength and tone can independently as well as in combination have an impact on function (Bartlett, 2013; Kim and Park, 2011; Ross and Engsburg, 2007). The effect of strength and tone on function for this study will be discussed further on in this chapter.

5.4.2 Functional Mobility Scale

The FMS is a measure of the participants' mobility at home and in the community. There were no significant differences between the groups at five, fifty and five hundred meters.

As expected the HIV infected and uninfected functional group were able to walk independently or with an assistive device over a distance of five hundred meters. This allows them to have a greater sense of independence when participating in the community. The non-functional group were limited to crawling at five and fifty meters and wheelchair use over 500 meters. This limits their ability to participate in the community. Limitation of independent mobility has been shown to have a negative impact on quality of life (Calley et al, 2012). Increased gait pathology in the non-functional groups as well as decreased gait speed are also known to negatively impact on social participation (Jaspers et al, 2013). A decline in gait function can be caused by an increase in weight as well as a decrease in muscle strength (Bell et al, 2002). For both groups the mean weight-for-age z scores (-0.67 HIV Infected; -0.66 HIV Uninfected) and BMI-for-age z scores (0.51 HIV Infected; 0.03 HIV Uninfected) fell within the median percentile, therefore an increase in weight was unlikely be the cause of poor gait function. Poor muscle strength and increased spasticity can impact gait and the impact of these will be discussed in the next section. These differences also lend support to stratifying the initial sample into functional and non-functional groups.

A range of tools is required to comprehensively assess the function of children with CP (Debuse and Bruce, 2011). The GMFM-66 is the most widely used tool but only assesses gross motor function in a test environment therefore it may not be a good reflection of how a child functions at home (Debuse and Bruce, 2011) while the FMS is the only measure to

assess a child's mobility using various assistive devices as well as in different environments (Harvey et al, 2008). These two outcome measures were used together to get a more complete assessment of activity (GMFM-66) and participation (FMS).

In conclusion, there was no statistical difference between the groups in terms of function and mobility thereby rejecting the null hypothesis. However, a clinically important difference was observed in favour of the HIV infected functional participants with regard to the GMFM especially Dimension E. However, no significant difference was noted between the HIV uninfected and infected functional participants in the FMS. As we know this group consisted of children with GMFCS level I and II therefore, they are able to walk independently. The FMS as a tool serves to report whether a participant can mobilise over a specific distance only while Dimension E of the GMFM looks at other components of walking like balance, running and stepping over objects. Therefore, this could explain why a greater difference was observed in walking with the GMFM as opposed to the FMS as it is more detailed and specific. Furthermore, there are no reported MCID values for the FMS.

5.5 Impairments

5.5.1 Muscle Tone

Four muscle groups were tested bilaterally using MAS. No significant differences were found between the HIV infected and HIV uninfected groups except for the right adductor tone in the non-functional group.

The HIV infected non-functional participants had mild tone compared to the HIV uninfected participants who had a greater frequency of severe tone particularly in the proximal adductor muscles. This increase in severe tone proximally could be the cause of limited ability to walk in children that were HIV uninfected and non-functional. This however, cannot be applied to the HIV infected group as they had a greater frequency of moderate tone proximally. Their inability to walk can perhaps be attributed to a decrease in their muscle strength which will be discussed further in section 5.5.2.

In order to comment on the cumulative difference in muscle tone, an average percentage of frequency across the two sides for each muscle group tested was calculated. This enabled the researcher to identify patterns between the two groups based on the

frequency of mild tone (graded 1 and 1+), moderate tone (grade 2) and severe tone (graded 3 and 4) in the functional and non-functional groups.

In the functional group, the frequency of mild spasticity was prevalent from proximal to distal in both groups. There were no participants with severe adductor tone (proximal) in the HIV infected group while the HIV uninfected group had no participants with severe tone in the plantarflexors (distal). The predominance of mild spasticity in the HIV infected group is consistent with group one in the study by Langerak et al (2014) who also had mild tone as well as a gait pattern that was closer to normal. However, almost a third of the HIV uninfected group presented with severe tone in their hamstrings. This could have a negative impact on gait in this group which could explain why this group scored 6.3% lower in Dimension E of the GMFM.

The HIV infected non-functional group still showed a predominance of moderate tone proximally and mild tone distally. Even though the HIV uninfected participants in this group had a predominance of severe tone proximally, there was also a distinct decrease in the severity of tone from proximal to distal. The results for both groups are inconsistent with two studies which have found tone to increase in severity from proximal to distal (Langerak et al, 2014; Ross and Engsburg, 2002). A possible explanation for this could be the fact that over 50% of the participants in both groups have had Botox at some point as an intervention to reduce spasticity in certain muscle groups. Administration of botox in the HIV infected group ranged from six months to a year (37%) prior to testing, to more than two years (16%) prior to testing. Similarly in the HIV uninfected group, 44% received Botox between six months and a year prior to testing while 28% received it more than two years prior to testing. This is in contrast to the study by Langerak et al (2014), where the participants had no Botox into the lower limbs prior to testing.

The HIV infected participants in this study had a predominance of mild tone from proximal to distal. Langerak et al (2014) found spasticity to increase from proximal to distal in the participants with a more pathological gait pattern. A decreased lean body mass as well as muscle atrophy are known complications of HIV as well as HAART. Furthermore, fat is redistributed centrally resulting in additional lipoatrophy peripherally in the limbs. This results in muscle weakness and wasting (Arpadi et al, 2014; Schiller, 2004; Grinspoon and Mulligan, 2003). This wasting and atrophy could possibly explain why there is mild tone however there are no studies that have described the quality and pattern of tone that is

prevalent in children with diplegia as a result of HIVE even though studies have reported spasticity and hyperreflexia as signs of HIVE (Donald et al, 2015; Govender et al, 2011).

Bartlett et al (2013) noted that spasticity is a primary impairment in CP and spastic muscles are known to be weak (Thompson et al, 2011). Therefore these results cannot be considered in isolation. The results of muscle strength testing will be further discussed.

5.5.2 Muscle strength

There were no consistent statistical differences between the two groups for all muscle groups tested. However the following trends were observed.

Muscle strength was weaker distally in the ankles compared to the proximal hip muscles for both infected and uninfected groups which is consistent with that of several studies that found muscle weakness to be more prevalent distally than proximally in children with CP when compared to normally developing children (Langerak et al, 2014; Ferland et al, 2012; Nyström et al; 2008; Wiley and Damiano, 1998). This could be as result of increased tightness in the gastrocnemius muscle when the knee is in extension therefore not allowing the muscle to produce an effective force (Wiley and Damiano, 1998). Additionally, the gastro-soleus complex is known to have a smaller cross-sectional area and is therefore unable to an adequate force that is required for function as there is incomplete activation of the muscle (Elder et al, 2003).

It is of great clinical significance to not that in the functional groups, the HIV infected participants were weaker than HIV uninfected participants in all muscle groups tested except ankle plantarflexion bilaterally. There is a correlation between plantarflexor strength and gait and the plantarflexors are crucial in generating the power that is required for gait (Nyström et al, 2011) in children with diplegia and GMFCS level I and II. The stronger plantarflexors in HIV infected participants could explain why this group performed 6.3% better in Dimension E of the GMFM which is that of walking, running and jumping compared to the HIV uninfected group.

Conversely the HIV infected participants in the non-functional group were stronger than HIV uninfected participants in all muscle groups except right knee extension and left hip abduction. The HIV infected participants had a predominance of moderate to mild tone as compared to the HIV uninfected groups who had more severe tone proximally. This could have allowed the HIV infected participants to move more easily through the range of movement and therefore produce a greater force.

Within the HIV infected group, the non-functional participants were weaker than the functional participants in all muscle groups tested except left elbow extension and right knee flexion. The difference in strength between the groups was greater in the lower limb muscles. The non-functional participants were 11.8% weaker in the left hip adductor and 27.3% weaker in the left hip flexor compared to the functional group. This was also true for the HIV uninfected participants where the muscle strength in all muscle groups was stronger in the functional group. The weakness of the non-functional HIV uninfected participants ranged from being 17% weaker in the left ankle plantarflexors to 43.9% weaker in the right hip flexors. This is consistent with the findings of Langerak et al (2014) who found that the muscle strength of diplegics as a result of HIVE with a more pathological gait pattern to be weaker and Thompson et al (2011) who found there to be progressive weakness in lower limb strength from GMFCS I to III.

The largest drop in strength was observed in the hip flexors followed by the knee flexors and extensors in the HIV uninfected group and hip flexion and abduction in the HIV infected group. This is partly consistent with Thompson et al (2011) who found the drop in strength to be most in the hip abductors followed by the knee extensors and with Nyström et al (2008) who found the biggest drop in strength to be in the hip abductors followed by hip extensors. The muscle strength of hip extensors was not measured in this study. The progressive weakness in the hip muscles from GMFCS I to III can explain why children at level III have difficulty to stand and walk independently. These muscles provide proximal stability in the stance phase and during weight bearing therefore weakness here will make it difficult to have stability during standing and walking. Furthermore, hip flexor and ankle plantarflexor strength have been associated with walking and stair climbing while hip abduction has been associated with running in ambulant children with diplegia (Ferland et al, 2012)

5.5.3 Muscle strength compared to normative data

5.5.3.1 HIV infected group

The muscle strength values of 14 muscle groups in the HIV infected group can be compared to muscle strength values of HIV infected children who had no indication of disability (Humphries et al, 2014) as the method of testing as well as the units of measure were the same. On average, the muscles strength of eight upper limb and six lower limb groups were 42.8% (34.7%-49.3%) and 70.4% (58.6%-75.8%) weaker respectively, compared to the non-disabled group of Humphries et al (2014). Overall in the present

study, the lower limb muscles were weaker than upper limb muscles while this was conversely true in the non-disabled group. The predominant weakness of lower limb muscles is consistent with diplegia where lower limbs are more affected than upper limbs. Humphries et al (2014) assessed children between the age of four and eight with a mean age of 6.4years as compared to the current study which included children up to the age of 16 with a mean age of 7.78 years. Both groups were receiving HAART at the time of testing. The weakness of the disabled group could be attributed to HIVE which was not present in the comparative group as well as the prolonged negative effect of the virus and HAART on muscle strength. Muscle strength may be affected by mitochondrial toxicity from the medication or wasting. Muscle bulk was not measured in this study but wasting can occur as a result of increased protein demand due to inflammation. Furthermore fat redistribution is a known side effect of HAART and results in peripheral lipoatrophy. All these factors can result in decreased muscle strength (Dudgeon et al, 2006; Grinspoon et al, 2003).

5.5.3.2 HIV Uninfected group

Lower limb strength profiles for children with CP were determined by Wiley and Damiano (1998), Nyström et al (2008) and Thompson et al (2011). It is difficult to compare the values obtained in the present study to the above as there are differences in age range, testing position, method and unit of measure used and the way in which the data was analysed. However, they all concluded that the lower limb strength of children with diplegia were significantly weaker than normally developing counterparts. In the most recent study, muscle strength ranged from 43%-90% of the control group (Thompson et al, 2011). On this basis we can conclude that the lower limb muscle strength of HIV uninfected children with diplegia is weaker than those of normally developing children.

There is a complex relationship between spasticity, ROM and selective motor control in children with CP (Ostenjø et al, 2004). Spasticity can be regarded as a primary impairment while decreased muscle strength can occur as a result of spasticity (Bartlett et al, 2013). In contradiction to this Ross and Engsburg (2002) determined that spasticity is not related to strength since weakness was present in all children with diplegia while spasticity was not. Furthermore, strength has been highly correlated to function (r=0.83) compared to spasticity (r=0.27) (Ross and Engsburg, 2007) and this is supported by studies that have shown that strength training programmes in children with CP improve GMFM scores and gait (Nyström et al, 2008). Additionally other studies have noted that strength programmes are effective in improving strength but not activity (Bania et al, 2016; Scholtes et al, 2008)

Therefore it can be seen that this complex relationship exists between impairment and function in children with diplegia.

5.5.4 Summary

In this study the HIV infected functional group performed better functionally than their HIV uninfected counterparts particularly in Dimension E of the GMFM. They tended to be weaker in all muscle groups except the plantarflexors and had a predominance of mild tone. Even though statistically, the tone of these groups was similar, the HIV uninfected group had a higher frequency of severe tone in their hamstrings. Therefore it is possible that the HIV infected participants performed better as they had stronger plantarflexors and milder tone than the HIV uninfected functional participants. It can be assumed that muscle tone may play an important role in function for this population of children, however further research is required in with larger sample sizes to confirm this.

To summarise, both groups had similar strength and tone profiles which have had an impact on function and gait. Since there were no significant statistical differences between the groups, the null hypothesis can be rejected for muscle tone and muscle strength.

5.7 Limitations of the study

The limitations of this study are as follows:

- The original sample size of the 33 participants in the infected groups and 31 in the uninfected groups was fair but once the group was divided into functional and non-functional groups, the sample size was diminished. This could have had an impact on statistical significance and generalisability of the results.
- Parents and caregivers of HIV infected participants were only asked the number of ARV medications that were being taken i.e. one, two or three so as to determine if they were taking triple therapy. The names of ARV's were not recorded. The side effects of certain ARV medications have been implicated in increasing neurological complications, therefore this information could have been useful to determine if there was a correlation between the groups and type of medication.
- Muscle tone is defined as a velocity-dependent resistance to passive movement at a joint. There is a complex relationship between muscle tone, range of motion (ROM) and selective motor control. An increase in muscle

tone can result in decreased range of motion at a particular joint which in turn affects normal movement (Ostenjø et al, 2004). It is therefore important to measure ROM and muscle tone and this was not done in this study.

- HIV negative participants were not confirmed as being negative using objective testing. This was assumed after no signs of HIV infection was found in the patients' hospital file and in the medical history taken.
- The diagnosis of HIVE was not confirmed by a medical doctor. Children that presented with spastic diplegia and were HIV infected were assumed to have HIVE.
- Gait analysis was not done as part of this study and would have been useful to give insight into the similarities and differences between the gait patterns of the two groups.
- Nutritional and socioeconomic status of the participants was not assessed.

5.8 Clinical Implications of the study

It is unclear what the natural progression of HIV infected diplegics will be as there are many factors that could impact function. Lifelong impact of the virus and medication may have negative effects. Therefore it is difficult to say whether they will follow the progression of CP diplegia and if management like orthopaedic surgery which is known to assist with maintaining function in CP will have the same effect on children with HIV.

Functional and non-functional children with HIV present differently with regards to strength and tone. Management in terms of therapy and surgery will need to address different problems in these groups and the outcome thereof will also vary as the natural progression for this population is not yet determined.

5.9 Research implications of the study

Further research is required to compare functional and non-functional groups with larger sample sizes to determine if the is a significant difference between the groups in terms of function, muscle tone and strength. Correlation between viral load and function may prove to be more significant if it is assessed using a larger sample size.

Further research is required in the adolescent HIV group to determine the natural progression of HIV infected adolescents with diplegia.

Further gait analysis research, with larger sample sizes, is required to determine whether there are similarities and differences in this area between HIV infected and uninfected participants.

CHAPTER 6 - CONCLUSION

There are many studies done, spanning over decades to better understand CP and spastic diplegia as a result of CP. In more recent times there has also been a fair amount of research to help us understand HIV encephalopathy in children. Diplegia can be a result of HIVE and to date only one study, done in Cape Town, has analysed and described this condition.

To our knowledge, this is the first study to be done to compare the demographics, anthropometrics, function, tone and muscle strength of 33 HIV infected children with diplegia to 31 HIV uninfected children with diplegia across GMFCS I to IV.

The two groups were well matched for age and anthropometrics. Demographically, there was a greater incidence of prematurity in the uninfected group. The majority of children in both groups attended a school for children with special educational needs. All except one HIV infected participant was on HAART, with the majority having initiated HAART under a year of age (78%) and only 16% below the age of six weeks old. Good virological control was evident in the majority (87.5%) of participants.

Due to the large difference in participation between the GMFCS levels, both groups were stratified into a functional group (GMFCS I and II) and a non-functional group (GMFCS III and IV) based on their ambulatory ability.

In the functional group, the HIV infected children were significantly younger and this group performed clinically better in the GMFM than the HIV uninfected participants. There were no consistent statistically significant differences between the groups for muscle strength and tone but there was a trend for the HIV infected group to be weaker and have a greater frequency of mild tone from proximal to distal compared to the HIV uninfected group.

In the non-functional group there was no significant difference for function and no consistent significant differences for strength and tone between the groups. However, the HIV infected groups tended to be stronger and have a greater frequency of mild rather than severe tone from proximal to distal.

For both HIV infected and HIV uninfected groups, the non-functional participants were weaker than the functional participants and lower limbs were weaker than upper limbs.

Among the HIV infected participants, the non-functional participants were significantly shorter than the functional participants.

This study highlights that HIV infected and uninfected participants with diplegia may present similarly in terms of function, strength and tone. However, further research is required with larger sample sizes to verify these results for children of different GMFCS levels.

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APPENDICES

Appendix 1

R14/49 Ms Tasvi Naik

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140936

NAME: (Principal Investigator)	Ms Tasvi Naik
DEPARTMENT:	Physiotherapy Rahima Moosa Mother and Child Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	A Comparison of the Clinical Presentation of HIV-Infected Spastic Diplegic Children to HIV-uninfected Spastic Diplegic Children in a South African Setting
DATE CONSIDERED:	03/10/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Carolyn Humphries and Joanne Potterton
APPROVED BY:	Professor Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	12/11/2014

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 Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized 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 the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL
Enquiries: Mrs. S. Jordaan
Tel: (011) 470 9030/4
Fax: (011) 477 4117
Email: sjordaan@icon.co.za

University of the Witwatersrand
Department of Physiotherapy
Faculty of Health Science
PARKTOWN
JOHANNESBURG
2001

Re:"A comparison of the clinic presentation of HIV – infected / uninfected spastic diplegic children in SA setting"

Dear Ms. Tasvi Naik,

Permission is granted for you to conduct the research as indicated in your request as per the title above.

The terms under which this permission is granted is contained in the Researcher Declaration form that you signed. Failure to comply with these conditions will result in the withdrawal of such permission.

Note that it is imperative that you notify the hospital of the actual start and end dates of your study by notifying the CEO's secretary preferably by email or fax.

Should the study commence more than 12 months from receipt of this letter then the Researcher Declaration form needs to be re-signed prior to commencement of the research. Your are strongly advised to keep a signed copy of the declaration form so as to ensure that the terms of this agreement are complied with at all times.

Yours sincerely,

Sjordaan

CHIEF EXECUTIVE OFFICER
SJ/cj. 2014 -08-28

ADDRESS: cnr. FUEL & CUDSTHOORN STREET CORONATIONVILLE 2093 / PRIVATE BAG X20 NEWCLARE 2112 JHB

Appendix 3

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 07 January 2015

TITLE OF PROJECT: A comparison of the clinical presentation of HIV-infected spastic diplegic children to HIV-uninfected spastic diplegic children in a South African setting

UNIVERSITY: Witwatersrand

Principal Investigator: T Naik

Department: Physiotherapy

Supervisor (If relevant): C Humphries and J Potterton

Permission Head Department (where research conducted): Yes

Date of start of proposed study: January 2015
Date of completion of data collection: December 2016

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 07 January 2015

.....
Approved/Not Approved
Hospital Management
Date: 12/01/15

Appendix 4

Information Sheet

A comparison of the clinical presentation of HIV-infected spastic diplegic children to HIV-uninfected spastic diplegic children in a South African setting

Dear Parent/Caregiver/ Guardian

My Name is Tasvi Naik. I am currently employed as a physiotherapist at West Rand CP School. As part of my Masters degree in Physiotherapy, I will be conducting research. In this study, I would like to find out if there are any differences in the way that HIV infected diplegic children present compared with HIV uninfected diplegic children in terms of physical function. I would like to invite your child to participate in this study.

What is involved?

Your child will undergo a once-off assessment of various physical functions at the hospital. This assessment will take an hour and a half to complete. The following assessments will be done in this time:

- GMFM-66: this is a standardised assessment tool. Here I will look at the way in which your child moves. It has 66 different types of tasks from lying through to sitting, standing and then walking. It will help me to have a clear understanding of how your child moves. As each activity is performed a score will be given. This test will take 45 minutes.
- Muscle strength: I will do this using a machine which I will hold against your child's arm and leg. Your child will be asked to push on the instrument as hard as they can and a reading will be taken. There will be no pain or discomfort during this test. I will be testing arm and leg strength and so your child may be tired after this test. This test should take 20 minutes to complete.
- Muscle tone using the Modified Ashworth Scale: this is an assessment of the amount of how tight your child's leg muscles are. During this test I will be feeling how your child's leg muscles react when I move it. He/she will not be required to do anything during this test. This test causes no pain or discomfort. It should also take 20 minutes to complete.
- There are no risks involved with these assessments but your child may be tires at the end of the session.
- I would also like you to please complete a questionnaire which will give me information about your child's medical history, including HIV status and background. This questionnaire is available in English. Should you require a translator to help you with the form, one will be provided.

- Participation in this study will not interfere with his/her current therapy program.
- You will be reimbursed for transport costs to the hospital up to the value of R50 per person.

Confidentiality

Information about your child will be kept safe and confidential. All information obtained will be used for the study purposes only. No names will be put on any of the study sheets or results.

Withdrawal

Your child may withdraw from this study at any time. This will not affect the current therapy that he/she receives at the hospital.

If you are willing to allow your child to participate in this study, please sign the consent form provided. If your child is over 6 years old, he/she will also be required to sign an assent form.

Thank you for taking the time to read this.

If you have any further questions or worries, please feel free to contact me, my supervisors or the chairperson of the Human Research Ethics Committee (Medical). The contact details are available below.

Thank you,

Tasvi Naik	Joanne Potterton	Carolyn Humphries
(Physiotherapist)	(Supervisor)	(Supervisor)
083 235 3567	011 717 3718	083 660 2725

Contact Details HREC

Ms Zanele Ndlovu- Administrative officer

011 717-1252

Appendix 5

CHILD Information Sheet

Hello,

My Name is Tasvi Naik. I am a Physiotherapist working at West Rand CP School and I am also studying further. As part of my studies I would like to find out how diplegic children do things. I would like to invite you to be part of this study.

If you say yes, I will do the following tests:

- GMFM-66: to see how well you can do certain tasks like lying, sitting and standing. This will take 45 minutes.
- Muscle strength: I will do this using a machine that I will hold against your arm and leg. This will give me an idea of how strong your muscles are. This will take 20 minutes.
- Muscle tone using the Modified Ashworth Scale: this test will give me an idea of how tight the muscles in your legs are. It will also take 20 minutes.
- Altogether we will be busy for an hour and a half.

I will be able to do all of these tests in one day at the hospital where you go for therapy.

I will also ask your parents/guardian to answer questions about your health and how you have been growing.

Any information that I get from your parents and from the tests will be kept safe and private. Your name as well as your parents' names will be kept a secret.

You may say 'No' if you do not want to take part in the study. You will still be doing your normal physio exercises even though you are taking part in the study. If at any time you want to stop the study, you may do so. This will not change your therapy at the hospital.

If you would like to help with this study, please sign the form provided.

You are welcome to ask me questions at any time.

Thank you for taking the time to read this.

Tasvi Naik

(Physiotherapist)0832353567

Appendix 6

Consent Form:

Research Tiltle: **A comparison of the clinical presentation of HIV-infected spastic diplegic children to HIV-uninfected spastic diplegic children in a South African special school setting**

I _____ have read the information sheet and understand the purpose of the study. I **give/ do not give** (please circle your choice) consent for my child_____ to participate in this study. I am aware that my child may withdraw at any time without any consequences. I understand that the procedures in the study will not harm my child.

_____ _____

(Parent/ Guardian Signature) Date

_____ _____

Researcher Signature Date

Appendix 7

Assent Form (To be used for both groups)

Research Title: **A comparison of the various clinical presentations of spastic diplegic children in a South African setting**

I _____ am **happy/ not happy (**please circle your choice) to take part in this study. I have read the information sheet and all my questions have been answered. I understand that I can stop at any point without any problems. I understand the tests that will be done and that they will not cause me harm in any way.

_____ _____

(Child Signature) Date

_____ _____

Researcher Signature Date

Appendix 8

Parent Questionnaire

SUBJECT NO:	**DOB**
Telephone No:	

BACKGROUND

DIAGNOSIS – Please be as thorough as you can	HIV Status:_____ If Positive, Please state at what age your child was diagnosed:_____ Is your child aware of his/her status? Yes☐ No☐
MEDICATION- Please list all the medication (acute as well as chronic) that the child is on as well as when they commenced this medication	
Birth History	full term ☐ prem_____(weeks) Normal Delivery ☐ Caesar ☐ Birth wt_____ Complications during pregnancy_____ _____ Complications at birth_____ _____ Complications after Birth_____

	_____
Developmental Milestones	Sat_____crawled_____ walked_____ first words_____ First Sentences_____
Family history- Please record if parents are deceased/ if there are any family illnesses	
Medical & Surgical history- please record any hospital admissions, surgery here	
School history- Please record when your child started school, names of schools as well as current grade	Age when child started school_____ Current Grade_____ Current School_____ Grades repeated_____ _____ Other information_____ _____

Appendix 9

Data Collection Sheet

1. Subject no:_____
2. Subject Age:_____
3. Group:_____
4. Weight_____ Height:_____
5. Medications:_____
6. GMFCS:_____

7. GMFM-66 Score:_____

Dimension A: Lying and Rolling	
Dimension B: Sitting	
Dimension C: Crawling & kneeling	
Dimension D: Standing	
Dimension E: Walking,running & jumping	

8. Modified Ashworth Scores:

Muscle	Score	
	L	R
Hip Adductors		
Hamstrings		
Gastrocnemius		
Soleus		

Score	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of range of motion when the affected part is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM

2	More marked increase in muscle tone through most of the ROM, but affected parts easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected parts rigid in flexion or extension

9. Muscle strength results:

Muscle/movement	Score					
	Trial 1		Trial 2		Average	
	L	**R**	**L**	**R**	**L**	**R**
Shoulder Abduction						
Shoulder forward flexion						
Elbow flexion						
Elbow extension						
Hip Abduction						
Ankle Plantar flexors						
Knee flexion						
Knee extension						
Hip flexion						

10. Additional Comments:

_____

_____

_____

_____

_____

Appendix 10

Methodology for assessing spasticity using the Modified Ashworth Scale

- The examiner will position the child correctly. The child will be asked to relax during this assessment. He/she will not be required to do any of the movements actively. It will be done for by the examiner.
- Hip Adductors- the child will be in a supine position with hips flexed at 45 degrees and knees relaxed in extension. Examiner supports proximally at greater trochanter. The other hand is placed proximal to the ankle. The knee is now taken from maximum hip adduction to maximum hip abduction.
- Hamstring- the child in supine position with head and neck aligned. The hip is flexed to 45 degrees for clearance of the heel during knee flexion. Examiner places one hand proximal to the knee and one hand proximal to the ankle. The knee is taken from maximal flexion to maximal extension.
- Gastrocnemius- supine with head and neck aligned. Hips are flexed 45 degrees and the knee at maximum extension. The examiner stabilises the leg with one hand proximal to the knee and other hand grasps the plantar aspect of the foot with thumb on lateral surface of the heel and fingers on medial surface. The ankle is taken from maximal plantar flexion to maximal dorsiflexion.
- Soleus- supine with head and trunk aligned. Hip and knee are both flexed at 45 degrees. The examiner stabilises the leg with one hand proximal to the ankle and other hand grasps the plantar aspect of the foot with thumb on lateral surface of the heel and fingers on medial surface. The ankle is taken from maximal plantar flexion to maximal dorsiflexion.
- Results will be recorded on a data collection sheet after measurement has been taken (Appendix 9)

Appendix 11

Methodology for assessment of muscle strength using a hand-held dynamometer

- Muscle strength measurements will include:
  - Shoulder abduction strength
    - Child will be positioned on a firm flat surface in supine, knees flexed and arms at sides
    - The assessor will hold the dynamometer against the dorsal surface of the forearm
    - The assessor will ask the child to push as hard as he/she can up to the side
  - Shoulder forward flexion strength
    - Child will be positioned on a firm flat surface in supine, knees flexed and arms at sides with forearms supine
    - The assessor will hold the dynamometer against the palmer surface of the forearm
    - The assessor will ask the child to push up as hard as he/she can keeping his/her arm straight
  - Elbow flexion strength
    - Child will be positioned on a firm flat surface in supine, knees flexed and arms at sides with forearms supine
    - The assessor will hold the dynamometer against the palmer surface of the forearm
    - The assessor will ask the child to bend his/her elbow as hard as he/she can
  - Elbow extension strength
    - Child will be positioned on a firm flat surface in supine, knees flexed, elbows flexed to 90 degrees, with forearms supine
    - The assessor will hold the dynamometer against the dorsal surface of the forearm
    - The assessor will ask the child to straighten his/her elbow as hard as he/she can
  - Hip flexion strength
    - Child will be positioned in sitting with both knees flexed off the table.
    - Assessor will stabilise at the pelvis and place the HHD on the anterior thigh, 3cm proximal to the patella
    - Assessor will ask the child to push up as hard as he/she can

- The alternate leg with be done as above.

- Hip Abduction strength
  - Child will be positioned in supine with both hips flexed off the surface
  - Assessor will hold the dynamometer on the lateral thigh area, 5cm proximal to the knee joint and stabilise at the pelvis
  - Assessor will ask the child to push back as hard as he/she can
  - The alternate leg with be done as above.
- Knee flexion strength
  - Child will be positioned in sitting with knees flexed to 90 degrees
  - Assessor will place the dynamometer on the posterior calf, 5cm proximal to malleoli and stabilise at pelvis and thigh.
  - Assessor will ask the child to bend his/her knee pushing as hard as he/she can
- Knee extension strength
  - Child will be positioned in sitting with knees flexed to 90 degrees
  - Assessor will place the dynamometer on the anterior tibia, 5cm proximal to malleoli and stabilise at pelvis and thigh
  - Assessor will ask the child to straighten his/her knee pushing as hard as he/she can
- Ankle Plantar flexors
  - Child will be positioned in supine with hips and knees flexed to 90 degrees and ankle in neutral
  - Assessor will place the dynamometer on the plantar surface of the metatarsal heads and stabilise the pelvis and lower leg
  - Assessor will ask the child to push his/her foot as hard as he/she can

GROSS MOTOR FUNCTION MEASURE (GMFM)
SCORE SHEET (GMFM-88 and GMFM-66 scoring)

Child's Name: _____ ID#: _____

Assessment Date: _____ (year / month / day)

GMFCS Level[1]: ☐ I ☐ II ☐ III ☐ IV ☐ V

Date of Birth: _____ (year / month / day)

Chronological Age: _____ (year / month / day)

Evaluator's Name: _____

Testing Condition (e.g., room, clothing, time, others present): _____

The GMFM is a standardized observational instrument designed and validated to measure change in gross motor function over time in children with cerebral palsy. The scoring key is meant to be a general guideline. However, most of the items have specific descriptors for each score. It is imperative that the guidelines contained in the manual be used for scoring each item.

SCORING KEY
0 = does not initiate
1 = initiates
2 = partially completes
3 = completes
9 (or leave blank) = not tested (NT) [used for the GMAE-2 scoring*]

It is important to differentiate a true score of "0" (child does not initiate) from an item which is Not Tested (NT) if you are interested in using the GMFM-66 Ability Estimator (GMAE) Software.

*The GMAE-2 software is available for downloading from www.canchild.ca for those who have purchased the GMFM manual. The GMFM-66 is only valid for use with children who have cerebral palsy.

Contact for Research Group:
CanChild Centre for Childhood Disability Research,
Institute for Applied Health Sciences, McMaster University
1400 Main St. W., Room 408,
Hamilton, ON Canada L8S 1C7
Email: canchild@mcmaster.ca Website: www.canchild.ca

CanChild
Centre for Childhood Disability Research

[1]GMFCS level is a rating of severity of motor function. Definitions for the GMFCS-E&R (expanded & revised) are found in Palisano et al. (2008) Developmental Medicine & Child Neurology 50:744-750 and in the GMAE-2 scoring software. http://motorgrowth.canchild.ca/en/GMFCS/resources/GMFCS-ER.pdf

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Check (3) the appropriate score: if an item is not tested (NT), circle the item number on the right column

Item	A: LYING & ROLLING	SCORE	NT
1.	SUP, HEAD IN MIDLINE: TURNS HEAD WITH EXTREMITIES SYMMETRICAL	0☐ 1☐ 2☐ 3☐	1
* 2.	SUP: BRINGS HANDS TO MIDLINE, FINGERS ONE WITH THE OTHER	0☐ 1☐ 2☐ 3☐	2
3.	SUP: LIFTS HEAD 45°	0☐ 1☐ 2☐ 3☐	3
4.	SUP: FLEXES R HIP & KNEE THROUGH FULL RANGE	0☐ 1☐ 2☐ 3☐	4
5.	SUP: FLEXES L HIP & KNEE THROUGH FULL RANGE	0☐ 1☐ 2☐ 3☐	5
* 6.	SUP: REACHES OUT WITH R ARM, HAND CROSSES MIDLINE TOWARD TOY	0☐ 1☐ 2☐ 3☐	6
* 7.	SUP: REACHES OUT WITH L ARM, HAND CROSSES MIDLINE TOWARD TOY	0☐ 1☐ 2☐ 3☐	7
8.	SUP: ROLLS TO PR OVER R SIDE	0☐ 1☐ 2☐ 3☐	8
9.	SUP: ROLLS TO PR OVER L SIDE	0☐ 1☐ 2☐ 3☐	9
* 10.	PR: LIFTS HEAD UPRIGHT	0☐ 1☐ 2☐ 3☐	10
11.	PR ON FOREARMS: LIFTS HEAD UPRIGHT, ELBOWS EXT, CHEST RAISED	0☐ 1☐ 2☐ 3☐	11
12.	PR ON FOREARMS: WEIGHT ON R FOREARM, FULLY EXTENDS OPPOSITE ARM FORWARD	0☐ 1☐ 2☐ 3☐	12
13.	PR ON FOREARMS: WEIGHT ON L FOREARM, FULLY EXTENDS OPPOSITE ARM FORWARD	0☐ 1☐ 2☐ 3☐	13
14.	PR: ROLLS TO SUP OVER R SIDE	0☐ 1☐ 2☐ 3☐	14
15.	PR: ROLLS TO SUP OVER L SIDE	0☐ 1☐ 2☐ 3☐	15
16.	PR: PIVOTS TO R 90° USING EXTREMITIES	0☐ 1☐ 2☐ 3☐	16
17.	PR: PIVOTS TO L 90° USING EXTREMITIES	0☐ 1☐ 2☐ 3☐	17
	TOTAL DIMENSION A		

Item	B: SITTING	SCORE	NT
* 18.	SUP, HANDS GRASPED BY EXAMINER: PULLS SELF TO SITTING WITH HEAD CONTROL	0☐ 1☐ 2☐ 3☐	18
19.	SUP: ROLLS TO R SIDE, ATTAINS SITTING	0☐ 1☐ 2☐ 3☐	19
20.	SUP: ROLLS TO L SIDE, ATTAINS SITTING	0☐ 1☐ 2☐ 3☐	20
* 21.	SIT ON MAT, SUPPORTED AT THORAX BY THERAPIST: LIFTS HEAD UPRIGHT, MAINTAINS 3 SECONDS	* 0☐ 1☐ 2☐ 3☐	21
* 22.	SIT ON MAT, SUPPORTED AT THORAX BY THERAPIST: LIFTS HEAD MIDLINE, MAINTAINS 10 SECONDS	0☐ 1☐ 2☐ 3☐	22
* 23.	SIT ON MAT, ARM(S) PROPPING: MAINTAINS 5 SECONDS	0☐ 1☐ 2☐ 3☐	23
* 24.	SIT ON MAT: MAINTAIN, ARMS FREE, 3 SECONDS	0☐ 1☐ 2☐ 3☐	24
* 25.	SIT ON MAT WITH SMALL TOY IN FRONT: LEANS FORWARD, TOUCHES TOY, RE-ERECTS WITHOUT ARM PROPPING	0☐ 1☐ 2☐ 3☐	25
* 26.	SIT ON MAT: TOUCHES TOY PLACED 45° BEHIND CHILD'S R SIDE, RETURNS TO START	0☐ 1☐ 2☐ 3☐	26
* 27.	SIT ON MAT: TOUCHES TOY PLACED 45° BEHIND CHILD'S L SIDE, RETURNS TO START	0☐ 1☐ 2☐ 3☐	27
28.	R SIDE SIT: MAINTAINS, ARMS FREE, 5 SECONDS	0☐ 1☐ 2☐ 3☐	28
29.	L SIDE SIT: MAINTAINS, ARMS FREE, 5 SECONDS	0☐ 1☐ 2☐ 3☐	29
* 30.	SIT ON MAT: LOWERS TO PR WITH CONTROL	0☐ 1☐ 2☐ 3☐	30
* 31.	SIT ON MAT WITH FEET IN FRONT: ATTAINS 4 POINT OVER R SIDE	0☐ 1☐ 2☐ 3☐	31
* 32.	SIT ON MAT WITH FEET IN FRONT: ATTAINS 4 POINT OVER L SIDE	0☐ 1☐ 2☐ 3☐	32
33.	SIT ON MAT: PIVOTS 90°, WITHOUT ARMS ASSISTING	0☐ 1☐ 2☐ 3☐	33
* 34.	SIT ON BENCH: MAINTAINS, ARMS AND FEET FREE, 10 SECONDS	0☐ 1☐ 2☐ 3☐	34
* 35.	STD: ATTAINS SIT ON SMALL BENCH	0☐ 1☐ 2☐ 3☐	35
* 36.	ON THE FLOOR: ATTAINS SIT ON SMALL BENCH	0☐ 1☐ 2☐ 3☐	36
* 37.	ON THE FLOOR: ATTAINS SIT ON LARGE BENCH	0☐ 1☐ 2☐ 3☐	37
	TOTAL DIMENSION B		

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Item	C: CRAWLING & KNEELING	SCORE				NT
38	PR: CREEPS FORWARD 1.8m (6')	0☐	1☐	2☐	3☐	38
* 39	4 POINT: MAINTAINS WEIGHT ON HANDS AND KNEES 10 SECONDS	0☐	1☐	2☐	3☐	39
* 40	4 POINT: ATTAINS SIT ARMS FREE	0☐	1☐	2☐	3☐	40
* 41	PR: ATTAINS 4 POINT WEIGHT ON HANDS AND KNEES	0☐	1☐	2☐	3☐	41
* 42	4 POINT: REACHES FORWARD WITH R ARM HAND ABOVE SHOULDER LEVEL	0☐	1☐	2☐	3☐	42
* 43	4 POINT: REACHES FORWARD WITH L ARM HAND ABOVE SHOULDER LEVEL	0☐	1☐	2☐	3☐	43
* 44	4 POINT: CRAWLS OR HITCHES FORWARD 1.8m(6')	0☐	1☐	2☐	3☐	44
* 45	4 POINT: CRAWLS RECIPROCALLY FORWARD1.8m (6')	0☐	1☐	2☐	3☐	45
* 46	4 POINT: CRAWLS UP 4 STEPS ON HANDS AND KNEES/FEET	0☐	1☐	2☐	3☐	46
47	4 POINT: CRAWLS BACKWARDS DOWN 4 STEPS ON HANDS AND KNEES/FEET	0☐	1☐	2☐	3☐	47
* 48	SIT ON MAT: ATTAINS HIGH KN USING ARMS MAINTAINS, ARMS FREE, 10 SECONDS	0☐	1☐	2☐	3☐	48
49	HIGH KN: ATTAINS HALF KN ON R KNEE USING ARMS MAINTAINS, ARMS FREE 10 SECONDS	0☐	1☐	2☐	3☐	49
50	HIGH KN: ATTAINS HALF KN ON L KNEE USING ARMS MAINTAINS, ARMS FREE 10 SECONDS	0☐	1☐	2☐	3☐	50
* 51	HIGH KN: KN WALKS FORWARD 10 STEPS ARMS FREE	0☐	1☐	2☐	3☐	51

TOTAL DIMENSION C ☐

Item	D: STANDING	SCORE				NT
* 52	ON THE FLOOR: PULLS TO STD AT LARGE BENCH	0☐	1☐	2☐	3☐	52
* 53	STD: MAINTAINS ARMS FREE 3 SECONDS	0☐	1☐	2☐	3☐	53
* 54	STD: HOLDING ON TO LARGE BENCH WITH ONE HAND LIFTS R FOOT 3 SECONDS	0☐	1☐	2☐	3☐	54
* 55	STD: HOLDING ON TO LARGE BENCH WITH ONE HAND LIFTS L FOOT 3 SECONDS	0☐	1☐	2☐	3☐	55
* 56	STD: MAINTAINS ARMS FREE 20 SECONDS	0☐	1☐	2☐	3☐	56
* 57	STD: LIFTS L FOOT ARMS FREE 10 SECONDS	0☐	1☐	2☐	3☐	57
* 58	STD: LIFTS R FOOT ARMS FREE 10 SECONDS	0☐	1☐	2☐	3☐	58
* 59	SIT ON SMALL BENCH: ATTAINS STD WITHOUT USING ARMS	0☐	1☐	2☐	3☐	59
* 60	HIGH KN: ATTAINS STD THROUGH HALF KN ON R KNEE WITHOUT USING ARMS	0☐	1☐	2☐	3☐	60
* 61	HIGH KN: ATTAINS STD THROUGH HALF KN ON L KNEE WITHOUT USING ARMS	0☐	1☐	2☐	3☐	61
* 62	STD: LOWERS TO SIT ON FLOOR WITH CONTROL ARMS FREE	0☐	1☐	2☐	3☐	62
* 63	STD: ATTAINS SQUAT ARMS FREE	0☐	1☐	2☐	3☐	63
* 64	STD: PICKS UP OBJECT FROM FLOOR ARMS FREE RETURNS TO STAND	0☐	1☐	2☐	3☐	64

TOTAL DIMENSION D ☐

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Item	E: WALKING, RUNNING & JUMPING	SCORE				NT
* 65	STD, 2 HANDS ON LARGE BENCH: CRUISES 5 STEPS TO R	0☐	1☐	2☐	3☐	65
* 66	STD, 2 HANDS ON LARGE BENCH: CRUISES 5 STEPS TO L	0☐	1☐	2☐	3☐	66
* 67	STD, 2 HANDS HELD: WALKS FORWARD 10 STEPS	0☐	1☐	2☐	3☐	67
* 68	STD, 1 HAND HELD: WALKS FORWARD 10 STEPS	0☐	1☐	2☐	3☐	68
* 69	STD: WALKS FORWARD 10 STEPS	0☐	1☐	2☐	3☐	69
* 70	STD: WALKS FORWARD 10 STEPS STOPS TURNS 180°, RETURNS	0☐	1☐	2☐	3☐	70
* 71	STD: WALKS BACKWARD 10 STEPS	0☐	1☐	2☐	3☐	71
* 72	STD: WALKS FORWARD 10 STEPS CARRYING A LARGE OBJECT WITH 2 HANDS	0☐	1☐	2☐	3☐	72
* 73	STD: WALKS FORWARD 10 CONSECUTIVE STEPS BETWEEN PARALLEL LINES 20cm (8") APART	0☐	1☐	2☐	3☐	73
* 74	STD: WALKS FORWARD 10 CONSECUTIVE STEPS ON A STRAIGHT LINE 3cm (2") WIDE	0☐	1☐	2☐	3☐	74
* 75	STD: STEPS OVER STICK AT KNEE LEVEL R FOOT LEADING	0☐	1☐	2☐	3☐	75
* 76	STD: STEPS OVER STICK AT KNEE LEVEL L FOOT LEADING	0☐	1☐	2☐	3☐	76
* 77	STD: RUNS 4.5m (15'), STOPS & RETURNS	0☐	1☐	2☐	3☐	77
* 78	STD: KICKS BALL WITH R FOOT	0☐	1☐	2☐	3☐	78
* 79	STD: KICKS BALL WITH L FOOT	0☐	1☐	2☐	3☐	79
* 80	STD: JUMPS 30cm (12") HIGH BOTH FEET SIMULTANEOUSLY	0☐	1☐	2☐	3☐	80
* 81	STD: JUMPS FORWARD 30 cm (12"), BOTH FEET SIMULTANEOUSLY	0☐	1☐	2☐	3☐	81
* 82	STD ON R FOOT: HOPS ON R FOOT 10 TIMES WITHIN A 60cm (24") CIRCLE	0☐	1☐	2☐	3☐	82
* 83	STD ON L FOOT: HOPS ON L FOOT 10 TIMES WITHIN A 60cm (24") CIRCLE	0☐	1☐	2☐	3☐	83
* 84	STD, HOLDING 1 RAIL: WALKS UP 4 STEPS HOLDING 1 RAIL ALTERNATING FEET	0☐	1☐	2☐	3☐	84
* 85	STD, HOLDING 1 RAIL: WALKS DOWN 4 STEPS HOLDING 1 RAIL ALTERNATING FEET	0☐	1☐	2☐	3☐	85
* 86	STD: WALKS UP 4 STEPS ALTERNATING FEET	0☐	1☐	2☐	3☐	86
* 87	STD: WALKS DOWN 4 STEPS ALTERNATING FEET	0☐	1☐	2☐	3☐	87
* 88	STD ON 15cm (6") STEP: JUMPS OFF BOTH FEET SIMULTANEOUSLY	0☐	1☐	2☐	3☐	88

TOTAL DIMENSION E ☐

Was this assessment indicative of this child's "regular" performance? YES ☐ NO ☐
COMMENTS:

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GMFM-88 SUMMARY SCORE

DIMENSION	CALCULATION OF DIMENSION % SCORES	GOAL AREA (indicated with ✓ check)
A. Lying & Rolling	Total Dimension A / 51 = ____ / 51 × 100 = ____ %	A ☐
B. Sitting	Total Dimension B / 60 = ____ / 60 × 100 = ____ %	B ☐
C. Crawling & Kneeling	Total Dimension C / 42 = ____ / 42 × 100 = ____ %	C ☐
D. Standing	Total Dimension D / 39 = ____ / 39 × 100 = ____ %	D ☐
E. Walking, Running & Jumping	Total Dimension E / 72 = ____ / 72 × 100 = ____ %	E ☐

TOTAL SCORE = (%A + %B + %C + %D + %E) / Total # of Dimensions

= ____ / 5 = ____ = ____ %

GOAL TOTAL SCORE = Sum of %scores for each dimension identified as a goal area / # of Goal areas

= ____ = ____ %

GMFM-66 Gross Motor Ability Estimator Score [1]

GMFM-66 Score = ____ ____ to ____ 95% Confidence Intervals

previous GMFM-66 Score = ____ ____ to ____ 95% Confidence Intervals

change in GMFM-66 = ____

[1] from the Gross Motor Ability Estimator (GMAE-2) Software

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TESTING WITH AIDS/ORTHOSES USING THE GMFM-88

Indicate below with a check (4) which aid/orthosis was used and what dimension it was first applied (There may be more than one)

AID	Dimension	Orthosis	Dimension
Rollator/pusher	☐ ____	Hip Control	☐ ____
Walker	☐ ____	Knee Control	☐ ____
H Frame crutches	☐ ____	Ankle-foot Control	☐ ____
Crutches	☐ ____	Foot Control	☐ ____
Quad Cane	☐ ____	Shoes	☐ ____
Cane	☐ ____	None	☐ ____
None	☐ ____	Other ____ (please specify)	☐ ____
Other ____ (please specify)	☐ ____		

GMFM-88 SUMMARY SCORE USING AIDS/ORTHOSES

DIMENSION	CALCULATION OF DIMENSION % SCORES	GOAL AREA (indicated with ✓ check)
F. Lying & Rolling	Total Dimension A / 51 = ____ / 51 × 100 = ____ %	A ☐
G. Sitting	Total Dimension B / 60 = ____ / 60 × 100 = ____ %	B ☐
H. Crawling & Kneeling	Total Dimension C / 42 = ____ / 42 × 100 = ____ %	C ☐
I. Standing	Total Dimension D / 39 = ____ / 39 × 100 = ____ %	D ☐
J. Walking, Running & Jumping	Total Dimension E / 72 = ____ / 72 × 100 = ____ %	E ☐

TOTAL SCORE = (%A + %B + %C + %D + %E) / Total # of Dimensions

= ____ / 5 = ____ = ____ %

GOAL TOTAL SCORE = Sum of %scores for each dimension identified as a goal area / # of Goal areas

= ____ = ____ %

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Appendix 13 The Functional Mobility Scale

Rating 6

Independent on all surfaces:

Does not use any walking aids or need any help from another person when walking over all surfaces including uneven ground, curbs etc., and in a crowded environment.

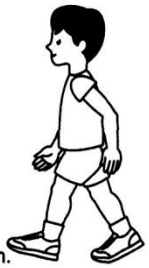


Rating 5

Independent on level surfaces:

Does not use walking aids or need help from another person. *Requires a rail for stairs.

*If uses furniture, walls, fences, shop fronts for support, please use 4 as appropriate description.



Rating 4

Uses sticks (one or two):

Without help from another person.



Walking distance	Rating: select the number (from 1–6) which best *describes current function*
5 metres (yards)	
50 metres (yards)	
500 metres (yards)	

Rating 3

Uses crutches:

Without help from another person.



Rating 2

Uses a walker or frame:

Without help from another person.



Rating 1

Uses wheelchair:

May stand for transfers, may do some stepping supported by another person or using a walker/frame.



Rating C

Crawling:

Child crawls for mobility at home (5m).

Rating N

N = does not apply:

For example, child does not complete the distance (500m).

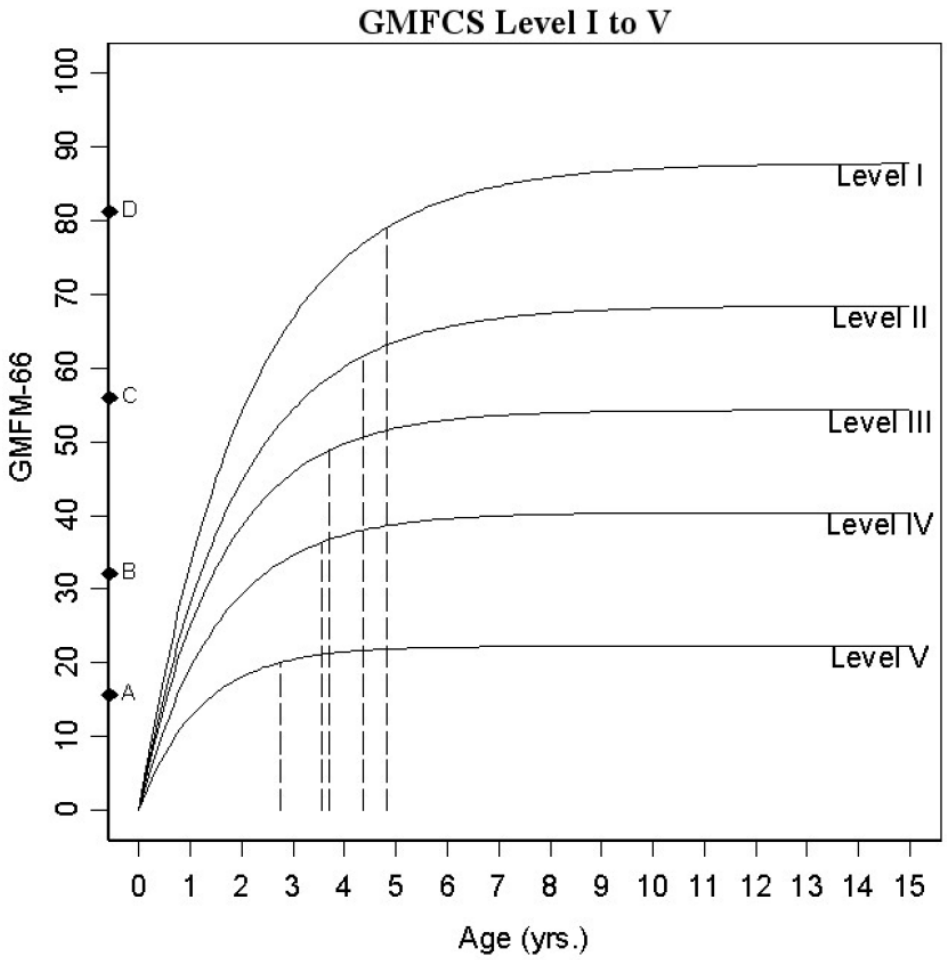
Appendix 14 The Gross Motor Curves

The Ontario Motor Growth Study

The Motor Growth Curves report patterns of gross motor development in children with cerebral palsy, classified according to each of the five levels of the Gross Motor Function Classification System (GMFCS) (Palisano et al., 1997). Children in this study were followed longitudinally for several years. The findings were published in a paper entitled 'Prognosis for Gross Motor Development in Cerebral Palsy. Creation of Motor Growth Curves', Rosenbaum et al., JAMA 2002; 288; 1357-63.

Motor Growth Curves from the Ontario Motor Growth Study

All 5 Curves (Levels I to V)



This graph shows the observed and predicted GMFM-66 scores for children in GMFCS Levels I through V. The curved solid lines indicate average performance. The horizontal dotted lines on the right of the figures indicate the band expected to encompass 50% of children's limits of development. The solid vertical lines indicate the average age-90 (the age in years by which children are expected to reach 90% of their motor development potential). The dotted vertical lines indicate the bands expected to encompass 50% of age-90 values around the average. The absence of 50% bands in level IV and level V indicates low variation in age-90 values.

JAMA 2002; 288;1357-63. Copyrighted 2002, American Medical Association

SOUTH AFRICAN ANTIRETROVIRAL TREATMENT GUIDELINES (CHILDREN) 2015

NEED HELP?
Contact the TOLL-FREE National HIV & TB Health Care Worker Hotline
0800 212 506 / 021 - 406 6782
Alternatively send an SMS or "Please Call Me" to 071 840 1572
www.mic.uct.ac.za

Eligibility Criteria

Eligible to start ART	Patients requiring fast track (i.e. start ART within 7 days of being eligible)
• All children < 5 years, irrespective of CD4 • Children 5 – 15 years: WHO clinical stage 3 or 4 OR CD4 ≤ 500 cells/µL	• Children < 1 year • WHO clinical stage 4 • MDR or XDR-TB • CD4 ≤ 200 cells/µL or < 15 %

Social Considerations

The following points are important considerations to make the principle of adherence to treatment probable:
- One identifiable caregiver who is able to supervise the child for administering medication
- Disclosure to another adult living in the same house, to supervise the child's ART when the other caregiver is unavailable
- Treatment of mother/caregiver/other family member is to be encouraged

Regimens

1st line

< 3 years or older children weighing < 10kg	ABC + 3TC + LPV/r	Children who started on ABC + 3TC + LPV/r before 3 years should remain on the same regimen after they turn 3
≥ 3 years and ≥ 10kg	ABC + 3TC + EFV	
Adolescents ≥ 15 years AND ≥ 40 kg AND CrCl > 80 mL/min	TDF + FTC (or 3TC) + EFV Provided as fixed dose combination (FDC)	Follow adult guidelines
Currently on d4T-based regimen	Change d4T to ABC if viral load (VL) is undetectable (< 50 copies/mL) If VL > 1000 copies/mL: Manage as possible treatment failure If VL 50 – 1000 copies/mL: Consult with expert or phone the HIV hotline	
Currently on ddI containing regimen	Change ddI to ABC, regardless of VL	

2nd line

Failed 1st line Protease Inhibitor (PI)-based regimen	
Failed regimen	**Action**
ABC + 3TC + LPV/r	Consult with expert for advice and consider resistance testing in patients on LPV/r > 12 months and adherent to treatment
d4T + 3TC + LPV/r	
Unboosted PI-based regimen, while taking rifampicin	

Failed 1st line NNRTI-based regimen	
Failed regimen	**Action**
ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r
d4T + 3TC + EFV (or NVP)	AZT + ABC + LPV/r

3rd line

Failing 2nd line regimen	Should be managed by a Paediatric Infectious Disease Specialist on the basis of genotype resistance testing. Access to third line ART is managed centrally by the National Department of Health

Monitoring

Baseline

Test	Purpose	Interpretation/Action
Height, weight, head circumference and development	To monitor growth and developmental stage	Use the "Road to Health" chart as tool Failure to maintain growth = progressive HIV infection or suspected TB – investigate further and refer patient Flattening of curve measuring head circumference = possible encephalopathy – investigate and refer
Verify HIV status	To ensure that national testing algorithm has been followed	Follow testing algorithm as per guidelines and document HIV status clearly
Screen for TB symptoms	To identify TB/HIV co-infection	Suspect TB in patients with the following symptoms: coughing, night sweats, unexplained weight loss, then confirm or exclude TB
WHO Clinical staging	To determine eligibility for ART	Children 5 – 15 years with WHO stage 3 or 4: Start ART
CD4 count	To do a baseline and to determine eligibility for ART in children aged 5 –15 years	Children < 5 years: Do not wait for CD4 before initiating ART Children aged 5 – 15 years: CD4 ≤ 500 cells/µL: Start ART CD4 > 500 cells/µL: Repeat CD4 every 6 months, until patient is eligible for ART
Hb or FBC	To detect anaemia or neutropenia	If Hb < 8, start ART and refer patient for management of anaemia

Include the following baseline tests if patient is starting the specific drug

Drug	Test	Purpose
LPV/r	Cholesterol and triglycerides	Baseline assessment
TB Treatment or jaundiced	ALT	To assess for liver dysfunction

Follow-Up Testing In Patients On ART

At every visit:
- Height, weight, head circumference (<2 years) and development
- Clinical assessment
- Ask about side-effects
- TB Screen

Test and frequency	Action/Interpretation
CD4 count At 1 year on ART, and annually if clinically indicated	Stop co-trimoxazole once ART-associated immune reconstitution has occurred for ≥ 6 months, i.e. CD4 count is as follows on TWO consecutive occasions 3 to 6 months apart: **1 – 5 years:** CD4 ≥ 500 cells/µL or ≥ 25% **≥ 5 years:** CD4 ≥ 350 cells/µL HIV-positive infants < 12 months should remain on prophylaxis
VL Month 6, 12 and then annually	**VL copies/ml** / **Response** > 1000: Begin step-up adherence package. Repeat VL after 3 months if child < 10 years, and after 3 months if child 10–15 years. If VL still > 1000 despite good adherence and child on **NNRTI** regimen: discuss with expert about switching to second line. If VL still > 1000 despite good adherence and child is on **PI-based** regimen: reinforce adherence and discuss with expert 50 – 1000: Begin step-up adherence. Repeat VL in 6 months < 50: Repeat VL annually, and routine adherence support. Patient is doing well

Do the following tests if the patient is on the drug that may cause the adverse event

Drug	Test	Frequency	Action/Interpretation
AZT	Hb or FBC	Month 1,2,3 and then annually	Hb > 8 gm%: Continue AZT Hb < 8 gm%: Use alternative - consult with expert
LPV/r	Cholesterol + Triglycerides (TG)	Annually	Consult with specialist if a significant difference is noted from patient's previous lipid profile
TB treatment or jaundiced or rash develops	ALT	Only if patient is jaundiced or on TB treatment, or rash develops	Consult with expert for advice, or phone the HIV hotline

Date published: June 2015

Children With Concomitant Tuberculosis

Children taking ART and TB treatment together will have to tolerate a large number of pills. If the child can't tolerate the large number of drugs, ART may have to be interrupted until TB therapy has been completed – however this should only be done if a child is stable and has a good CD4 count, and in consultation with a treatment expert. Always review suppression if on ART more than 6 months

Current ART regimen	Recommendations	
EFV-based regimen	No dose adjustments or changes in ART regimen and standard dose TB treatment should be added	
LPV/r-based regimen	**AND** receiving a **rifampicin**-containing TB regimen: Additional **ritonavir** should be added according to the paediatric dosing chart. TB treatment should be dosed at standard doses	
NVP-based regimen	≥ 3 years OR ≥ 10kg	Switch NVP to EFV
	< 3 years OR < 10kg	Consult with expert or the HIV hotline

Isoniazid Preventive Therapy

IPT is indicated for HIV-positive children with a direct TB contact (someone with TB who resides with the child), after active TB has been excluded in the child with symptom screening (symptoms include: coughing, night sweats, unexplained weight loss, persistent fever of more than two weeks, poor weight gain, fatigue)

Dose: Isoniazid (INH) 10mg/kg/day for 6 months (max dose: 300mg daily)

Crush appropriate fraction of the 100mg INH tablet and dissolve in water or multivitamin syrup before giving it to the child

Add pyridoxine (Vitamin B6) 25mg daily in children > 5 years, or 12.5mg daily in children < 5 years for duration of IPT

Practical Advice For Administration of ARVs

- It is important to check regularly that children receive the correct dose, based on their weight
- In older children or adolescents ensure that maximum doses are not exceeded

ARV	Advice
Abacavir (ABC)	Advise caregivers about the potential hypersensitivity reaction: If patient on ABC develops fever, rash, gastrointestinal and respiratory symptoms, the patient should be taken to the hospital. In patients who have had a hypersensitivity reaction, ABC would be stopped and never rechallenged. All tablet formulations, except the 60 mg tablet, must be swallowed whole and NOT chewed, divided or crushed
Efavirenz (EFV)	Tablets must not be chewed, divided or crushed; swallow whole with or without food e.g. yoghurt or banana. Capsules may be opened and powder contents dispensed in water or mixed with a small amount of food (e.g. yoghurt) to disguise peppery taste and immediately ingested. Food, especially high-fat meals, increases absorption. Best given at bedtime to reduce CNS side effects, especially during first 2 weeks
Lamivudine (3TC)	No food restrictions; oral solution may be stored at room temperature. Tablets are scored and can be easily divided; may be crushed and mixed with a small amount of water or food and immediately ingested
Lopinavir + ritonavir (LPV/r) Also with OR Kaletra®	Dose is calculated on lopinavir component. Solution is best taken with food as it increases absorption. If there is no food, then the patient can take the medicine without food. Solution should be refrigerated. If no fridge is available, it can be stored at room temperature at 25°C for 6 weeks. Techniques to increase tolerance & palatability: coat mouth with peanut butter, dull taste buds with ice, follow dose with sweet food. Tablets must not be chewed, divided or crushed; swallow whole with or without food. Many drug interactions
Nevirapine (NVP)	Once-daily dosing during the first 2 weeks of treatment reduces frequency of rash. If a mild rash occurs during the induction period, continue once daily dosing and only escalate dose to twice daily once the rash has subsided and the dose is well tolerated. NVP should be permanently discontinued and not restarted in children who develop severe rash, especially if accompanied by fever, blistering or mucosal ulceration. No food restrictions. Tablets can be crushed and mixed with a small amount of water or food and immediately ingested. Avoid NVP if rifampicin is being co-administered. Consider drug-drug interactions
Ritonavir (RTV)	Only recommended use at present is as booster for lopinavir/ritonavir when co-administered with rifampicin-containing TB treatment. Should be taken with food. May be stored at room temperature, limited shelf life of 6 months. May need to use techniques described for Kaletra® to improve tolerance of bitter taste
Stavudine (d4T)	Capsules may be opened and powder contents dispensed in water (stable in solution for 24 hours) or mixed with a small amount of food (e.g. yoghurt)
Zidovudine (AZT)	No food restrictions and oral solution may be stored at room temperature. Capsules may be opened and powder contents dispensed in water or mixed with a small amount of food (e.g. yoghurt) and immediately ingested. Currently available tablets are not scored. Use with caution in children with anaemia, due to potential for bone marrow suppression

Appendix 16 Correlation Analyses

1. Correlation Analysis between GMFM and Age

Group	Pearson's Correlation (r)	Probability Value (p)
HIV infected	0.18	0.12
HIV uninfected	0.43	0.02**
Functional HIV infected	0.18	0.5
Functional HIV uninfected	0.66	0.03**
Non functional HIV infected	0.2	0.4
Non functional HIV uninfected	-0.2	0.5

* Correlation was significant at the 0.1 level (2-tailed)

** Correlation was significant at the 0.05 level (2-tailed)

2. Correlation analysis between Viral Load and Muscle strength

Muscle Group	Pearson's Correlation (r)	Probability Value (p)
Shoulder Abduction Left	0.37	0.03**
Shoulder Abduction Right	0.22	0.24
Shoulder Forward Flexion Left	0.22	0.23
Shoulder Forward Flexion Right	0.36	0.04**
Elbow Flexion Left	0.30	0.09
Elbow Flexion Right	0.27	0.14
Elbow Extension Left	0.23	0.21
Elbow Extension Right	0.22	0.23
Hip Abduction Left	0.14	0.45
Hip Abduction Right	0.06	0.74
Ankle Plantarflex Left	-0.03	0.89
Ankle Plantarflex Right	0.02	0.92
Knee Flexion Left	0.42	0.02**
Knee Flexion Right	0.18	0.33
Knee Extension Left	0.46	0.01**

Knee Extension Right	0.48	0.01**
Hip Flexion Left	0.35	0.05**
Hip Flexion Right	0.19	0.31

* Correlation was significant at the 0.1 level (2-tailed)

** Correlation was significant at the 0.05 level (2-tailed)

Appendix 17 Turnitin Originality Report

Turnitin Originality Report
Final Dissertation 29 Aug 2016 by Tasvi Naik
From Research Reports/Dissertations Part 1 (Moodle TT) (2016 Physiotherapy Postgraduate Research Information (Moodle TT))

- Processed on 29-Aug-2016 8:58 PM SAST
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