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An investigation of HIV sensory neuropathy in children living with HIV

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An investigation of HIV sensory neuropathy in children living with HIV

Natalie Alice Benjamin-Damons

Thesis submitted to the Faculty of Health Sciences; University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy



WITS
UNIVERSITY

Johannesburg 2019

Declaration

I Natalie Alice Benjamin-Damons declare that this Thesis is my own, unaided work. It is being submitted for the Degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_____

(Signature of candidate)

11th day of February 2019 in Parktown, Johannesburg

Dedication

For Ryan, Zachary, Eli and Ezra

Presentations arising from this research project

World Congress of Physical Therapy - 2015

An investigation of peripheral neuropathy in children who are infected with HIV - classic platform presentation at the WCPT Congress 2015 in Singapore.
Abstract number: A-613-0000-02812

Wits School of Health Sciences Research Day – 2015

An investigation of peripheral neuropathy in children who are infected with HIV

World Congress of Physical Therapy – 2017

The effect of peripheral sensory neuropathy on gross motor function in children who are infected with HIV – Rapid 5 platform presentation at the WCPT Congress in Cape Town
Abstract reference number: A-804-0000-01284

Rahima Moosa Mother and Child Hospital World AIDS day Conference – 2017

The prevalence of HIV sensory neuropathy in children living with HIV

Abstract

Prevalence of HIV-SN

The global estimate of people living with human immunodeficiency virus (HIV) in 2016 was 36.7 million, including 2.1 million children (<15 years). Sub-Saharan Africa accounts for 64% of the world's population living with HIV, including 19.4 million adults and children in Southern and Eastern Africa. In South Africa, 7.1 million are reported to be living with HIV, with an estimated 360,000 children (0-14 years). The profile of HIV has changed since the advent of ART which revolutionised the treatment of HIV and significantly lessened mortality and opportunistic infections. To date, South Africa has the largest ART programme in the world with a steady reduction in the thresholds for initiating therapy since 2004. HIV-SN is a common co-morbidity in the adult population.

There is a dearth of literature on the prevalence of HIV-SN in children. Until recently it was thought that HIV-SN did not develop in HIV infected children or that only a small percentage is affected by it. The most recognised form is distal sensory or axonal neuropathy, which is directly related to infection and often compounded by anti-retroviral therapy. Parasthesiae and pain are the most common presenting complaints, followed by weakness or loss of motor milestones. Studies on HIV-related peripheral neuropathy, its impact on function and mobility as well as management, have been focused on the adult population.

The main aim of the study was therefore to determine what the current frequency rates of HIV-SN are in the paediatric population as well as how it impacts on their gross motor function and overall quality of life. Further to this we aimed to design and test an intervention programme to address any gross motor issues that may be present.

Methods

Study one: A cross-sectional study was conducted to ascertain the frequency of HIV-SN in children infected with HIV, who attend Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa. After obtaining informed consent from the caregivers and assent from the children, participants were assessed for HIV-SN using the Brief Peripheral Neuropathy Screen (BPNS) and pin-prick sensation. We defined HIV-SN as the presence of at least one bilateral sign. Gross motor function was assessed using the Movement-ABC-2® (M-

ABC-2®). The M-ABC-2® assesses a child's performance in balancing, throwing, and manual dexterity tasks, benchmarked against age-appropriate norms. Basic demographic, anthropomorphic, and most recent HIV disease information was obtained from the children's medical files. The Pediatric Quality of Life Questionnaire was administered and assesses the parents and child's perception of their current quality of life in the following domains: physical functioning; emotional functioning; social functioning and school functioning

Study two:

Part one: A literature review was conducted to determine existing evidence for the management of peripheral neuropathies irrespective of the cause. Details were summarised and used to substantiate exercise selection as determined by the Delphi survey.

Pat two: A Delphi Survey was conducted to determine the current physiotherapy management practices for HIV-SN. A total of eight physiotherapists participated in the Delphi survey. Two rounds were sufficient to reach consensus on the intervention programme that was designed for Study three.

Study three:

A case series design was used to test the intervention as the sample was too small to conduct a randomised control trial. Twenty-eight participants agreed to do the exercise programme. Baseline assessments of the BPNS, M-ABC-2® and the PedsQL™ were done and repeated at the end of the intervention period.

Results

Study one HIV-SN frequency:

A total of 135 participants between the ages of four to ten years were assessed. Fifty three percent were male. The mean age was six years (SD ±1). Statistical analysis revealed a frequency rate of 25.9% for HIV-SN. The most common presenting symptom was pain No associated risk factors for developing the condition could be isolated.

Gross motor function

Of those who presented with SN, 23% participants fell into the Red category for gross motor function, which indicates poor motor function. The remainder were 39% and 48% in the

Amber and Green categories respectively. However, there was no association between having SN and any of the sub-scales of the M-ABC-2® or the summative traffic light categories.

Quality of life

Almost all participants in the study reported a satisfactory quality of life.

There was also no correlation between quality of life and neuropathy status nor gross motor function and neuropathy status.

Study two

This study interrogated existing literature for treatment strategies used in the management of neuropathy irrespective of the cause. Following the review, very few randomised controlled trials were available to assess. Literature reviews of trials provided more information. The most common intervention strategies identified were exercise, functional electrical stimulation and pharmacotherapeutics.

In the Delphi survey, strategies with the highest consensus were exercise, education of the child and caregiver as well as referral to both an occupational therapist and/or a psychologist. The types of exercise with the most consensus were proprioception, balance and strengthening, followed by circulatory, weight-bearing and endurance exercise. The least popular selection was stretching. Most of the choices were based on clinical experience rather than research evidence, with only two participants consistently citing this as the reason for their selection. Education of the child and caregiver was a consistent selection with very high consensus. An intervention programme and information booklet were designed based on the outcome of the literature and the Delphi survey results and tested in study three.

Study three

Twenty-eight participants were enrolled in the intervention study. At baseline 12 participants tested positive for HIV-SN, which is 51.8 % frequency and at the final assessment seven participants tested positive which is a frequency of 36.8 %.

There was an overall decrease in the reporting of symptoms such as pain, hot, cold and pins and needles. There was a significant decrease in the presence of decreased vibration sense on the right between periods one (start of the intervention) and three (end of the intervention) where $p = 0.021$.

There was a statistically significant change in the balance score between periods one (start of the intervention) and two (mid-way through intervention) where $p = 0.044$. When looking at the zoning of Green, Amber and Red, there was an overall improvement of 30% in motor ability. The overall test score showed a statistically significance between period one and two ($p < 0.001$) as well as between period one and three ($p = 0.023$).
For the PedsQL™ values remained relatively unchanged and could not be assessed for significance.

Conclusion

A high frequency rate of HIV-SN was identified in this study, with most being asymptomatic but had experienced pain at some point in the past. Of these children with HIV-SN, a large number presented with gross motor limitations as identified by the M-ABC-2®, but they all reported a relatively satisfactory quality of life. A well designed intervention can improve the signs and symptoms associated with HIV-SN when administered over a six week period. After this, the participants plateaued but did not return to their baseline level of function.

Recommendation

Children living with HIV should be routinely assessed for the presence of HIV-SN, education of the child and the caregiver is essential in managing the condition effectively and timeously. Further research assessing management strategies for HIV-SN is needed.

Acknowledgements

Firstly, I would like to thank God for granting me the opportunity to do my PhD. For carrying me through what has been the darkest time in my life with my cancer diagnosis and for His Grace that ensured I finish this project.

To Prof Joanne Potterton who has been extremely patient, supportive and encouraging through all the ups and downs of this journey. I appreciate everything you have done and thank you for pushing me to completion.

To Prof Peter Kamerman for his guidance and sharing his expertise.

To my family who has had to exercise extreme patience with me and who provided support when I needed it most. To my boys who had to endure mommy-time in front of a laptop and helped me keep the balance.

To my support structure of dear friends: Preshani and Vanesh who kept me focused, listened to my frustrations and provided encouragement when I needed it most. I could not have done it without you!

To my former colleagues Douglas and Witness who called and e-mailed regularly to check on my progress and provided words of encouragement along the way.

To the staff at Empilweni services and Research Unit: Research assistants; Prof Ashraf Coovadia, Dr Renate Strehlau; Prof Louise Kuhn; Prof Stephan Arpadi; Dr Karl Technau, and all the support staff who welcomed me so warmly and assisted whenever they could.

To the participants of this study, their parents and caregivers without whom this project would not have been possible.

To patient X for permission to take and use photographs of him doing the assessments.

To Ryan, who has been my pillar of strength and support (even though it wasn't always what I expected, it was what I needed) thank you for being there for me and grounding me. I appreciate you.

For financial support I would like to thank the following:

South African Society of Physiotherapy (SASP)

University of the Witwatersrand Faculty Research Grant

National Research Foundation Thuthuka Grant

National Research Foundation sabbatical grant

University of Witwatersrand Enabling Grant

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List of abbreviations

ART – antiretroviral treatment

ARV - antiretroviral

BPNS – Brief peripheral neuropathy screen

CD4- cluster of differentiation 4

GMF – gross motor function

HAART – Highly Active Anti-Retroviral Treatment

HIV-SN – Human immunodeficiency virus associated sensory neuropathy

Ht. – height

ICD- 10 - International Classification of Disease version 10

ICF – International classification of function

ICIDH - International Classification of Impairment, Disability and Handicap

M-ABC- Movement -ABC version 2

PEDsQL- Paediatric evaluation of quality of life

QoL – quality of life

UNAIDS - Joint United Nations Programme on HIV/AIDS

WHO – World Health Organisation

Wt. - weight

Chapter 1: Introduction

1.1 Background

The global estimate of people living with human immunodeficiency virus (HIV) in 2016 was approximately 36.7 million, consisting of 2.1 million children (<15 years) (UNAIDS, 2017b). Sub-Saharan Africa accounts for 64% of the world's population living with HIV, which includes 19.4 million adults and children in Southern and Eastern Africa (UNAIDS, 2017b). In South Africa, 7.1 million are reported to be living with HIV, with an estimated 360,000 children (0-14 years) (Statistics South Africa, 2017). A recent report by UNAIDS in 2016 showed a decline in new HIV infection from 1.8% to 1.3% and a 33% decline in the number of children living with HIV in comparison to the 2013 report (UNAIDS, 2016a).

1.1.1Sensory neuropathy in HIV

Sensory neuropathy (SN) may develop in five to 30% of human immunodeficiency virus – strain 1 (HIV) infected adult patients depending on their stage of disease (Maritz *et al.*, 2010; Kamerman *et al.*, 2012). This figure is in excess of 50% in patients on stavudine-based antiretroviral therapy (Maritz *et al.*, 2010; Wadley *et al.*, 2011; Cherry, Wadley and Kamerman, 2016). Parasthesiae and pain are the most common presenting complaints, followed by weakness or loss of motor ability (Shankar *et al.*, 2005).

The most common form of HIV-related neuropathy is distal sensory or axonal neuropathy, which is directly related to HIV infection and often compounded by anti-retroviral therapy (Donald *et al.*, 2012a). However, the frequency of SN in children is not well documented in the international or South African context even though HIV-related SN is known to be increasing with more children living longer in the Highly Active Anti-Retroviral Treatment (HAART) era.

Studies on HIV-sensory neuropathy, its impact on function and mobility as well as management, have been focused to the adult population (Wulff, Wang and Simpson, 2000; Botes and Levay, 2004; Cherry *et al.*, 2005; Gonzalez-Duarte, Cikurel and Simpson, 2007; Ellis *et al.*, 2010; Wadley *et al.*, 2011a). Very little has been done in the paediatric population, other than estimates of its prevalence (Araujo, Nascimento and Garcia, 2000; Esteban *et al.*, 2008; Govender *et al.*, 2011; Donald *et al.*, 2012b)[the latter two studies having been conducted

in the same Western Cape, South African hospitals]. The studies by Govender et al (2011) and Donald et al (2011) assessed the extent of neurological complications and neurobehavioural problems in a group of children attending infectious disease clinics in the Western Cape. The researchers established that HIV-associated neurologic complications are common and span a wide spectrum of disorders, but the focus of these studies remained on the central nervous system.

1.1.2 Effect of HIV on motor development

In 2006, Foster and colleagues conducted a retrospective analysis on the motor development of 62 HIV infected children under the age of three years. The study established that there were statistically significant increases in the prevalence of abnormal neurological signs and motor impairments in infants presenting with more advanced HIV disease. This persisted despite immune reconstitution in children on HAART (Foster *et al.*, 2006). Jelsma et al (2011) conducted similar study in Cape Town, comparing the motor development of orphaned children with and without HIV infection. Participants in the study were of average age of four years and data collection was done between 2006 and 2007. The findings of the study were that the children infected with HIV were significantly delayed compared to their healthy counterparts (Jelsma, Davids and Ferguson, 2011). The study conducted by Govender et al (2011) only used a screening tool for motor development and therefore could not make robust conclusions about gross motor development (Govender *et al.*, 2011). There is a dearth of knowledge regarding the gross motor function of children infected with HIV that are older than three years of age.

1.1.3 Physiotherapy in patients infected with HIV

Sowers and colleagues (2013) conducted a systematic review on the effects of exercise on individuals with HIV disease and revealed that regular exercise has no detrimental effect on the immune system over time and that cardiovascular fitness improves. Again, this has been focused to the adult population and has not considered the impact of SN on gross motor development and function in children (Sowers, Galantino and Kietrys, 2013).

1.2 Conceptual Framework

This section outlines the concepts used to support the rationale, answer the research questions, develop, implement, report and evaluate the research (Kitchel and Ball, 2014, Smyth, 2004).

The International Classification of Function, Disability and Health provides a framework which can be used to describe sensory neuropathy in children living with HIV. The ICF is a classification system developed by the World Health Organization (WHO) to provide a common language and universal conceptual framework to describe health and health-related states. This concept was first introduced in 1980 as the International Classification of Impairment, Disability and Handicap (ICIDH). In 2001, it was renamed ICF to reflect more positive aspects of health. The term "consequences of disease" is now referred to as "components of health"; all positive components of health are collectively termed "functioning", and all negative components are collectively termed "disability".

A combined bio-medical psychosocial model provides a framework for understanding and approaching the relationship between the patient, the family, the healthcare system, and society. This multi-directional model incorporates three different perspectives of health (i.e. biological, medical, and social) 2. The ICF model is depicted in figure 1.1. A health condition is an umbrella term for a disease, disorder, injury or trauma. A health condition may also include other circumstances, such as ageing, stress, congenital anomaly, or genetic predisposition. Health conditions are coded using the WHO's sister classification system, the International Classification of Disease, version 10 (ICD-10).

Functioning is the core of the model and consists of three components: (i) body functions and structures, (ii) activities, and (iii) participation. Body functions are physiological functions of body systems and include psychological functions.

Body structures are anatomical parts of body such as organs, limbs and their components. Impairments are problems in body function or structure such as significant deviation or loss (*e.g.* decreased sensation in the lower limb). Activity is the execution of a task or action by an individual (*e.g.*, walking). Participation is involvement in a life situation (*e.g.*, attending school or playing sport). Activity limitations are difficulties an individual may have in executing activities. Participation restrictions are problems an individual may experience in involvement in life situations. Contextual factors are the factors that together constitute the complete context of an individual's life, and in particular the background against which health states are classified.

There are two components of contextual factors: Personal factors and Environmental Factors. Personal factors include internal features of the individual that are not associated with the health condition such as lifestyle and experience, background, education, and coping styles. Environmental factors make up the physical, social and attitudinal environment in which people live and conduct their lives.

Although the ICF is an appropriate model to identify the presence and severity of specific impairments, activity limitations and participation restrictions, it is not intended as a measure of health impact. To measure a specific health outcome, a standardized outcome measure with sound psychometric properties must be administered.

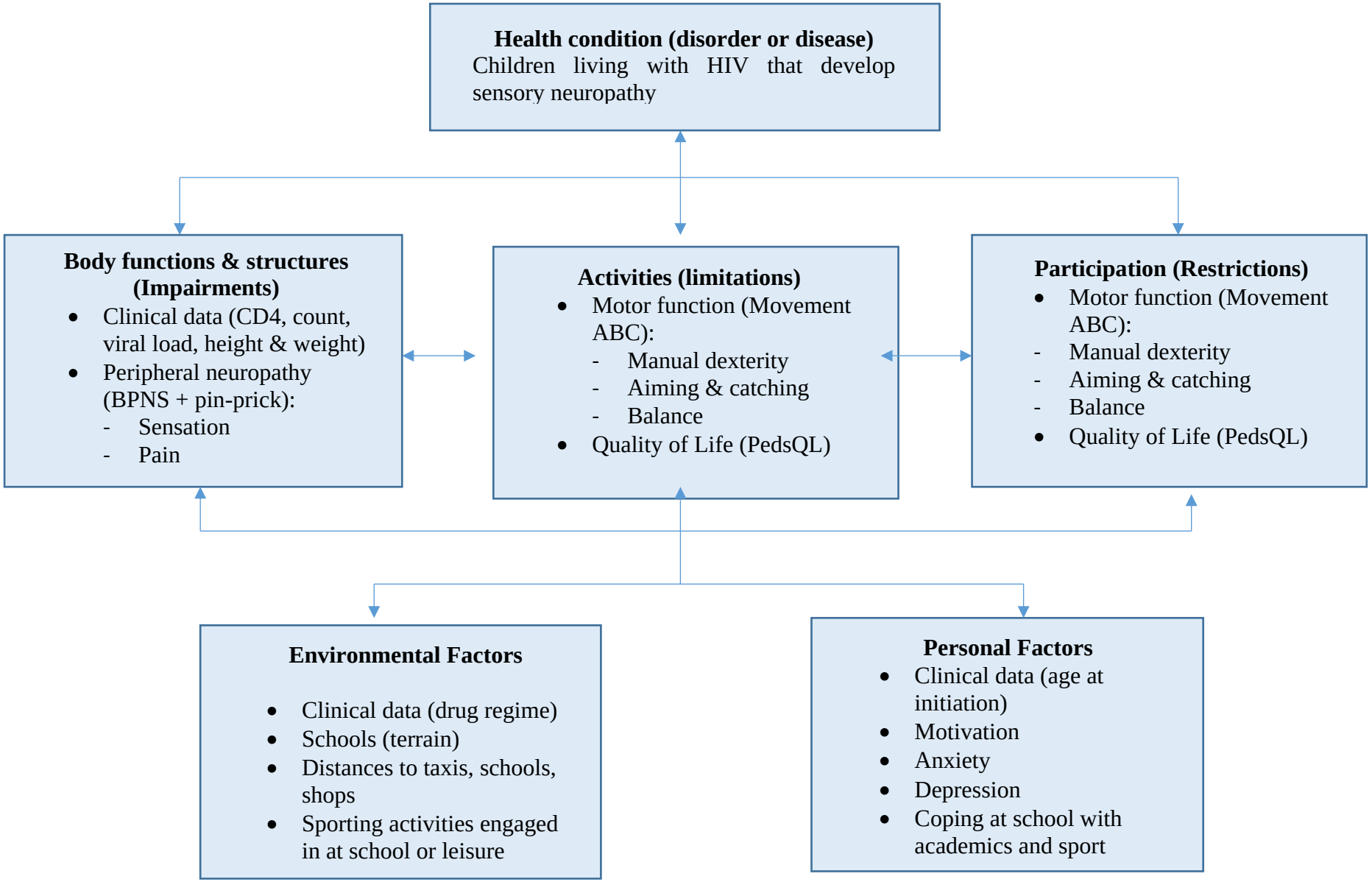


Figure 1.1 The conceptual framework for HIV-SN in children (adapted from Kostanjsek, 2011)

1.3 Significance and novelty of the study

Sensory neuropathy (SN) is a known complication of HIV in adults but the prevalence of the condition in the paediatric population, the effects of the neuropathy on gross motor function and the quality of life of children with HIV-related sensory neuropathy (HIV-SN) is unknown. The relationship between HIV-SN, activities and limitations are clearly depicted in figure 1.1. This study is novel in that research of this nature in the paediatric population has never been done before in South Africa, Africa or the world.

The study aimed to establish the frequency of HIV-SN in children and identify specific developmental or gross motor function problems in which physiotherapy intervention is needed, to ensure that HIV positive children who present with SN develop adequate motor skills so that they are able to function maximally at home, school, in their communities and thus, in society as a whole. The results of this study will make a significant contribution to the body of knowledge in the management of children infected with HIV. This is aligned with the National Strategic Plan of South Africa 2017-2022 (South African National Department of Health, 2017).

1.4 Research question

What is the prevalence of HIV sensory neuropathy and how does it impact on gross motor function (GMF) of children infected with HIV and can physiotherapy intervention make a positive difference in managing the condition?

1.5 Aim

This study aimed to determine the proportion of children infected with HIV that develop SN, the effect of the neuropathy on gross motor development/ function and how it impacts on their daily life. In addition to this the study investigated the changes, if any, a structured physiotherapy home programme can make to improve mobility and quality of life.

1.6 Objectives

The objectives of the study were as follows:

1.6.1 To determine the prevalence of HIV-related sensory neuropathy in children attending Rahima Moosa Mother and Child Hospital.

1.6.2 To determine the extent of the SN.

1.6.3 To determine the factors associated with SN.

1.6.4 To assess whether SN affects the quality of life in children infected with HIV.

1.6.5 To describe the gross motor function of children infected with HIV, who develop sensory neuropathy compared to those children who do not develop SN.

1.6.6 To develop a physiotherapy intervention programme, to manage SN, by reviewing existing literature and using the Delphi Technique to collate expert opinion.

1.6.7 To determine the outcome of this intervention programme on the gross motor function, mobility and the quality of life.

This study was conducted in three phases which are detailed in Table 1 below

Table 1.1The link between the study phases and objectives

Study Phases	Study objectives	Components of the ICF
Study one – **The prevalence of SN was established as well as the impact it has on gross motor development and quality of life**	1.6.1 To determine the prevalence of HIV-related sensory neuropathy in children attending Rahima Moosa Mother and Child Hospital. 1.6.2 To determine the extent of the SN. 1.6.3 To determine the factors associated with SN. 1.6.4 To assess whether SN affects the quality of life in children infected with HIV 1.6.5 To describe the gross motor function of children infected with HIV, who develop sensory neuropathy compared to those children who do not develop SN.	Body functions and structures: Impairments: Clinical data; sensory neuropathy Activities: motor function; QoL Personal factors Environmental factors Impairment Impairments and activities Activities Activities Participation restrictions
Study two – **An intervention programme was developed based on literature and expert input**	1.6.6 To develop a physiotherapy intervention programme, to manage SN. by reviewing existing literature and using the Delphi Technique to collate expert opinion	
Study three – **A pilot test of the intervention was done**	1.6.7 To determine the outcome of this intervention programme on the gross motor function, mobility and the quality of life	Impairments Activities Participation restrictions Personal factors

1.7 Definition of terms

HIV-SN: A debilitating disorder that presents with numbness, a burning sensation on the soles of the feet or pins and needles. In more advanced cases the patient may have difficulty walking.

Human Immunodeficiency Virus - associated sensory neuropathies (HIV-SN) include the distal sensory peripheral neuropathies (DSP) due to HIV and antiretroviral toxic neuropathies (ATN) (Botes and Levay, 2004; Maritz *et al.*, 2010)

Gross motor development: The changes that occur in our ability to move and our movement in general (Port and Van Gelder, 1995)

Gross motor function: The ability to move within all environments at an age-appropriate level

Intervention programme: An intervention is a combination of program elements or strategies designed to produce behaviour changes or improve health status among individuals or an entire population. Interventions may include educational programs, new or stronger policies, improvements in the environment, or a health promotion campaign.

health.mo.gov/data/intervention mica/index_4.html

1.9 Outline of study

Chapter 1 Introduction	• In previous pages, an introduction to the topics of HIV related SN and gross motor development was given, the problem was presented and the aims, objectives were defined.
Chapter 2 and 3 Literature Review	• A review of current literature on HIV-SN, gross motor development and physiotherapy intervention strategies is provided in chapter 2. • Information on the most recent research available in the field, a critique of previous studies conducted in the field, as well as gaps in the literature are highilighted in this chapter. • Individual tests and tools used in the study are discussed in detail. • Validity and reliabilty of each tool is discussed
Chapter 4, 5 and 6 Methodology and results	• The methodology employed for each study is discussed • Results are presented and a general summary of findings is given at the end of this chapter
Chapter 7 Discussion	• The findings of each study are discussed and related to the literature available on the topic
Chapter 8 Conclusions, limitations and recommendations	• The main findings are concluded, limitations of the study are discussed and future recommendations are stated in this final chapter of the thesis.

Figure 1.1 Outline of the study

Chapter 2: Literature Review

2.1 Introduction

It is important to understand the concept of HIV-related sensory neuropathy (HIV-SN), its definition, mechanisms, diagnostic criteria and management. This literature review aims to describe HIV, HIV-SN and how it influences daily activities and movement. The literature review also will address assessment of the child with neurological deficits and gross motor development.

The literature was obtained through comprehensive searches on major databases (Pubmed, PEDro, Swetswise, Science Direct, Medline and Biomed central via the Wits website as well as Googlescholar). Keywords used in the searches were: Human Immunodeficiency Virus, paediatric HIV, management of paediatric HIV, sensory neuropathy, chemotherapy-induced HIV-SN, distal sensory polyneuropathy, neurodevelopment, physiotherapy in HIV, exercise in HIV, motor development, gross motor assessment, phenotyping of SN, Movement ABC, Pediatric quality of life inventory, brief peripheral neuropathy screen.

Overview of the International Classification of Functioning, Disability, and Health (ICF)
"Impairments are problems in the body function or structure as a significant deviation or loss" (World Health Organisation, 2001) short version, p16.
"Activity is the execution of a task or action by an individual" (World Health Organisation, 2001) short version, p12. "Activity limitations are difficulties an individual may have in executing activities" (World Health Organisation, 2001) short version, p121.
"Participation is the involvement in a life situation" (World Health Organisation, 2001) short version, p121 "Participation restrictions are problems an individual may experience in involvement in life situations" (World Health Organisation, 2001) short version, p121.

The concepts of the ICF covered in this review are as follows:
Body functions & structures (Impairments): Clinical data (CD4, count, viral load, height & weight) and sensory neuropathy (BPNS and pin-prick) Activities (limitations): Motor function (Movement ABC) and Quality of Life (PedsQL)
Participation (Restrictions): Motor function (Movement ABC) and Quality of Life (PedsQL)

Environmental Factors: Clinical data (drug regime); Schools (terrain); Distances to taxis, schools, shops; Sporting activities engaged in at school or leisure

Personal Factors**:** Clinical data (age at initiation)**;** Motivation**;** Anxiety**;** Coping at school with academics and sport.

2.1.1 Background and prevalence

The global estimate of people living with human immunodeficiency virus (HIV) in 2016 was 36.7 million, including 2.1 million children (<15 years) (UNAIDS, 2017a). Sub-Saharan Africa accounts for 64% of the world's population living with HIV, including 19.4 million adults and children in Southern and Eastern Africa (UNAIDS, 2017b). In South Africa, 7.1 million people are reported to be living with HIV, with an estimated 360,000 children (0-14 years) (Statistics South Africa, 2017). A report by UNAIDS in 2016 showed a global decline in new HIV infection from 1.8% to 1.3% and a 33% decline in the number of children living with HIV in comparison to new infections reported in 2013 (UNAIDS, 2016a).

South Africa has the biggest and most high profile HIV epidemic in the world, with an estimated seven million people living with HIV in 2016. In the same year, there were 270,000 new infections while 110,000 South Africans died from AIDS-related illnesses see figure 2.1 below (UNAIDS, 2017b). This is a significant decrease from 2013.

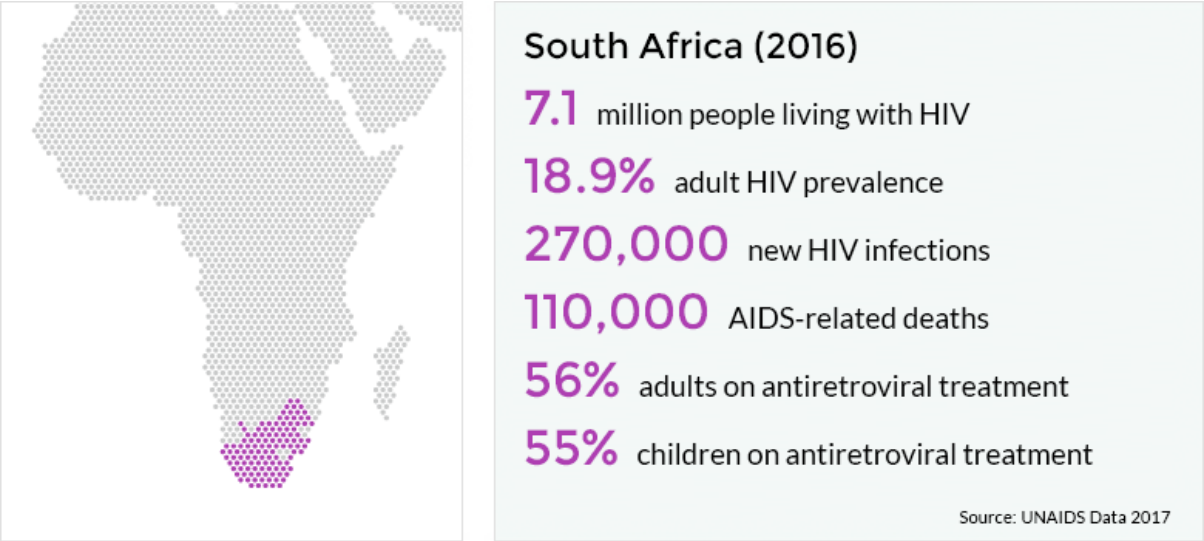


Figure 2.1 HIV statistics for 2016 (UNAIDS)

The introduction of Antiretroviral Therapy (ART) to South Africa in 2004, led to a decrease in mortality and morbidity of HIV infected children and increased their life expectancy into adolescence and beyond (WHO, 2006). The profile of HIV has changed since the advent of ART. ART has 'revolutionised the treatment of HIV, significantly lessening mortality and opportunistic infections' (Ciccolo, Jowers and Bartholomew, 2004 page 487). To date, South Africa has the largest ART programme in the world with a steady reduction in the thresholds for initiating therapy since 2004. Neonates born in a hospital setting with existing HIV programmes, that are exposed to HIV are started on ART within hours of birth (Ministry of Health and Social Welfare, 2015).

In Sub-Saharan Africa, ARV treatment has become increasingly accessible over the last decade and in South Africa about 3.4 million (56 %) people living with HIV are on ART (UNAIDS, 2016b). African estimates of children who have access to ART showed that the number of children receiving ART has increased from 14500 in the year 2000 to 875000 in 2015 (UNAIDS, 2016b), 51% of children living with HIV in Southern and Eastern Africa are receiving ART (UNAIDS, 2017a). There is still an abundance of HIV infected children who do not have access to treatment because of insufficient health care services as well as educational and political complications.

The role of ART is reducing plasma HIV load and increasing CD4 cell count which results in the prevention of opportunistic infections, thereby decreasing the burden of HIV (Amirayan-Chevillard *et al.*, 2000; Ciccolo, Jowers and Bartholomew, 2004). Globally, the number of AIDS related death decreased by 26.7% between the year 2000 and 2015 from 1.5 million deaths to 1.1 million deaths (UNAIDS, 2016a). Brady *et al*. (2010) reported a decline in deaths of children infected with HIV due to opportunistic infections from 37% in 1994-1996 to 24% after 2000 in the United States of America. Thus, HIV has become a chronic medical condition as fewer cases progresses to AIDS (Earls, Raviola and Carlson, 2008). Previously, management was only aimed at treating health problems whereas now it is also focussed on improving patients' quality of life (QoL) (Isanaka, Duggan and Fawzi, 2009; Das *et al.*, 2010; Xu *et al.*, 2010).

The survival rate of children living with HIV has increased over the last decade. The WHO has therefore recommended that ART be initiated immediately after exposure to HIV or diagnosis of HIV in children under the age of five (World Health Organization, 2010). Although early initiation of ARV therapy may be appropriate for infants as it has been seen to increase life

expectancy, continuing the treatment for life may lead to episodes of disability and impairments owing to the long-term toxicity effects of ARV therapy (Foster and Lyall, 2008).

2.1.2 Pathology of HIV

HIV belongs to a class of viruses known as retroviruses, which carry their genetic material in the form of ribonucleic acid (RNA) rather than deoxyribonucleic acid. HIV primarily infects the mononuclear cells, especially CD4 and macrophages, but B cells are also infected (Shankar *et al.*, 2005; Sowers, Galantino and Kietrys, 2013). The virus affects the T-lymphocytes which are white blood cells that carry the antigen for white blood cells. The CD4 cells are vital in the initiation of an immunological response and thus are a clear indicator of the presence of the virus. The normal CD4 cell count is 1000/mm^3 and a decrease of this amount shows a decrease in normal function of the immune system (National Department Health Republic of South Africa, 2010).

Transmission

The major route of HIV infection in children is mother-to-child transmission (MTCT), which occurs during pregnancy (intrauterine), at delivery (intrapartum) or through breast-feeding (postpartum). A study done in 2006, estimated that 65% of the cases occur perinatally during labour and 35% occur during the intrauterine period, mainly in the last weeks of pregnancy (de Brito *et al.*, 2006). MTCT accounts for more than 90% of new HIV infections amongst children (Herrero, *et al*., 2013). Less common modes of transmission may be by infected blood products, contaminated needles or through child sexual abuse. Factors influencing high MTCT rates in developing countries include difficulty of prognosis during pregnancy, lack of compliance with ART and poor post-exposure prophylaxis (Operates *et al.*, 2017) Fernandes *et al*., 2010; Matilda, *et al*. 2007).

2.1.4 Diagnosis and staging of HIV

The WHO (World Health Organization, 2010) have very specific guidelines for the diagnostic testing for HIV and recommend that HIV serological assays are used under quality-assured, standardized and validated laboratory conditions. This should be done for all HIV

exposed infants within four to six weeks of exposure. .HIV virological assays are used for the purpose of clinical diagnostic testing when serological assays have a 99% sensitivity.
The staging of HIV in children is specific and has been summarised by WHO it is reflected in the table 2.1 below:

Table 2.1 Clinical staging of HIV of infants and children (WHO, 2010)

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Unexplained persistent hepatosplenomegaly Papular pruritic eruptions Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Unexplained persistent parotid enlargement Lineal gingival erythema Herpes zoster Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Fungal nail infections
Clinical stage 3
Unexplained moderate malnutrition not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5 °C, intermittent or constant, for longer than one month) Persistent oral Candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Acute necrotizing ulcerative gingivitis/periodontitis Lymph node TB Pulmonary TB Severe recurrent bacterial SNeumonia Symptomatic lymphoid interstitial SNeumonitis Chronic HIV-associated lung disease including bronchiectasis Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5×109/L3) or chronic thrombocytopenia (<50 × 109/L3)
Clinical stage 4 [a]
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy SNeumocystis SNeumonia Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding SNeumonia) Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site) Extrapulmonary TB Kaposi sarcoma Oesophageal candidiasis (or candiadisis of trachea, bronchi or lungs) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age more than 1 month Extrapulmonary cryptococcosis including meningitis Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated non-tuberculous mycobacterial infection Cerebral or B cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy HIV-associated cardiomyopathy or nephropathy

[a]Some additional specific conditions can be included in regional classifications (e.g. penicilliosis in Asia, HIV-associated rectovaginal fistula in Southern Africa, reactivation of typanosomiasis in Latin America).
Ref: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf

2.1.5 Medical Management of HIV

The South African National department of Health (NDoH) aims to increase survival and decrease HIV-related morbidity and mortality by improving access to ART for children (Ministry of Health and Social Welfare, 2015). This is in keeping with the aims of the WHO. When a child is on ART:

» The CD4 count should rise and remain above the baseline count

» The viral load should be undetectable (<50 copies/mL) and remain undetectable

In some cases suppression of the viral load and maintenance of the CD4 count as well as the prevention of secondary opportunistic infections is the best outcome. The decision to start ART treatment is based on a combination of clinical status, HIV viral load and CD4 count, except in infants who should all start ARV treatment shortly after diagnosis, because they have a higher risk of disease progression (National Department Health Republic of South Africa, 2010). It is recommended by the NDoH guidelines that infants and children infected with HIV in their first years of life be treated regardless of CD4 percentage or number.

ART is the combination of three or more antiretroviral drugs (Weichster-Felder and Golden, 2002, Thorne and Newell, 2007 WHO). Antiretroviral therapy consists of two nucleoside reverse transcriptase inhibitors (NRTIs) combined with either one non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) (WHO, 2010). The prescribed NRTI's are: Abacavir (ABC), Lamivudine (3TC) and Stavudine (d4t); the NNRIT's are Efavirenz (EFV) and the protease inhibitor is Lopinavir/ ritonavir

Limited ARVs are available for use in children and HIV treatment for this population is more costly than in adults infected with HIV. There a few health facilities (including laboratories and clinics) available that address the needs of paediatric patients (AIDSinfo, 2006) (HIV/AIDS, 2015). The combination of lamivudine (3TC), efavirenz (EFV) and didanosine (DDI) is an option that can be used as a once-daily dose and has produced good viral results, clinical efficiency and improved compliance when used in adults (Landman *et al*., 2003). A study done by Nacro *et al*., 2011 on children between the ages of 30 months and 15 years,

found that a combination of 3TC – EFV – DDI taken once daily was efficient in immunological recovery, a twofold rise in the CD4 count after one treatment was seen, and medication was well tolerated (Nacro *et al*., 2011).

The current first line regimen for infants, children and adolescents in South Africa are summarised in table 2.2 below:

Table 2.2 Recommended ART combinations for age

Child	Regimen
Children < 3 years or older children weighing <10kg	ABC + 3TC + LPV/r
Children 3 – 10 years and > 10kg Adolescents 10 – 15 years or < 40kg	ABC + 3TC + EFV Children who started on ABC + 3TC + LPV/r before 3 years must remain on the same regimen at 3 years
Children on Stavudine (d4t)	Change all d4t to ABC
Children on ddl	Change all ddl to ABC

http://www.mic.uct.ac.za/sites/default/files/image_tool/images/51/Children%202016.pdf

Studies have indicated that ART in children saves lives; as seen in Africa and other regions around the world (Hassan *et al*., 2012, Nicol *et al*., 2011). With the introduction of ART a decrease in hospital admission and the number of incidences of opportunistic infections were found with the introduction of ART into the public sector (Nwosu *et al.*, 2017), proving that early initiation of ART had been favourable in HIV infected children (de Jose *et al*., 2013). The Paediatric Clinical Trials Group followed a cohort of children living with HIV from 1993 to 2007 and found that the incidences of cardiomyopathy were six times less since ART (Patel *et al.*, 2010). A decrease in viral load to minimal detected levels and an increase in CD4 count was also noted (Bacha *et al*., 2012, Isaakidis *et al*., 2010).

Sutcliffe and colleagues (2008) found improvements in growth parameters of children living with HIV that were on ART where the weight for age was significantly lower than average prior to the commencement of ART. In low to middle income countries children living with HIV that have good tolerability to ART still present with stunted growth and are underweight. Some do not improve their CD4 T-cell count or viral loads after being on treatment for several years (Mutwa *et al*., 2014).

Side effects of ART

Research has shown that ARV treatment has brought about new challenges in HIV infected individuals, including the effects of Stavudine-related toxicities (Operates *et al.*, 2017). The most reported Stavudine related side effect is HIV-SN. Another major side effect associated with ART is decreased physical fitness and fatigue. Hendrickson *et al.* (2008) documented the prevalence of musculoskeletal impairments such as myopathy and muscle weakness in HIV-infected children. In a study conducted from 1995 to 1998 the prevalence of neurological impairments included 2.4% of the participants, showing signs and symptoms of HIV associated myopathy (Maschke *et al.*, 2000).

Damage to the peripheral nerves results in HIV-SN, causing weakness, balance deficits, numbness and pain. Therefore, HIV-SN can be a significant barrier to functional ability and QoL. Symptoms of HIV-SN are paraesthesia, numbness or tingling, or muscle weakness. Areas of the body may become abnormally sensitive leading to an exaggerated experience of touch (allodynia) and proprioception. In such cases, pain may occur in response to a stimulus that does not normally provoke pain (NINDS, 2014).

NRTIs are included in all first-line paediatric ARV regimens in Africa. As a result of NRTI use, specifically Stavudine, HIV-SN is a common condition in African children on ARV treatment (Peters *et al.*, 2014). As a result of the high prevalence of SN, WHO (2006) recommended that the dose of Stavudine be decreased from 40mg to 30mg to reduce toxicities (Pahuja *et al.*, 2012). A study regarding the prevalence of SN post dose reduction was investigated by Pahuja *et al.*, (2012). The results stipulated that the incidence of SN increased with higher dosages as observed in a 40mg dose compared to 30mg dose. A 90.4% prevalence of HIV-SN per year was observed in the 40mg users, compared to 40.5% per year in the 30mg users, an evident relationship between Stavudine and the prevalence of HIV-SN has been shown. Stavudine has since been discontinued (NDoH Guidelines) and replaced with Abacavir

2.2 Diagnosis and staging of HIVE

Signs and symptoms of HIVE usually develop in the first 24 months after birth and the children present with delayed cognitive, language and motor development (Baillieu and Potterton, 2008; Hilburn, Potterton and Stewart, 2010). HIVE is also considered to be one of the more severe clinical signs (Donald *et al.*, 2014) of HIV infection.

The American centre for disease control and WHO have similar diagnostic criteria for HIVE, the comparison is in table 2.3 below:

Table 2.3 Comparison of CDC and WHO criteria for HIVE diagnosis

CDC Classification	**WHO Classification**
At least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings: a) Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests b) Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by CT or MRI c) Acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia or gait disturbance	At least one of the following progressing over at least 2 months in the absence of another illness: a) Failure to attain, or loss of developmental milestones or loss of intellectual ability b) Progressive impaired brain growth demonstrated by stagnation of head circumference c) Acquired symmetrical motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia and gait disturbances

Children with HIVE require ongoing intervention from a multidisciplinary team to ensure optimal developmental outcomes (Potterton, Stewart, Cooper and Becker, 2009).

2.3 HIV sensory neuropathy

There is a dearth of literature on the prevalence of HIV-SN in children (Peters *et al.*, 2014). Until recently it was thought that HIV-SN did not develop in HIV infected children. According to a cross sectional study performed by Araujo, Nascimento and Garcia (2000), children experience less severe symptoms of neuropathy, but prevalence was similar to that of adults at 34%. A presentation by Leach-Lemens at the 19th International AIDS Conference in 2012, commented that HIV-SN was identified in one-in-four children in rural Mopani District in South Africa (Leach-Lemens, 2012).

2.4.1 Prevalence HIV-SN

Studies on HIV-related sensory neuropathy, its impact on function and mobility as well as management, have been focused to the adult population (Wulff, Wang and Simpson, 2000; Keswani *et al.*, 2002; Botes and Levay, 2004; Gonzalez-Duarte, Cikurel and Simpson, 2007; Gonzalez-Duarte, Robinson-Papp and Simpson, 2008; Wadley *et al.*, 2011;Evans *et al.*, 2011).Two international studies investigated peripheral neuropathy in children infected with HIV. In 2000, Araújo *et al* conducted a study in Brazil which had a convenience sample of 39 children infected with HIV. They established that 34% of the subjects presented with symptoms and signs of peripheral nerve involvement, but that it was less severe in comparison to adults. Esteban *et al* (2008) conducted a study in Peru and assessed a cohort of 90 children. The prevalence of distal sensory polyneuropathy (DSSN) was established to be 13%. The sample sizes for both these studies were relatively small and neither investigated the extent of the DSSN or how it affected mobility and quality of life.

A local study conducted by Govender *et al* (2011) at two hospitals based in the Western Cape, found an approximate prevalence of 5%. This value is far less than the internationally reported statistics (Araujo *et al.*, 2000; Esteban *et al.*, 2008). The average age at which HIV-SN was identified, is nine years. The authors emphasise that neuromuscular complications of HIV is under-reported in children. In a more recent study conducted in the Limpopo province by Peters *et al* (2014), the authors specifically investigated the prevalence of peripheral neuropathy in children. They conducted a cross-sectional study with 182 participants and found that 27% of the children reported symptoms of HIV-SN while the Neuropathy Disability Score was positive

for 14%. Twenty-four percent of the participants fulfilled the criteria for HIV-SN (Peters *et al.*, 2014).

2.4.2 Pathology of HIV-SN

Peripheral neuropathy has several possible causes and can be seen at all stages of HIV infection. The inflammation can be due to an infection most commonly, HIV itself. HIV-SN is linked to side effect of some antiretroviral drugs such as, didanosine (ddI), Stavudine (d4T) zalcitabine (ddC) and protease inhibitors (Ferrari *et al.*, 2006) or medications used for opportunistic infections such as tuberculosis (isoniazid), antimicrobials and antineoplastic agents (Aziz-Donnelly and Harrison, 2017).

Ferrari *et al*, 2006 reviewed the literature on HIV-associated neuropathies: a summary of the findings is given in table 2. 4 below:

Table 2.4 Summary of peripheral nerve disorders associated with HIV

HIV-associated SNS disorder	**Clinical features**	**Mechanism**
I. Distal symmetrical polyneuropathy (DSP)	Painful feet, herpathia (feet), mild muscle weakness, depressed or absent ankle reflexes; impaired pain and temperature sensation	Loss of myelinated and unmyelinated fibres with axonal degeneration and macrophage degeneration
II. **Toxic neuropathy from antiretroviral drugs (ATN)**	Similar clinical picture to DSP	Mitochondrial toxicity due to prolonged NRTI use
III. **Diffuse infiltrative lymphocytosis syndrome (DILS)**	Acute or subacute painful multifocal symmetrical neuropathy	Persistent peripheral blood polyclonal CD8 lymphocytosis
IV. **Inflammatory Demyelinating Polyneuropathies (IDP)**	Weakness in arms and legs with minor sensory symptoms	Demyelinating neuropathy with onion bulb formations, macrophage activation and infiltration by mononuclear cells of nerve fascicles and endoneurial oedema

V.	**Mononeuritis multiplex**	Sensory involvement with numbness and tingling in distribution of one peripheral nerve trunk, progresses to symmetrical neuropathy	Early – self-limited dysimmune neuropathy Later -CMV infection, varicella zoster and hepatitis C infections
VI.	**Progressive radiculopathy**	Low back pain with radiation into one leg followed by progressive weakness in that leg	Attributed to CMV infections but may also be caused by lymphoma, syphilis, mycobacterial infections, herpes simplex virus and cryptococcus
VII.	**SN associated with immune reconstitution**	Rapidly progressing motor neuropathy	Immune-mediated inflammatory response

Clinical Features

Sensory neuropathy is one of the common complications of HIV (McArthur *et al.*, 2000; Brew, 2003; McArthur, Brew and Nath, 2005; Hogan and Wilkins, 2011). In adults 30 to 60% of human immunodeficiency virus infected patients, depending on their stage of disease, may develop peripheral neuropathy (Maritz *et al.*, 2010; Cherry, Wadley and Kamerman, 2016b) Paraesthesia and pain are the most common presenting complaints, followed by weakness or loss of motor ability (Shankar *et al.*, 2005). The most common form of HIV-related sensory neuropathy is distal sensory or axonal neuropathy, which is directly related to HIV infection and often compounded by anti-retroviral therapy (Donald, Tobin and Stringer, 2011). Studies have shown that more than 50% of adult patients with SN are on stavudine based ART (Maritz *et al.*, 2010; Cherry, Wadley and Kamerman, 2012).

The pathophysiology of HIV-SN has been shown to have a variety of mechanisms such as: i) an indirect inflammatory process as a result of the virus which is most common (Aziz-Donnelly and Harrison, 2017) ii) DRG and axon apoptosis and neurodegeneration (Kamerman *et al.*, 2012) and iii) mitochondrial dysfunction (Höke and Cornblath, 2005; Höke, Morris and Haughey, 2009). HIV-SN inflammatory changes affect the dorsal root ganglia (DRG) and degeneration of longer length unmyelinated peripheral nerves (Kamerman *et al.*, 2012). The same process affects the axons of the small and large myelinated fibres with accompanying

loss of myelination (Aziz-Donnelly and Harrison, 2017). With the indirect inflammatory process, the virus infects the cells of the monocyte-macrophage lineage which then secrete inflammatory cytokines, chemokines and viral proteins (Aziz-Donnelly and Harrison, 2017). Mitochondrial dysfunction is related to the use of ARV's and its side effects (Ferrari *et al.*, 2006). A more recent review by Centner, Bateman and Heckmann (2013) a diagrammatic summary of the pathological process is provided, see Figure 2.2 below:

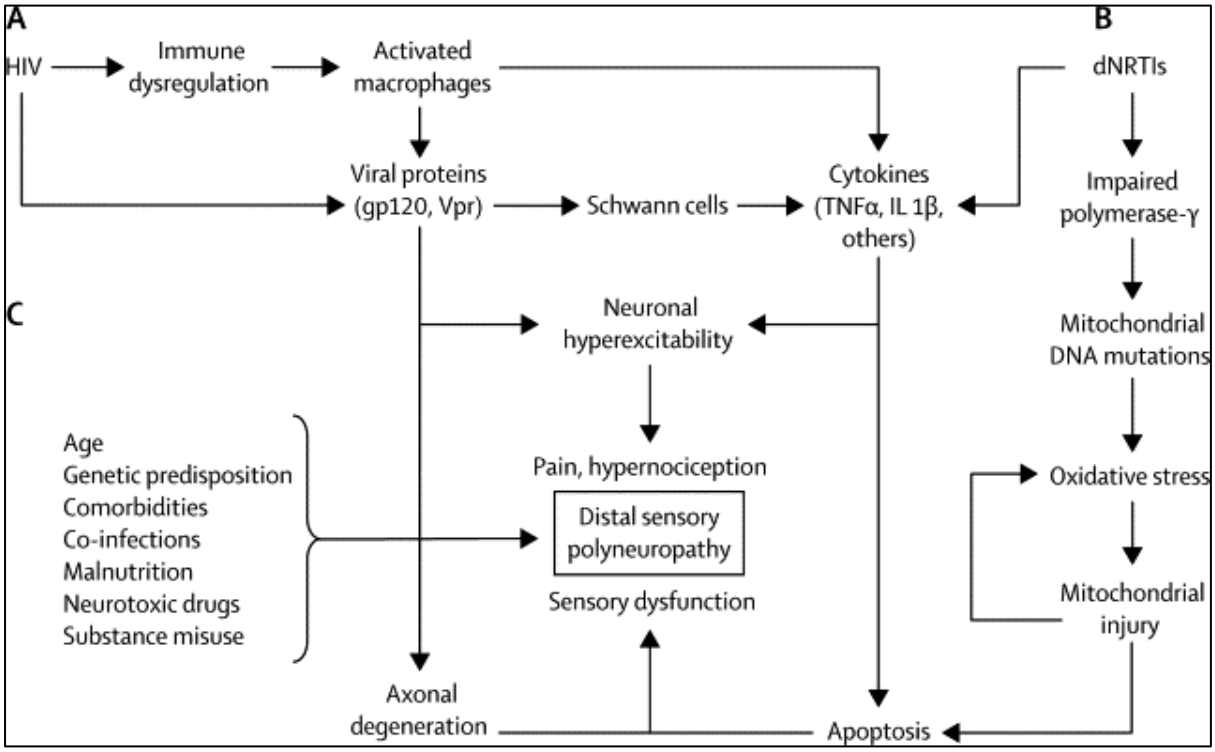


Figure 2.2 Pathogenesis of HIV-SN (reproduced with permission from the authors Centner, Bateman and Heckmann, 2013)

Figure 2.2 Key: (A) HIV-infected macrophages resident in or infiltrating the dorsal root ganglion become activated and release proinflammatory and pronociceptive cytokines—e.g., TNFα and IL 1β.27 Activated macrophages provide a source of viral surface gp120, which, when bound to chemokine receptors on Schwann cells, initiates an inflammatory cascade leading to cytokine-mediated neuronal apoptosis and axonal degeneration.27,28 Macrophages might also provide a source of other viral proteins acting in a similar manner.30 By acting directly on axons, gp120 induces further axonal degeneration independently of inflammatory intermediaries.29 Binding of gp120, Vpr, and possibly other viral proteins to neuronal chemokine receptors results in neuronal hyperexcitability and painful symptoms.26,30 (B) dNRTIs inhibit mitochondrial polymerase-γ, the enzyme that catalyses replication and repair of mitochondrial DNA, resulting in accumulation of mitochondrial DNA mutations, defective respiratory chain subunits, impaired oxidative phosphorylation, and oxidative stress, driving apoptotic processes in distal axons.31 In the dorsal root ganglion, dNRTIs are associated with upregulation of chemokines and chemokine receptors, contributing to the inflammatory background.32 (C) The final phenotype of distal sensory polyneuropathy is characterised by pain and nerve dysfunction, to which other host and comorbid factors can contribute synergistically. DNRTIs=dideoxynucleoside reverse transcriptase inhibitors. Gp120=glycoprotein 120. TNFα=tumour necrosis factor α. IL 1β=interleukin 1β. Vpr=viral protein R. Activated macrophages Viral proteins (gp120, Vpr) Neuronal hyperexcitability

Schwann cells Cytokines (TNFα, IL 1β, others) Mitochondrial injury Oxidative stress Mitochondrial DNA mutations Sensory dysfunction Pain, hyper nociception Immune dysregulation Impaired polymerase-γ dNRTIs Age Genetic predisposition Comorbidities Co-infections Malnutrition Neurotoxic drugs Substance misuse HIV Apoptosis Axonal degeneration Distal sensory polyneuropathy A

2.4.3 Diagnosis of HIV-SN

HIV-SN is diagnosed by assessment of clinical signs, specifically pin-prick sensation, vibration sense and ankle reflexes. In addition, clinical symptoms of pain, altered sensation and numbness. Standardised tools for assessing and diagnosing HIV-SN is the Brief Peripheral Neuropathy Screen (BPNS) as described and validated by Cherry *et al* (2005), the neuropathy symptom score (NSS) and Single-question neuropathy screen (SQNS)(Kandiah *et al.*, 2010). Since it is primarily a sensory neuropathy, the focus is on assessing the peripheral sensory system of vibration sense, ankle reflexes and pin-prick sensation, hence the BPNS was selected for use in this study. The tool is described in more detail in Chapter2.

2.4.4 Medical management of HIV-SN

Currently, HIV-SN is primarily managed with pharmaceutical products. These products only treat the painful symptoms experienced by a patient (Gonzalez-Duarte, Cikurel and Simpson, 2007). Anti-depressants, opioids and anti-epileptics are used in the treatment of pain associated with HIV-SN (Ellis *et al.*, 2010). However, physiotherapy management protocols in children have not been established. This may be as a result of the lack of patient reporting the symptoms of HIV-SN as they could be unaware that these symptoms are abnormal. Additionally, until recently, health professionals believed that HIV-SN did not develop in children (Araujo *et al.*, 2000) and thus HIV-SN in children has only recently been subject to investigation.

2.4.5 Physiotherapy in patients with HIV

Maintenance of endurance, strength and range of joint movement (active and passive) are important components of any motor function treatment plan. Neuromuscular facilitation and inhibition, positioning and splinting are modalities used to influence tone where abnormal changes have occurred. Gait training, the use of assistive devices, training in motor planning,

balance and endurance exercises are also included (Sowers, Galantino and Kietrys, 2013). Coates (1990) stated that with HIV-SN the physiotherapy indications and procedures employed should be no different in HIV than those utilised for similar lesions through other causes.

A study conducted by Nardone, Grasso and Schieppati (2005), found that both static and dynamic balance are negatively affected in patients with neuropathies, Jáuregui-Renaud (2013) concurred and added that static balance is affected to a greater extent than dynamic balance.

A systematic review on the effects of exercise on individuals with HIV disease, by Kietrys and colleagues (2002) revealed the following results:

1. Although intense bouts of exercise may result in transient immunosuppression, there is no evidence that regular exercise in individuals with HIV disease results in a detrimental effect on the immune system over time;
2. Some studies have shown actual improvement in immune system function in response to regular exercise;
3. Improved cardiovascular function has been observed in response to aerobic exercise and
4. Resisted exercise may be effective in counteracting wasting syndrome and improving strength and lean body mass.

Fillipas *et al* (2006) conducted a study to determine self-efficacy in patients with HIV. The study established that patients improved self-efficacy, cardiovascular fitness as well as overall cognitive functioning. Early intervention with exercise is important to stave off opportunistic infections throughout the spectrum of HIV disease (Sowers, Galantino and Kietrys, 2013).

In patients with HIV-related peripheral neuropathy, it is important to implement proper foot care and supportive shoes when weight-bearing activities are performed (Galantino *et al.*, 1998). It is also important to address issues of postural stability, balance and correct gait patterns.

Somarriba recommends regular physical activity for persons living with HIV across all age groups (Somarriba *et al*., 2010). Incorporating physical activity as part of a routine is beneficial in increasing bone density, stabilising BP and improving anthropometric markers such as waist circumference. This was found in the normal population of children and adolescents. It is known that HIV infection has detrimental effects on exercise endurance, negatively impacting their physical function and QoL (Haskell *et al*., 2009). Persons with HIV generally have a decreased ability to do daily activities. These persons can also incur impairments and have a

decreased ability to participate in the community (World Health Organization, 2001). Literature has shown that habitual exercise improves exercise endurance in some chronically ill populations (Baigis *et al*., 2002). A systematic review by Neto *et al.* 2012, found that consistent strength and endurance exercise resulted in a decrease in functional limitations and physical disability (Neto *et al.*, 2013). HIV-infected individuals who do regular exercise can improve their general mood, life satisfaction, QoL questionnaire scores and a decrease in reported depression (O Brien *et al*., 2004). Adults with diabetes and cardiovascular morbidities often have a sedentary lifestyle (Biswas *et al*., 2015). However, a moderate amount of physical activity done by patients with HIV can have a positive effect on their ability to combat metabolic abnormalities and decrease the risk of acquiring acute infections.

Somarriba et al established that exercise intervention is safe for children with HIV (Somarriba *et al*., 2010). This is supported by the findings of Best, where short term as well as long term exercise promotes children's executive function (Best, 2010). Physical activity done at a moderate level is also proven to have a positive impact on a child's immune system. Studies conducted in Miami on children with HIV and reduced endurance showed that children who are active have improved muscular strength, motor skills and cardiovascular fitness as compared to inactive children (Steele *et al.*, 2008). Specific programmes that were structured to improve children's strength, endurance and flexibility were shown to be safe in children who were six years and older (Faigenbaum, 2000). In 2010 Miller *et al*., conducted a study on a group of 34 HIV-infected children aged six years and older. The participants completed a 24 session exercise training programme while being supervised at the hospital. Results from the study reported a clinically significant improvement in strength, flexibility, cardiorespiratory fitness and lean body mass (Miller *et al*., 2010).

Therapies that work on nutrition and physical activity can complement medical management in an HIV-infected individual (Somarriba *et al.*, 2010). Physiotherapists play a vital role in the management and diagnosis of physical dysfunction that is present in patients infected with HIV (Bopp *et al*., 2003, Lima *et al*., 2007).

2.5 Gross motor development

2.5.1 Definition

"*Development, then, can be envisioned as a changing landscape of preferred, but not obligatory, behavioural states with varying degrees of stability and instability, rather than as a prescribed series of structurally invariant stages leading to progressive improvement" Esther Thelen, p 77, Mind as motion, 1995* (Port and Van Gelder, 1995).

Payne and Isaacs refer to motor development as: "The changes that occur in our ability to move and our movement in general" (Payne and Isaacs, 2008). Early childhood is an important period in gross motor development as it fosters greater interaction with the environment (Zadeh and Alvar, 2014). Physical growth is rapid, movement and mobility skills develop, the basis of communication, speech and social development begins as well as the start of cognitive and emotional skills (Fernald *et al.*, 2009).

Gross motor skills are attained and matured through practice at primary school level. These skills are an integral part of cognitive functions such as learning (Lopes *et al.*, 2013; Cameron *et al.*, 2016).

2.5.2 Effect of HIV on motor development

Stephen Arpadi reported in 2000 that as many as 50% of children living with HIV have delayed growth (Arpadi, 2000). In 2006, Foster and colleagues conducted a retrospective analysis on the motor development of 62 HIV-infected children under the age of three years. The study established that there were statistically significant increases in the prevalence of abnormal neurological signs and motor impairments in infants presenting with more advanced HIV disease. This persisted despite immune reconstitution (Foster *et al.*, 2006). In a study investigating the motor performance of children who were not on ARV's, Smith et al found that 33% of their study population showed signs of motor impairment and no improvement six months after initiating treatment (Smith, Adnams and Eley, 2008). These findings were comparable to that of Potterton et al (2009) where 87% of the study population presented with delayed motor development.

Jelsma and colleagues (2011) conducted a similar study in Cape Town, comparing the motor development of orphaned children (mean age: 4 years) with and without HIV infection. They found that the children infected with HIV were significantly delayed in motor development compared to their healthy counterparts (Jelsma, Davids and Ferguson, 2011). However, they were unable to conclude whether the differences were due to HIV status or the environment in which the children lived (orphanage). In the study conducted by Govender *et al* (2011) the researchers only used a screening tool for motor development and therefore could not make robust conclusions about gross motor development. There is a dearth of knowledge regarding the gross motor function of children infected with HIV that are older than three years of age.

A review by Lowenthal *et al* (2014) included children over the age of three years and refer to affected development as growth failure. They reported that growth failure is a hallmark of chronic HIV infection, where children present with stunting. Further to this, they found that despite being on ART, these children never reach their optimum height potential (Lowenthal *et al.*, 2014). The findings of Lowenthal et al are supported by a study done in Malawi and South Africa that investigated the physical development of children living with HIV. They concluded that 59% of the children in the study were stunted, 18% were underweight and the children living with HIV had poorer general physical functioning (Sherr *et al.*, 2018). In contrast to this, Potterton and colleagues found in their study that the participants did not present with stunting, but definite overall developmental delay (Potterton, Hilburn and Strehlau, 2016).

In a more recent study by Benki-Nugent et al (2017) conducted in Nairobi on 79 babies living with HIV that are on treatment, the findings showed a significant delay in attainment of milestones such as sitting unsupported, walking unsupported and throwing toys when compared to HIV uninfected children. They also found that there was an improvement in the first six months of ARV treatment (Benki-Nugent *et al.*, 2017).

The impairments seen in infants are likely to persist and affect gross motor performance throughout childhood unless they are addressed. It is thus clear that HIV impacts negatively on gross motor development and that physiotherapists have a role to play in improving this domain Impairments in physical functioning are common in children with chronic pain, and many report withdrawal from physical activities such as sports, walking and running (Palermo, 2000; Kashikar-Zuck *et al.*, 2001). Physical functioning is a multidimensional domain encompassing

a number of constructs such as physical fitness, physical activity, functional capacity, and subjective disability, which are related, but distinct aspects of functioning. Physical functioning has been identified as an important outcome domain to assess in clinical trials of pain interventions (Wilson and Palermo, 2012).

2.5.3 Assessment of Gross Motor Development

Determining outcome of treatment or the effect of disease is an essential component of research and intervention. In research studies conducted internationally, the most common standardised tools to investigate gross motor development in children over three years of age are the Movement ABC® (M-ABC) (Henderson and Sugden, 1992) and/ or the Bruininks-Oseretsky Test of motor Proficiency® (BOTMP) (Deitz, Kartin and Kopp, 2007).

The Bruininks-Oseretsky Test of Motor Proficiency (Bruininks, 1978) is a standardized, norm-referenced measure. This test was recently revised and published as the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (Deitz, Kartin and Kopp, 2007). The BOT-2 is an individually administered assessment of fine and gross motor skills of children and youth, four to 21 years of age. It is intended as a discriminative and evaluative measure to characterize motor performance, specifically in the areas of fine manual control, manual coordination, body coordination, and strength and agility (Deitz, Kartin and Kopp, 2007)

The Bayley Scales of Infant and Toddler Development – version III (Bayley, 2006 most recent version) is a developmental assessment tool used in preschool aged children. This measure consists of a series of developmental play tasks and takes between 45 – 60 minutes to administer. The Bayley is used widely in both clinical and research to identify developmental delays and to determine the need for early intervention. For research purposes it is used to assess developmental outcome related to medical diagnoses such as prematurity and genetic disorders (Lowe *et al.*, no date). The BSID is designed to assess infants and toddlers from 16 days to 42 months of age.

Both the BOTMP and the Bayley scales are valid and reliable, but did not meet the needs of the study in terms of time constraints (BOTMP) and age range (Bayley III). We therefore selected to use the Movement-ABC which is described in more detail below.

2.5.4 The Movement-ABC

The Movement-ABC assesses the developmental status of FMS; with a focus on detection of delay or deficiency in a child's movement skill development (Vallaey and Vandroemme, 1999). The Movement-ABC test is a revision of the Test of Motor Impairment (TOMI) and originates from the Oseretsky scales for the motor capacity of children (Simons, 2004; Burton and Miller, 1998). The test is suitable for children between 4 and 12 years of age and consists of 32 items, subdivided into 4 age bands. Each age band includes 8 individual test items measuring movement skills in three categories: manual dexterity skills, ball skills and balance skills. Taking the test requires 20 to 30 minutes. A total impairment score expresses the child's test performance. Each item is rated on a 6-point rating scale, where 5 equates to the weakest performance and 0 equals the best performance. Profile scores provide more specific information on the child's movement skill performance of each individual category. Qualitative observations are optional (Henderson and Sugden, 1992).

The M-ABC has been normed for children four to sixteen years of age and it includes a screening checklist to be used by teachers and parents. The norm-reference examination is done by a therapist to establish the specific areas of difficulty. The checklist has four sections with twelve questions and a fifth section with questions about the child's behaviours related to motor activities. Each of the first four sections has questions regarding the child's performance in one of the following environments: Child stationary, environment stable (e.g. cutting); child moving, environment stable (e.g. walking); child stationary, environment changing (e.g. catching); and child moving, environment changing (e.g. running and kicking a ball). A total score is calculated and used to determine if the child is at risk for movement problems (below 15% but above 5% cut-off score) or has movement problems (below the 5% cut-off score).

The norm-referenced examination has three sections, each section containing items for each of three age bands: 4 - 6 years; 7 – 8 years and 9 – 10 years. Items are divided into manual dexterity, ball skills and static and dynamic balance sections including activities such as threading beads, putting pegs in a pegboard, catching and throwing a bean bag, balancing on one leg, jumping, hopping and heel-to-toe walking. A total score is used to determine if performance is within normal ranges, if a motor impairment is present or if the impairment is serious (Henderson and Sugden, 1992). This tool will be further discussed in chapter three.

2.6 Quality of life

The WHO (1997) defines QoL as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". Additionally, QoL is a multi-dimensional construct which covers many domains: physical, social, cognitive and psychological (Eiser and Morse, 2001). Living with a childhood chronic disease like HIV/AIDS may result in motor or cognitive problems, resulting in delayed developmental milestones. This can further lead to impairment and/or loss of function. These children may have increased dependence on a caregiver or parent and consequently, may have decreased participation in social or school-based activities, resulting in an impaired QoL (Grootenhuis, de Boone and van der Kooi, 2007) .

Groontenhuis (2007) describes that "health-related quality of life (HRQoL) refers to the specific impact of an illness, injury or medical treatment on an individual's QoL". Thus, HRQoL was introduced into HIV/AIDS research, to evaluate the effect of anti-retroviral therapy on children's QoL (Banerjee, Pensi and Banerjee, 2010). Assessment of HRQoL has become increasingly important since patients have improved longevity attributable to advances in medical treatment (Garvie *et al.*, 2009).

Since the advent of ART, HIV has become a chronic disease (Russell and Seeley, 2010) impacting various aspects of children's' development and lives. Chronic health conditions put children at risk of developing low self-esteem as well as social and behavioural difficulties (Remien and Mellins, 2007). HIV/AIDS and its consequences can affect the well-being and livelihood of children. It is therefore necessary to manage HIV infected children holistically, looking at both their disease and treatment (Harding, 2001).

HIV-SN leads to numerous impairments and functional limitations which may affect Quality of life (QoL) in HIV-infected children (Birugama & Rhoda, 2012). This supports the findings of a qualitative study by Punpanich et al. done in Thailand. They conducted interviews with the caregivers of children living with HIV. Some of the key findings were that HIV had impacted all aspects of health, the children complained of low levels of energy, performed poorly at school and were unable to achieve optimal treatment adherence (Punpanich, Gorbach and Detels, 2012). These findings were supported by a South African study by Skeen *et al* in 2014 in which children living with HIV reported lower health and educational quality of life.

Factors contributing to this were poor school attendance, poor living conditions and living with ailing family members (Skeen *et al.*, 2014). Similar findings for factors attributing to poor quality of life was reported by Xu *et al* (2010) in Thailand and Chitah, Jonsson and Sheshaman (2016) in Zambia Additional factors included were the time caregivers spent with them and whether the child knew their caregivers' HIV status (Xu *et al.*, 2010) as well as levels of CD4 counts during a period of declining health (Chitah, Jonsson and Seshamani, 2016).

A previous study of Italian children done in 2010 also established that the participants experienced significantly reduced physical functioning compared to their healthy counterparts (Bomba *et al.*, 2010). In her research thesis on health-related quality of life (HRQoL) in children living with HIV, Goldberg (2011) found differences suggesting that the study population had significantly lower QoL in all domains. Of these, physical functioning was reported to be the lowest scoring domain which agreed with the findings of Bomba et al (2010). She attributed these findings to the pre-existing growth stunting and weakness as reported by other studies (Isanaka, Duggan and Fawzi, 2009; Potterton, Stewart, Cooper, Goldberg, *et al.*, 2009). The main aim of physiotherapy is to improve the QoL in HIV infected patients. This can be achieved through an exercise program consisting of strengthening, stretching and cardiac exercises as described by Mutimura et al in their study on adults living with HIV. (Mutimura, et al., 2008). Das et al investigated QoL by comparing children living with HIV to children diagnosed with cystic fibrosis (CF), the latter also being a chronic disease with a major impact on QoL. Their findings were that children living with HIV were functioning comparatively better, but still reported lower physical and psychosocial functioning (Das *et al.*, 2010). The main aim of physiotherapy is to improve the QoL in HIV infected patients. This can be achieved through an exercise program consisting of strengthening, stretching and cardiac exercises (Mutimura *et al.*, 2008).

2.6.1 Assessment of QoL

PedsQL™ 4.0 Generic Core Scales is an assessment tool which was designed to measure the core health dimensions of physical, mental and social well-being as described by WHO (Varni *et al*, 2001; Varni *et al*, 2006). The tool measures HRQoL in children and adolescents aged two to 18 years. The details of the tool is provided in chapter three.

2.7 Conclusion

HIV infection in children has been associated with growth disturbances, developmental delay and neurological impairments (Hilburn, Potterton and Stewart, 2010; Potterton, Hilburn and Strehlau, 2016) including sensory neuropathy (HIV-SN) and fatigue (Loades *et al.*, 2018). Furthermore, the side-effects associated with ART need to be managed in the treatment of an HIV-infected child. Fatigue, pain, neuropathy, depression and insomnia are the most frequently reported symptoms in the post-ART era (Ciccolo, Jowers & Bartholomew, 2004).

Studies on HIV-related sensory neuropathy, has mostly been done on the adult population living with HIV (Wulff, Wang and Simpson, 2000; Botes and Levay, 2004; Cherry *et al.*, 2005; Ellis *et al.*, 2010;Wadley *et al.*, 2011b). There is a dearth of literature for the paediatric population, other than estimates of its prevalence (Araujo *et al.*, 2000; Esteban *et al.*, 2008; Govender, Eley, Walker, Petersen and. Wilmshurst, 2011; Donald *et al.*, 2012b; Peters *et al.*, 2014). The studies by Govender *et al*. (2011) and Donald *et al*. (2011) assessed the extent of neurological complications and neuro-behavioural problems in a group of children attending infectious disease clinics in the Western Cape. The researchers established that HIV-associated neurologic complications are common and span a wide spectrum of disorders, but the focus remained on the central nervous system.

This review provided an overview of HIV, HIV-SN and how it affects development and gross motor function. Tools used to assess gross motor function and QoL are discussed in more detail in the following chapter.

Chapter 3: Measuring instruments

In this chapter the outcome measures chosen to assess the participants will be discussed in more detail. The link between each objective and the instruments as well as the component of the ICF it measures is given in Table 3.1 below:

Table 3.1 Study objectives linked with the instruments used and the ICF components

Study objectives	Instruments used	ICF component
1 To determine the frequency of HIV-related sensory neuropathy in children attending Rahima Moosa Mother and Child Hospital. 2 To determine the extent of the SN. 3 To determine the factors associated with SN. 4 To assess whether SN affects the quality of life in children infected with HIV. 5 To describe the gross motor function of children infected with HIV, who develop sensory neuropathy compared to those children who do not develop SN.	BPNS BPNS Clinical data PEDsQL M-ABC	Body function and structure (Objectives 1-3) Activity limitation and Participation restrictions (Objective 5 & 6)
7. To determine the outcome of this intervention programme on the gross motor function, mobility and the quality of life.	M-ABC, PEDsQL, BPNS	All three components

3.1 The Movement- ABC (M-ABC-2®)

In research studies conducted to investigate gross motor development, the most common standardised test used, is the Movement ABC® (M-ABC-2®) (Henderson and Sugden, 1992) and is regarded as the "gold standard" for motor assessment in children with motor co-ordination difficulties (Venetsanou *et al.*, 2011). The fundamental aim of the M-ABC is to identify children with movement difficulties and to describe the characteristics of the difficulties. It has been updated and the newer version standardised by Henderson et al (2007) using a sample of 1172 subjects. Schulz et al (Schulz *et al.*, 2011) conducted confirmatory factor analyses in their study that confirmed the structural validity of the M-ABC-2®



Figure 3.2 The contents of the M-ABC-2® kit

Figure 3.2 above, shows the contents of the M-ABC2 kit and the items used to test each component. These are described in detail below:

The M-ABC has been normed for children four to ten years of age and it includes a screening checklist to be used by teachers and parents. The norm-reference examination is done by a therapist to establish the specific areas of difficulty. The checklist has four sections with twelve questions and a fifth section with questions about the child's behaviours related to motor activities. Each of the first four sections has questions regarding the child's performance in one of the following environments: Child stationary, environment stable (e.g. cutting); child moving, environment stable (e.g. walking); child stationary, environment changing (e.g. catching); and child moving, environment changing (e.g. running and kicking a ball). A total score is calculated and used to determine if the child is at risk for movement problems (below 15% but above 5% cut-off score) or has movement problems (below the 5% cut-off score).

3.1.1 Components of the M-ABC-2®

The norm-referenced examination has three sections, each section containing items for each of three age bands: 4 - 6 years; 7 – 8 years and 9 – 10 years. Items are divided into manual dexterity, ball skills and static and dynamic balance sections including activities such as threading beads, putting pegs in a pegboard, catching and throwing a bean bag, balancing on one leg, jumping, hopping and heel-to-toe walking. A total score is used to determine if performance is within normal ranges, if a motor impairment is present or if the impairment is serious (Henderson and Sugden, 1992).

a) Manual Dexterity

This is done with the child static, seated at a table with their feet supported. Brief description of what child is required to do

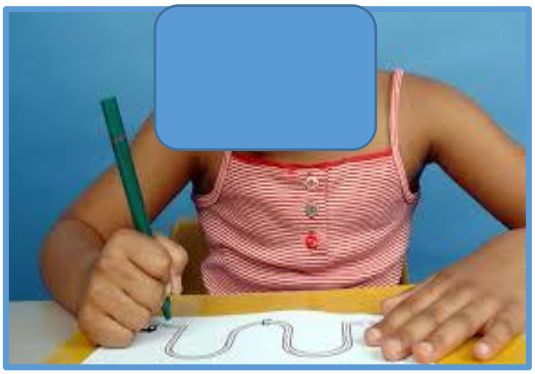


Figure 3.3 Demonstration of the drawing activity of the M-ABC-2®



Figure 3.4 Demonstration of the coin-posting activity of the M-ABC-2®

b) Aiming and catching

This is done with the environment stable and the child moving. Describe activity

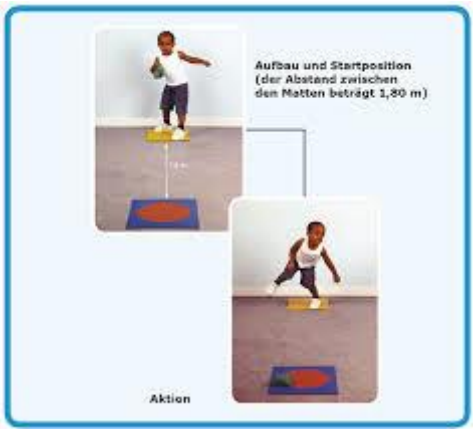


Figure 3.5 Demonstration of aiming and catching activity of the M-ABC-2®

c) Balance

This is done with the child moving, walking on a line as well as with the child stable – standing on a balance beam.



Figure 3.6 Demonstration of the balance activity of the M-ABC-2®

3.1.2 Reliability of the M-ABC-2®

In a critical review of studies using the M-ABC-2®, Venetsanou et al (2011), investigated the psychometric properties of the M-ABC-2®. The authors concluded that, inter-rater reliability of the M-ABC is good (kappa coefficients ranged from .95 to 1.00), test re-test reliability of the total score is good (ICC were high, ranging from 0.92 for children 9–10 years old to 0.98 for children 5–6 years old, section scores are moderate and individual item scores are poor. They recommend further research in areas of reliability for confirmation.

3.1.3 Validity of the M-ABC-2®

An investigation into the validity of the M-ABC-2® was conducted by Van Waelvelde et al (2004). By conducting a correlation analysis between items within the test, they established that there was a great variation from highly significant correlation to non-significant results, between individual items. However, the concurrent validity of the total impairment score of the M-ABC was established. Schulz et al (2011) utilised the same data for the standardisation of the MABC-2 ® using the Confirmatory Factor Analysis method and were able to confirm the structural validity of the M-ABC-2®.

3.2 Paediatric Quality of Life Inventory (PedsQL™)

This is a quality of life questionnaire that has been developed by Dr James Varni, 1998 (USA) The PedsQL™ builds on and expands a programmatic instrument development effort by Varni and his associates during the past 15 years in paediatric populations. The PedsQL™ 1.0, originally derived from a paediatric cancer database, was designed as a generic quality of life inventory to be utilized noncategorically, i.e., across multiple paediatric populations.
Given that instrument development is an iterative process, the PedsQL™ 2.0 and 3.0 were further advancements in the measurement model, including additional constructs and items, a more sensitive scaling range, and a broader age range for patient self-report and parent proxy-report. The PedsQL™ has resulted from a rapid cycle improvement strategy, and has been field tested with children and adolescents in paediatrician's offices, hospital specialty clinics, and community settings. The PedsQL™ has been translated into numerous languages and used internationally.

3.2.1 Objective of the PedsQL™

The objective of the PedsQL™ is to assess health related quality of life in children in various disease areas. It is applicable for healthy school and community populations, as well as with paediatric populations with acute and chronic health conditions.

Varni et al (2007 and 2008) conducted field trials to assess reliability, validity, responsiveness and practicality of the PedsQL™. Internal consistency and reliability was found to be excellent with alpha values greater than 0.70 for the self- and proxy-report and alpha values reaching 0.90 for the full 23-item scale. Validity of the PedsQL™ was done using comparisons to other measures of disease burden. The PedsQL™ was found to be responsive to clinical change as well. It is short and takes less than five minutes to complete. The guidelines for administration are provided in Appendix 8

3.3 The Brief Peripheral Neuropathy Screening Tool

The Brief Peripheral Neuropathy Screen (BPNS) is described by Cherry et al (2005) an extensive screening tool that incorporates both symptoms and positive bedside examination findings for neuropathy, has been demonstrated to accurately detect peripheral nerve dysfunction in HIV-infected individuals and is considered sufficient for tracking trends in large cohorts. The tool is used to assess the presence of symptoms such as pain, burning, tingling, hot and cold sensations. Objectively, it assesses the ankle jerk reflex and vibration sense, with a sensation being felt for longer than ten seconds being regarded as normal. Since the tool has only been validated in the adult population, the researcher included pin-prick testing. The pin-prick test is a test of a person's ability to detect a cutaneous pain sensation and to differentiate such sensations from pressure stimuli. It is performed with a pin or needle gently applied to a skin area where it cannot be observed by the subject. The purpose of "pinprick" testing for pain sensation is to assess the integrity of non-myelinated pain fibres and their input as part of the spinothalamic pathway (separate from dorsal column functions). Only stimuli that assess pain, rather than light touch, are useful.

The purpose of pin-prick testing for pain sensation is to assess the integrity of non-myelinated pain fibres and their input as part of the spinothalamic pathway, separate from dorsal column functions. The dorsal column conveys localized sensations of fine touch,

vibration, two-point discrimination, and proprioception from the skin and joints. This highlights the importance of making the assessment more comprehensive by including the pin-prick sensation, but ensuring that the participants understand the instructions well.

The purpose of the tool is to screen for the presence of peripheral neuropathy. This tool has been selected because it has been widely used in clinical trials investigating peripheral neuropathy associated with HIV. The classification properties of the BPNS in children have not been validated, the researcher selected to use the BPNS as the backbone of a general neuropathy screen, with the addition of pin-prick sensitivity. As such we feel that we addressed the main recommendation of England et al (2005), and Haanpaa et al (2011) with regards to detection of peripheral neuropathy and neuropathic pain.
It can be administered by physiotherapists as they are trained to do neurological examinations and the test encompasses both clinical signs and symptoms suggestive of neuropathy. A detailed description of the tool and how it is administrated follows in chapter four.

3.3.1 Validity of the BPNS

Cherry et al (2005) validated the BPNS as part of the NeuroScreen (comprised of the Brief Neurocognitive Screen [BNCS] and the BPNS) assessment tool. The results of the study the BPNS gave a correct diagnostic classification rate of 78%; sensitivity of 49% (95% CI); specificity 88%. Using an assumption of a 40% prevalence of DSSN, the Positive Predictive Value (PPV) of the BPNS was 72%.

3.4 The WHO Child Growth Standards

The WHO Child Growth Standards were developed using data collected in the WHO Multicentre Growth Reference Study. The site presents documentation on how the physical growth curves and motor milestone windows of achievement were developed as well as application tools to support implementation of the standards.

Z score is a statistical measure that reflects the relative deviance form the median value/standard. It is a pure number and is measured as SD (Standard Deviation) in statistical terms. A Weight-for-Age Z score (WAZ) should be understood as the number of standard

deviations of the actual weight of a child from the median weight of the children of his/her age as determined from the standard sample. This is prefixed by a positive sign (+) or a negative sign (-) depending on whether the child's actual weight is more than the median weight or less than the median weight. When the actual weight of a child is exactly equal to the median, the resultant WAZ is zero. (http://monitoringevaluation.weebly.com/monitoring--evaluation.html)

Table 3.2 Categories of Z-score range for weight according to agreed global standards (WHO)

Z-score range	Category
-1 < WAZ < 0	Normal (Well nourished)
-2 < WAZ < -1	Marginally Underweight (Mildly Malnourished)
-3 < WAZ < -2	Moderately Underweight (Moderately Malnourished)
WAZ < -3	Severely Underweight (Severely Malnourished)

A below median WAZ is called Underweight and is an indication of malnutrition.

A Height-for-Age Z score (HAZ) should be understood as the number of standard deviations of the actual height of a child from the median height of the children of his/her age as determined from the standard sample. This is prefixed by a positive sign (+) or a negative sign (-) depending on whether the child's actual height is more than the median height or less than the median weight.

When the actual height of a child is exactly equal to the median, the resultant HAZ is 0 (zero).

As per the agreed global standards, the following categories can be formed:

Table 3.3 Categories of Z-score range for height according to agreed global standards (WHO)

Z-score range	Category
-1 < HAZ < 0	Normal (Well nourished)
-2 < HAZ < -1	Marginally Stunted (Mildly Malnourished)
-3 < HAZ < -2	Moderately Stunted (Moderately Malnourished)
HAZ < -3	Severely Stunted (Severely Malnourished)

The case of having a below median HAZ is called stunting and is an indication of malnutrition.

In conclusion, this chapter provides an overview of each instrument used for data collection in this study. The psychometric properties are provided as well as the reason each tool has been selected. In the following chapter the details of how each instrument was applied is provided. In the following chapter the methodology and results for study one will be presented.

Chapter 4 Methodology and Results Study One: Frequency Study

Introduction

This chapter gives an outline of research methods that were followed in the study. It provides information on the participants, that is, the criteria for inclusion in the study, who the participants were and how they were sampled. The researcher describes the research design that was chosen for the purpose of this study and the reasons for this choice. The instruments that were used for data collection are described in detail in the preceding chapter and the procedures that were followed to carry out this study are included in this chapter. The researcher also discusses the methods used to analyse the data. Lastly, the ethical issues that were followed in the process are also discussed. Since the project was completed in phases, each phase will be outlined separately, followed by the results and a summary for that specific phase.

4.1 Objectives

The objectives of study one was to:

1. Determine the prevalence of HIV-associated sensory neuropathy (HIV-SN).
2. Describe the presentation of HIV-SN.
3. To determine the factors associated with having HIV-SN.
4. To assess whether having HIV-SN affected quality of life.
5. To describe whether having HIV-SN impacted on gross motor function.

4.2 Study design

Sample population

A prospective cross-sectional cohort study was conducted. Approximately 500 children between the ages of six months and eighteen years attend the Empilweni Services and Research Unit (ESRU) based at Rahima Moosa Mother and Child Hospital (RMMCH). To determine the prevalence of SN a sample of 200 children was screened to estimate the expected prevalence of 30% with 95% confidence, to an accuracy of within 5%. Children infected with HIV, between the ages of three and ten years, that attend the Empilweni Services and Research

Unit (ESRU) clinic based at Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa, were eligible to participate in the study.

Inclusion Criteria:

a) All children between three and ten years of age, and who were attending the ESRU clinic as part of the CHANGES study.

Exclusion Criteria

a) Acute medical conditions that required admission to hospital
b) Tuberculosis of the spine
c) Any neurological or musculoskeletal conditions that affected gross motor function adversely

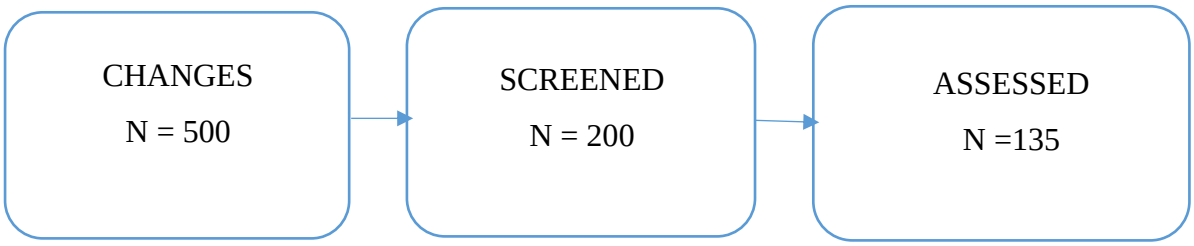


Figure 4.1 Flow chart of participant recruitment

4.3 Ethical considerations and confidentiality

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee, Clearance number: M 120767 (Appendix 11). Permission to conduct the research at the site was granted by the hospital manager (Appendix 6)

Signed consent was obtained from Parents/ Guardians/ Caregivers (written if they are literate, or verbal if they were not) of the participants after explaining the purpose and procedure of the study as well as that the risks involved (in their home language and with the assistance of a translator, if needed). Emphasis was made that declining to participate will not affect their access to the same healthcare services as other patients and that they had the right to withdraw at any time. (Appendix 11)

Following the consent of the parents/ caregivers, verbal assent was obtained from the participants older than eight years of age, after describing the study in their home language (Appendix 12).

Participants were reassured that all results were for purposes of the study only and that it will be held in confidence. All data collected will be kept for a period of ten years in the safe at the Department of Physiotherapy on completion of the study.

4.4 Study procedure

Patients attending the ESRU clinic were invited to participate in the study by giving them a short introduction to the study while they were waiting in the waiting area for their doctor's appointment. Emphasis was placed on participation being voluntary.

Following informed consent of caregivers and verbal assent of the participants, the clinic records were accessed and basic demographic details and medical information (history of HAART, CD4 T-cell counts, current viral load, and other medication) extracted. Age, height, and weight were recorded as part of routine follow-up measurements at the clinic. Data collection was done over a period of two years.

Patients are not routinely assessed for neuropathy, the BPNS (Appendix 13) was used and pin-prick sensation was included to ascertain whether participants present with SN and if so, the level and extent of the SN. The BPNS is described in detail in Chapter 3. The BPNS was developed for use in adults living with HIV, we expanded the number of signs assessed to include pin-prick sensitivity to enhance its testing sensitivity. The classification properties of the BPNS in children have not been validated, we chose to use the BPNS as the backbone of a general neuropathy screen, with the addition of pin-prick sensitivity. As such we feel that we addressed the main recommendation of England et al (2005), and Haanpaa et al (2011) with regards to detection of peripheral neuropathy and neuropathic pain.

The following case definitions: No SN (no signs or symptoms of SN present); Asymptomatic SN (one or more signs, but no symptoms present) and Symptomatic SN (one or more signs and

symptoms present); see Figure 4.2 below. Data was captured manually, recorded in Microsoft Excel.

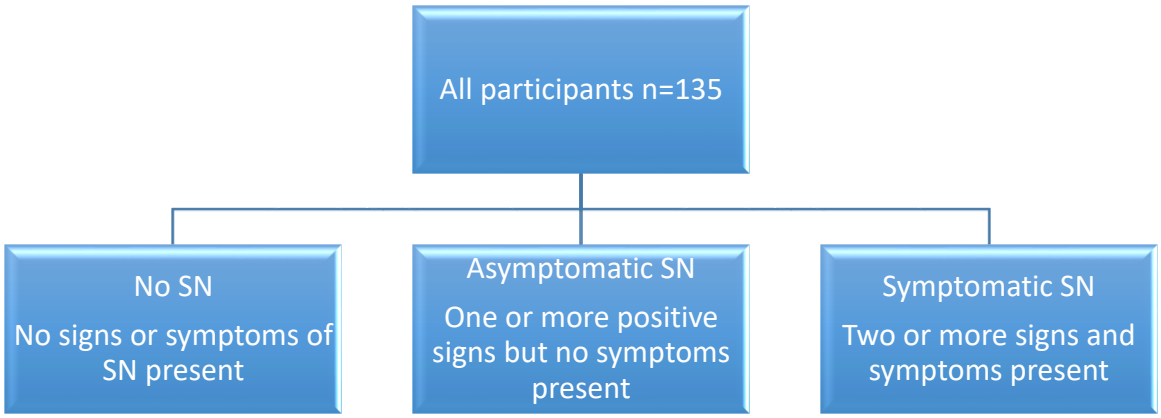


Figure 4.2 Diagram of case ascertainment

The PedsQL™ was administered by research assistants to determine quality of life and level of pain experienced, if any, due to the SN

To determine objective five, a quasi-experimental study was conducted to ascertain the levels of gross motor function of children infected with HIV and who develop SN. Participants were assessed in the order they were able to attend the clinic,
The M-ABC-2® was conducted to determine the gross motor function levels of the participants at baseline.

4.5 Data collection process and data management

Prior to commencing data collection, the researcher practised using the M-ABC-2® on six typically developing children to become familiar with the test procedures and scoring. Training on the BPNS was provided by an expert in the field of clinical assessment and peripheral neuropathy. No training was required for the administration of the PedsQL™, as it is a straightforward questionnaire, with standardised instructions provided by the authors. However, because the questionnaire was being administered by research assistants, the researcher explained the questionnaire to the research assistants, emphasising the importance of not rephrasing or asking leading questions. I also emphasised that the participants needed to

answer the questions posed to them and that parent or caregiver responses were not acceptable. Where the participants were unable to answer, no score was given, and the raw score was adjusted accordingly.

4.5.1 Main study data collection procedure

a) Screening

A total of two hundred children fell within the age range required for the study and were invited to participate. However, only 180 agreed to participate and of these, 135 met the inclusion criteria. The research assistants (RA) explained the study proposal and process to potential candidates in their native languages. Those who were interested were issued a consent form with an information letter in their preferred language (English/ Afrikaans/ Zulu or Setswana). Consent was signed by the parent or caregiver and verbal assent was obtained from participants older than eight years of age. Two hundred children were invited to participate but only 135 met the inclusion criteria or agreed to participate.

b) Assessments

Assessments were conducted by the researcher and began with the BPNS. Participants were seated on a plinth, with the feet supported on a step for the vibration sense and pin-prick assessment and then feet unsupported for the reflex assessment. Before beginning the assessment, each component was explained and then tested.

4.6 The Brief Peripheral Neuropathy Screen

The description of the BPNS is provided in Chapter three. I will now discuss the procedure of testing using the BPNS

4.6.1 Vibration

For the vibration sense test, the researcher placed the tuning fork behind the ear and on the hand for the participant to understand the sensation being assessed. The vibration sense that was assessed was that of the big toe, the time period which the sensation was felt was taken and captured. Testing always began on the right lower limb for consistency.

The following instruction was used as per the BPNS screening tool:

Strike the end of a 128 Hz tuning fork hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the participant's wrist to be sure that they can recognise the vibration or "buzzing" quality of the tuning fork. Instruct the participant to tell you when the "buzzing" stops. Again, strike the ends of the tuning fork hard enough so that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint. Start your stopwatch from the time you strike the tuning fork and stop it when the participant says that they can no longer feel the "buzzing". Repeat for the other great toe.



Figure 4.3 Demonstration of vibration sense assessment technique

4.6.2 Reflexes

Reflexes of the ankle were taken in the sitting position with the feet unsupported. The following instruction was used:

With the participant seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the participant's ankle to 90 degrees. Using a reflex hammer, the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner's hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck. Use reinforcement, if necessary, by having the participant perform the Jendrassick manoeuvre.

Scoring of the reflexes were as follows:

Ankle reflexes

0 = absent

1 = Present

2 = unable/did not assess

The test was repeated at least three times if there were absent or delayed reactions. It was noted retrospectively that the test did not allow to score for delayed reflexes, even though this was recorded on the sheet.

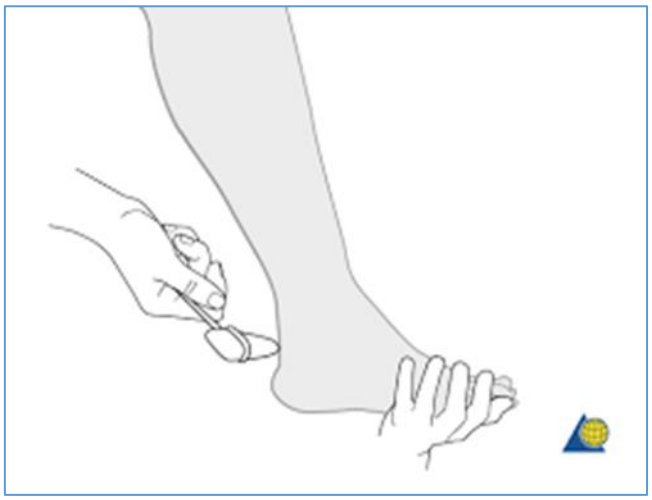


Figure 4.4 Demonstration of ankle reflex testing

4.6.3 Pin-prick

Pin-prick sensation was tested using a large standard safety pin and followed a dermatomal distribution. To maintain consistency, testing always began on the right lower limb. Many of the participants required reassurance that the test was not harmful or painful

For demonstration purposes, the researcher tested an area on the right arm with the participant's eyes open and then repeated the demonstration with the eyes closed. Once the participant seemed to understand, the test was done on the leg following the L3, L4, L5, S1 distribution from the knee downwards.

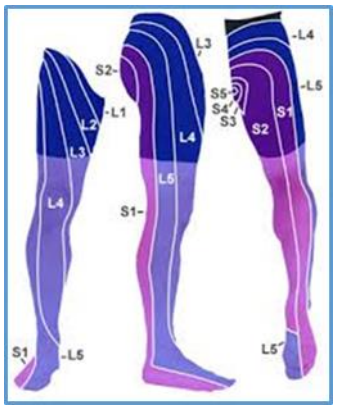


Figure 4.5 Dermatomal representation for pin-prick testing

4.7 M-ABC-2®

The M-ABC-2® was conducted next and activities were done according to the age of the participant. All scoring was done manually.

The assessment is divided into three components, namely manual dexterity, aiming and catching and balance.

4.7.1 Manual dexterity

Manual dexterity was assessed with the participant seated at a table of a comfortable height and their feet were supported on the floor. The test items were placed in front of the participant on the table and the procedure for each item was explained prior to beginning the test. For this component, the researcher opted to start with the drawing test to ascertain hand dominance as the remaining tests distinguish between dominant and non-dominant. For each component the time taken to complete the test was recorded on the score sheet. However, the iPad® screen was not visible to the participant. If the participant refused to do the test, the letter 'R' was recorded, if they were unable to do the test, the letter 'I' was recorded, indicating inappropriate. When needed, the researcher would repeat a component and use standard encouraging such as: 'focus on the activity', look at what you are doing', 'do it as fast as you can'

Components tested for each age group were as follows:

Table 4.1 Item score sheet for Manual Dexterity (md)

Item code	Name of item Age band 1 3-6 years	Name of item Age band 2 7-10 years	Raw score (best attempt)	Item standard score
MD 1	Posting coins Preferred hand	Placing pegs Preferred hand		
	Posting coins Non-preferred hand	Placing pegs Non-preferred hand		
MD 2	Threading beads	Threading lace		
MD 3	Drawing trail 1	Drawing trail 2		

4.7.2 Aiming and catching

In the catching category, participants for age band one was required to stand on a mat, two metres away from the researcher and catch the bean bag. Each participant was allowed five practice catches and ten trials of the activity. The number of correctly executed catches out of ten was recorded. For age band two, a tennis ball was used of the bean bag.

For the aiming activity, the participant stood on a mat placed two metres from the target mat. The instruction was that they should stay on the mat and throw the bean bag aiming for the orange circle. The participant was allowed five practice throws and the number of successful hits out of ten as well as the hand used, was recorded. For age band one, the whole mat was the target. For age band two they had to aim for the orange circle. If they hit the circle only it was regarded as a successful hit.

Table 4.2 Item score sheet for Aiming and Catching (a &c)

Item code	Name of item Age band 1 3-6 years	Name of item Age band 2 7-10 years	Raw score (best attempt)	Item standard score
A&C 1	Catching beanbag with two hands	Catching tennis ball with two hands		
A&C 2	Throwing beanbag onto mat	Throwing beanbag onto mat		

4.7.3 Balance

Age band one:

For the ‘one-leg balance’ activities the participants were required to stand on one leg, on a mat. The time (in seconds) that they were able to successfully balance for was taken and recorded. Each participant had two trials for each leg.

For ‘walking heels raised’, they were required to walk along a line of two meters long. The number of correct consecutive steps from the beginning of the line or whether line was walked

successfully was recorded. A second trial was not required if the participant managed to complete 15 steps or completed the whole line in fewer than 15 correctly executed steps.
For the 'Jumping on mats' activity the participants were required to jump on each mat with a maximum of five mats placed consecutively. The number of correct consecutive jumps was recorded. See Table 4.3, page 52.

Age band two:
For the 'one-board balance' activities the participants were required to stand on one leg, on a balance board. The time (in seconds) that they were able to successfully balance for was taken and recorded. Each participant had two trials for each leg.
For 'walking heel-to-toe forward', they were required to walk along a line of two meters long. The number of correct consecutive steps from the beginning of the line or whether line was walked successfully was recorded. A second trial was not required if the participant managed to complete 15 steps or completed the whole line in fewer than 15 correctly executed steps.
For the 'Jumping on mats' activity the participants were required to jump on each mat, one leg at a time, with a maximum of five mats placed consecutively. The number of correct consecutive jumps were recorded for each leg. See Table 4.3 below

Table 4.3 Item score sheet for Balance activities

Item code	Name of item Age band 1 3-6 years	Name of item Age band 2 7-10 years	Raw score (best attempt)	Item standard score
Bal 1	One-leg Balance best leg	One-leg Balance best leg		
	One-leg balance other leg	One-leg Balance other leg		
Bal 2	Walking heels raised	Walking heel-to-toe forwards		
Bal 3	Jumping on mats	Hopping on mats best leg		
		Hopping on mats other leg		

A total of 135 (n) participants were recruited over a period of two years, with once weekly visits to the clinic by the researcher. Participants generally did not attend the clinics during school holidays and researcher visits were increased to three mornings a week when the academic calendar allowed. Assessments were only conducted in the mornings as the clinic closes at 13h00 daily.

All data sheets were scored according to the test administration criteria. All raw data were captured on a Microsoft Excel spreadsheet.

4.8 Data analysis

All data were exported to R (v3.3.3) R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.] For analysis. Descriptive statistics such as the mean, standard deviation, and range were used to describe the demographics of the participants and the prevalence of SN. Confidence intervals were calculated using bootstrapping methods (1000 resamples with replacement, using the boot package; Canty & Ripley, 2017) at the 95% level (Davison & Hinkley, 1997). A 95% confidence interval is a range of values that you can be 95% certain contains the true mean of the population. With large samples, you know that mean with much more precision than you do with a small sample, so the confidence interval is quite narrow when computed from a large sample.

Where data were not normally distributed, the Wilcoxon Mann-Whitney or Chi-squared tests were applied to test for statistical significance which was set at 0, 05.

4.9 Results

Due to the small sample size, the prevalence rate could not be established statistically and the findings are therefore reported as frequencies. This affects the generalisability of the results, but provide an important insight to how often HIV-SN is seen in children living with HIV.

Data is expressed in tables and figures such as box and whisker plots. For box and whisker plots, the following definition was used: A box and whisker plot—also called a box plot—displays the five-number summary of a set of data. The five-number summary is the minimum, first quartile, median, third quartile, and maximum.

In a box plot, we draw a box from the first quartile to the third quartile. A vertical line goes through the box at the median. The whiskers go from each quartile to the minimum or maximum.

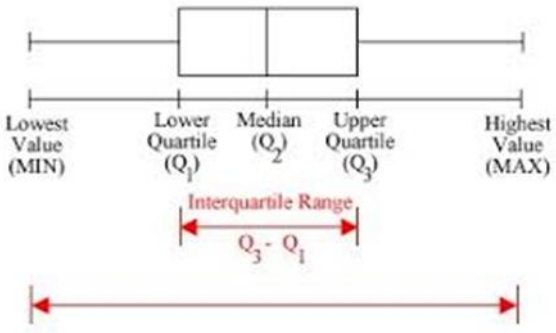


Figure 4.6 Example of a box and whisker plot graph

4.9.1. The frequency of HIV-associated sensory neuropathy (HIV-SN)

Description of study population

Table 4.4 Table of demographic, anthropometric and HIV clinical status data

Demographics	
N (total)	135
Sex	46.6% female
Age (years)	Mean 6.8 (±1.6)
ART start age months/years?	0.27; (range 0-2)
Years on ART	Mean = 5.2; (range 3.16 - 9.25)
Anthropometrics	
Weight for age z-score (WAZ)	Mean = -0.82 ± 0.95
Height for age z-score (HAZ)	Mean = -1.26 ± 1.03
HIV clinical status	
CD4 Cell Count	Mean = 1213 (range 111 - 2808)
Viral Load	Mean = 1.709 (range 1.301 – 4.863)

The table depicts the total number of participants n=135, where 46.6% (n=63) were female and n=72 males (53.4%). The mean age of the children was 6.9 years (SD = 1.7). The youngest child was 3.26 years and the oldest was 10.54 years.

The average age of commencing ART was 27 months, while the average time of being on the treatment was 5.2 years (62.4 months).

Weight and height z-scores

Most of the participants fall below the average (z-score of 0) weight- and -height for age scores. For weight, the minimum z-score is -2.65, while the max is 1.58. The mean z-score value is -0.79. For height, the minimum z-score is -3.27, while the max is 2.11. The mean z-score value is -1.32. What this tells us is that the participants were both shorter and weighed less than they should have for their age.

Viral load distribution

From the table, the minimum viral load = 1.301; max = 4.863; mean = 1.709. It is possible to see that most of the children included in the sample fall below a viral load of 2 (log 10/ml) with many having a viral load of 0, however, there are still a substantial number of data points which well exceed this average.

The average CD4 cell count is 1213 cells per cubic millimetre, indicating that they are well controlled. It is important to note that the range is quite large starting at 111 (indicating they are immunocompromised) to 2808, indicating that they are healthy. A normal CD4 count is from 500 to 1,400 cells per cubic millimetre of blood. CD4 counts decrease over time in persons who are not receiving antiretroviral therapy. At levels below 200 cells per cubic millimetre, patients become susceptible to a wide variety of opportunistic infections, many of which can be fatal.

Medication

Figure 4.7 below depicts the number of participants on a specific regime of antiretroviral therapy (ART), where NA represents missing data. Most participants were on the 3TC, ABC, EFV combination as per the National Department of Health Guidelines (2015). All participants had been exposed to Stavudine (D4T) at some point in their care regime.

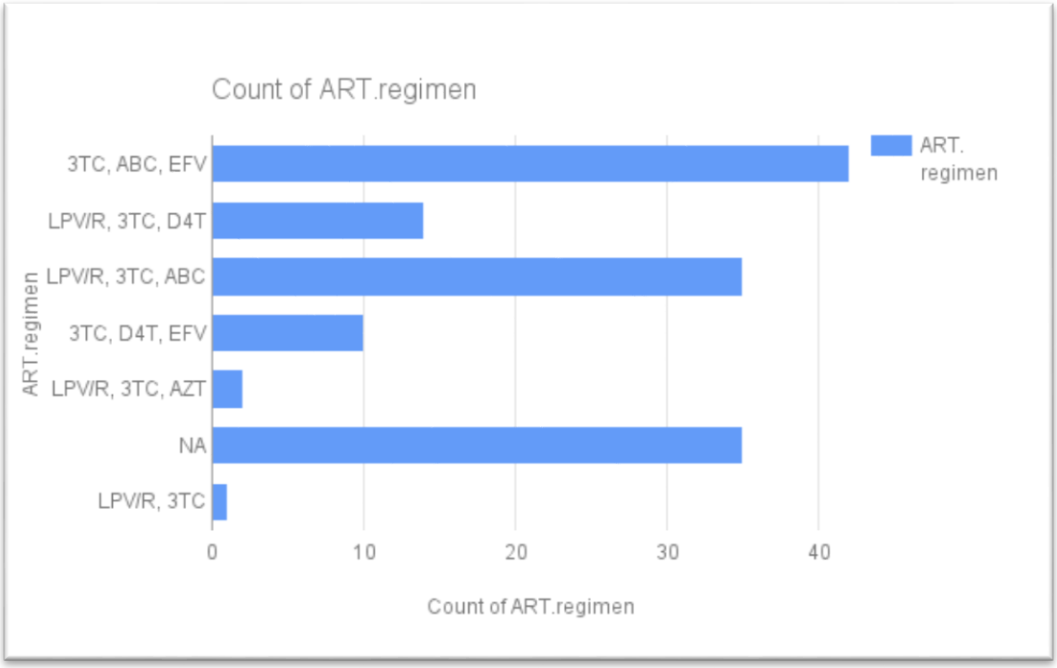


Figure 4.7 Graph of ART regimen used in the clinic

Frequency of HIV-SN

For the purposes of analysis of the results, the following case definition for SN was used: At least one bilateral sign (reduced/absent vibration sense, absent ankle jerk reflexes and reduced pin-prick sensation). As seen in figure 4.8, a total of 36 (25.9% of 135) children in the sample met this definition of SN, with 24.1% having previous symptoms, and 7.8% had current symptoms. When reduced pin-prick sensation was excluded from the analysis, the frequency of SN was reduced to 18 children out of 135(13.3%).

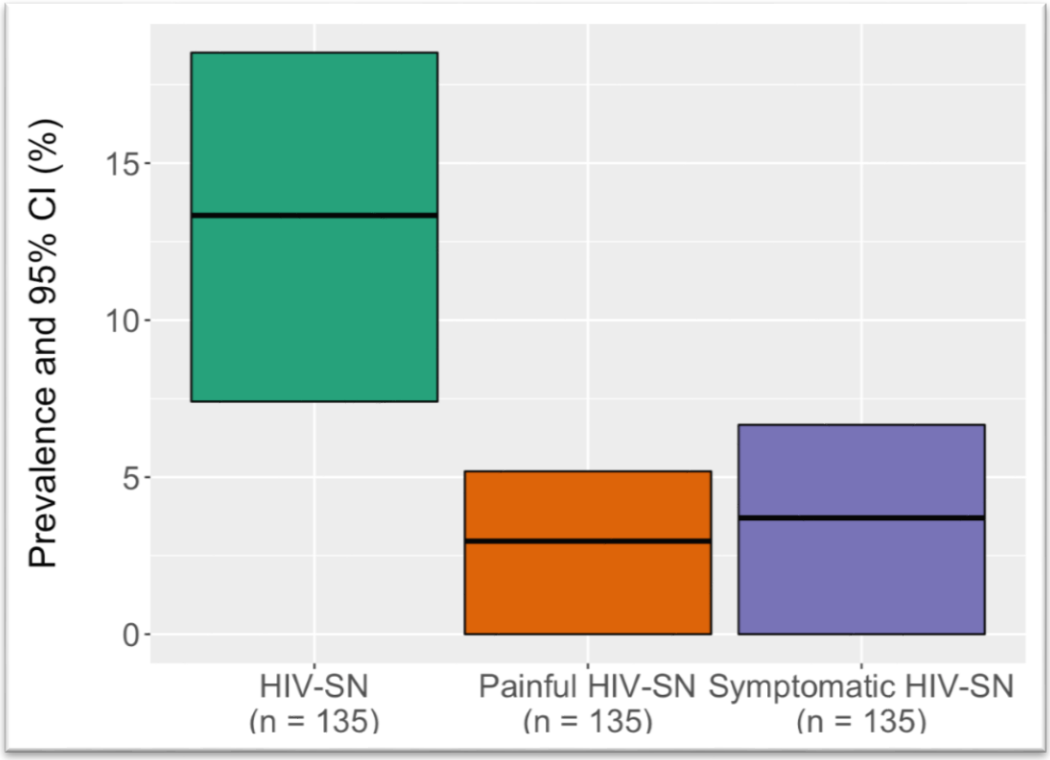


Figure 4.8 Frequency of HIV-SN

Point frequency

For point frequency, the following was used: (18/135) = 13.3% (95% CI = 7.4; 19.3). This confidence interval is illustrated in figure 4.9 below and suggests that the population frequency for HIV-SN lies somewhere in between 7.4% and 19.3%.

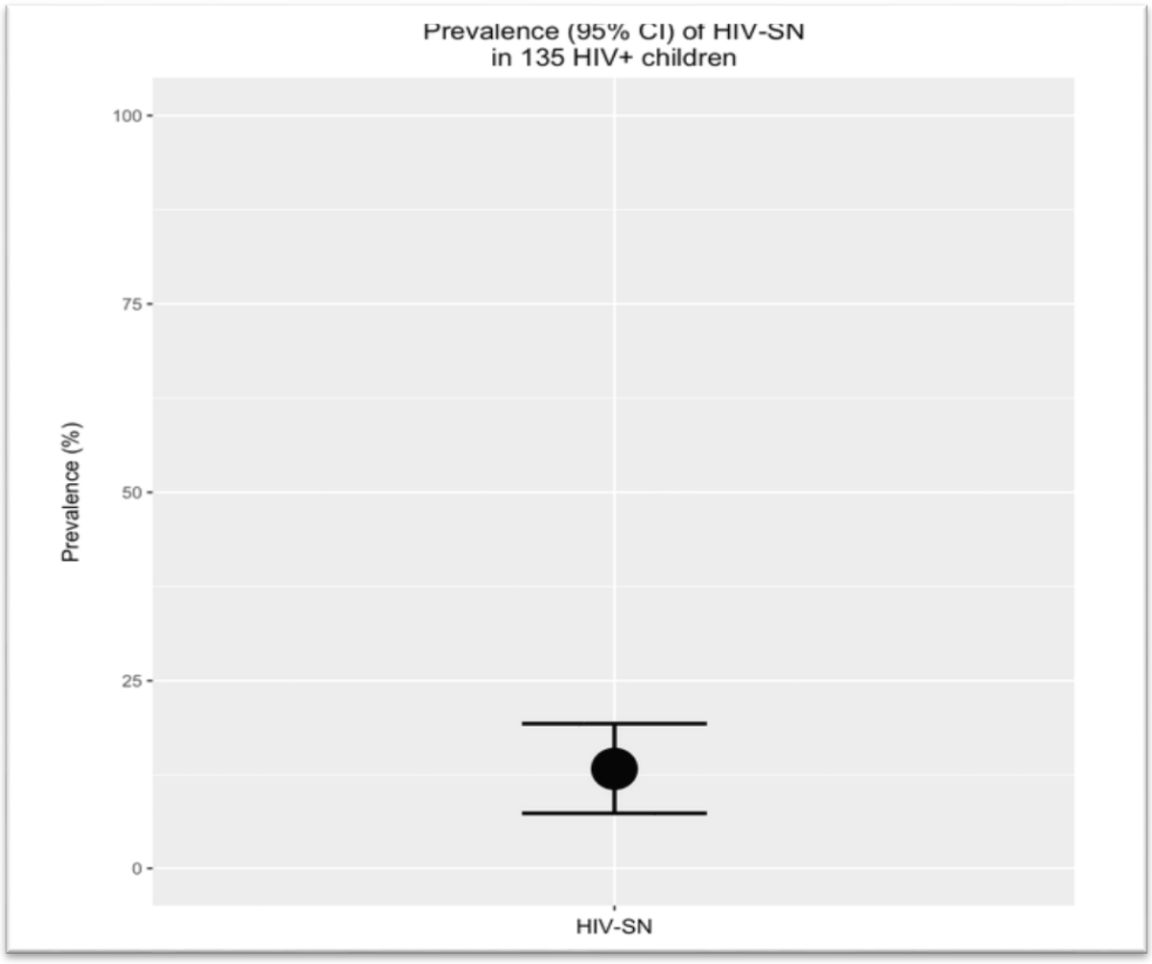


Figure 4.9 Illustration of point frequency including confidence intervals

As seen in figure 4.9, out of the N=18 children who have neuropathy, N= 13 do not have symptomatic SN, while N = 5 do. This means that there is a point frequency of 27.8% (CI = 5.6; 44.4) out of the N = 18.

4.9.2 Presentation of HIV-SN

Of the five participants with symptomatic HIV-SN, all reported having previous pain, four had current pain, three had experienced painful cold, two had itching symptoms, and one had numbness, cramping and pins and needles, respectively.

Of the N=18 participants the frequency of signs was 94% for reduced or absent vibration sense and 6% for absent reflexes.

For symptomatic SN the following case definition was used: At least one bilateral sign (reduced/absent vibration sense, absent ankle jerk reflexes and reduced pin-prick sensation), plus at least one bilateral symptom (pain/aching/burning, tingling/pins-and-needles, numbness). Under this definition, five children (3.7%) of the sample were classified as having symptomatic SN.

4.9.3 Risk factors for SN

Predictors for symptomatic HIV-SN were not explored due to the small sample size. The following factors were examined: Age, sex, height for age, weight for age, CD4 T-cell count, and viral load.

Age

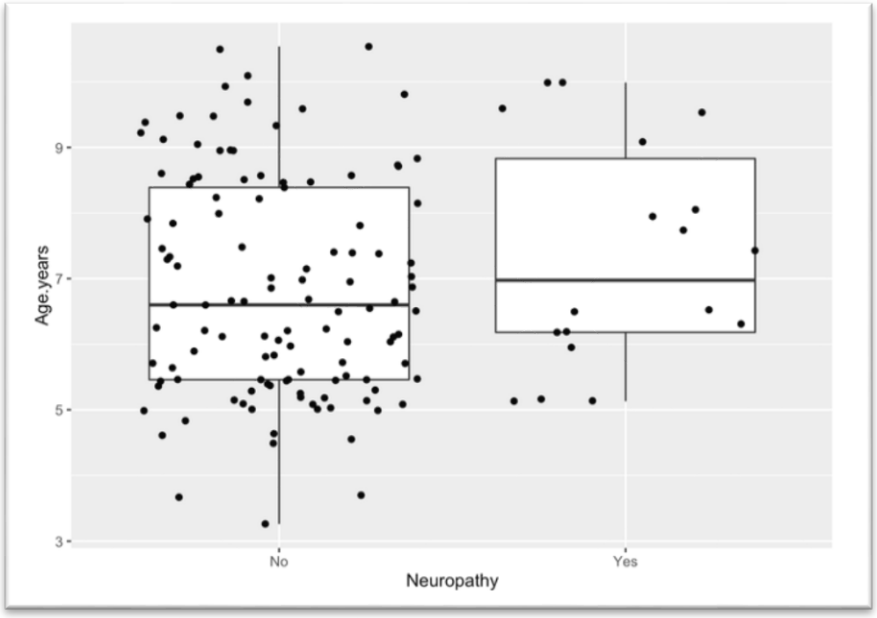


Figure 4.10 Graph comparing age versus neuropathy status

The data were not normally distributed based on the boxplots, so a Wilcoxon-Mann-Whitney test was performed. Figure 4.10 shows that no significant difference in age was found between the two groups (Z = -1.2137, p-value = 0.2275; CI = -1.32; 0.33). The average age was 6.8 years. Eight children were between the ages of 3 and 5 years. Children older than 5 years are more likely to develop neuropathy.

Sex

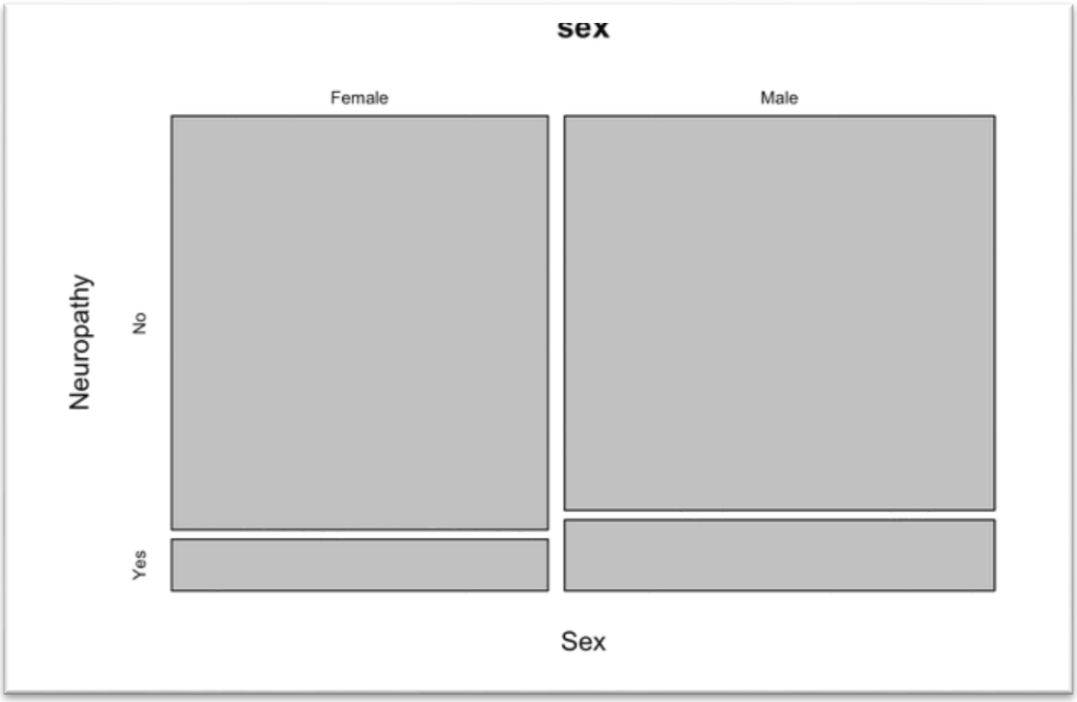


Figure 4.11 Graph comparing gender versus neuropathy status

Figure 4.11 above, is a mosaic plot detailing the count of male and female participants. A chi-square test was performed to determine if there is any association between sex and neuropathy, and the results suggested that there was no association.
Chi-squared = 0.50481, p-value = 0.6135.

Height

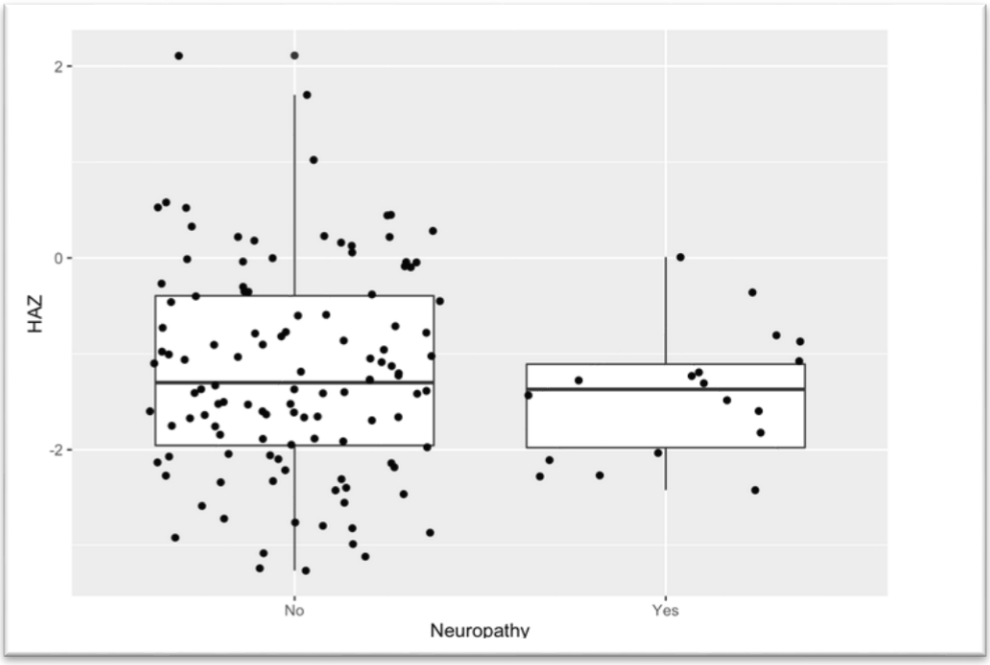


Figure 4.12 Boxplot comparing participant's height versus neuropathy status

Figure 4.12 is a boxplot of the distribution of the HAZ of children based on their neuropathy categorization. The data were not normally distributed based on the boxplots, so a Wilcoxon-Mann-Whitney test was performed. No significant difference in height was found between the two groups (Z = 0.75688, p-value = 0.4533; CI = -0.28; 0.66).

Weight

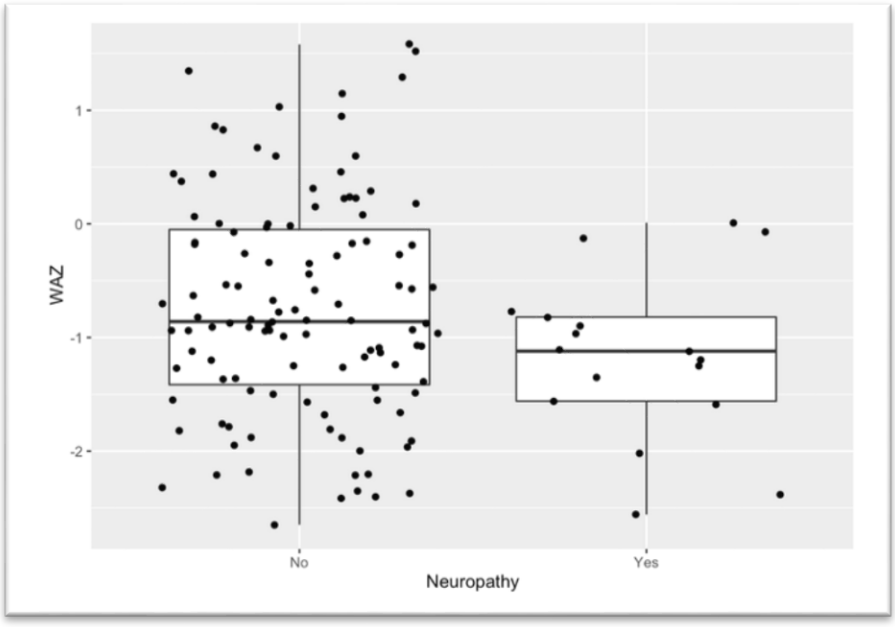


Figure 4.13 Boxplot comparing participants' weight versus neuropathy status

Figure 4.13 is a boxplot of the distribution of the WAZ of children based on their neuropathy categorization.

No significant difference in weight was found between the two groups (Z = 1.7052, p-value = 0.08857; CI = -0.05; 0.85) when applying the Wilcoxon-Mann-Whitney test.

CD4 count

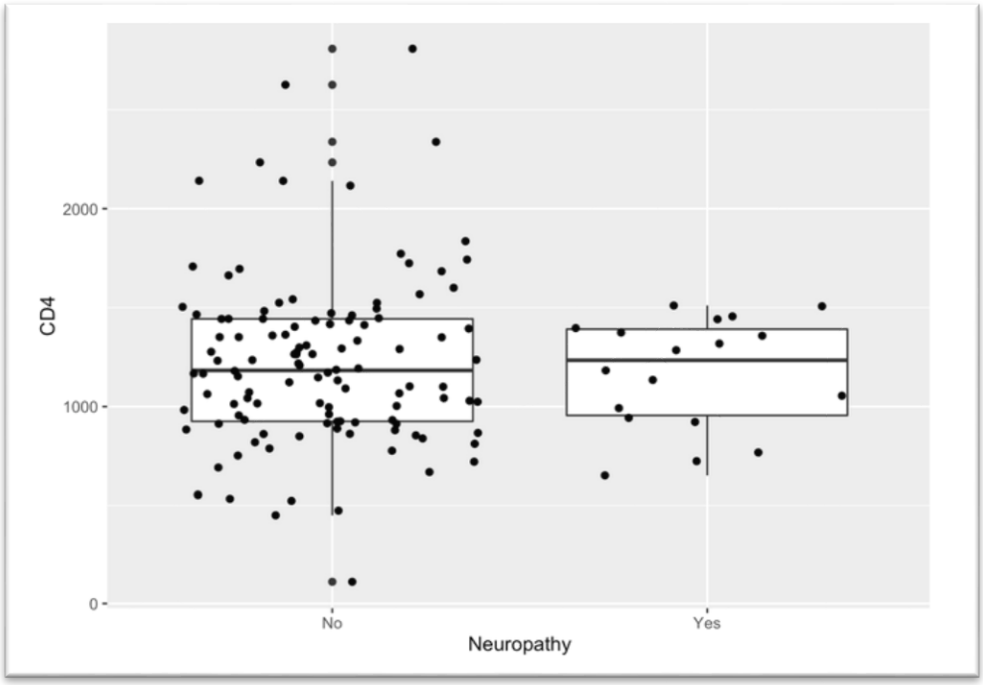


Figure 4.14 Graph showing the distribution of the CD4 count

Figure 4.14 is a boxplot of the distribution of the Cd4 count of participants based on their neuropathy categorization.

The data were not normally distributed based on the boxplots, so a Wilcoxon-Mann-Whitney test was performed. No significant difference in Cd4 count was found between the two groups (Z = 0.1044, p-value = 0.9189; CI = -156; 187).

Viral Load

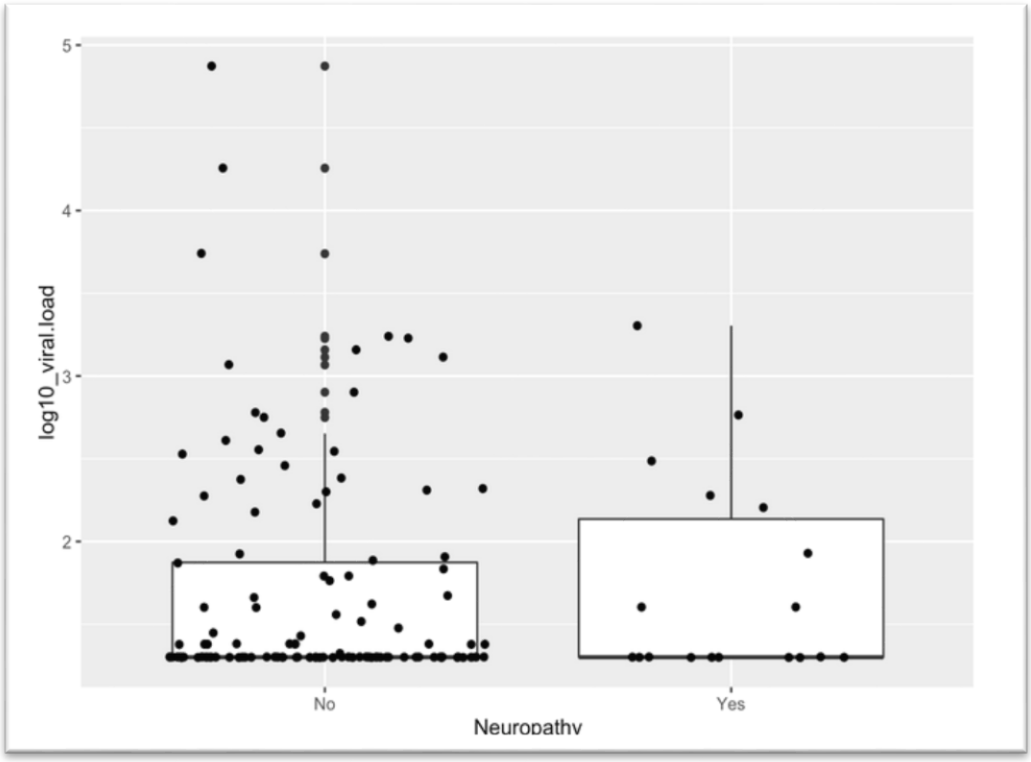


Figure 4.15 Graph of the viral load vs neuropathy status

Figure 4.15 is a boxplot of the distribution of the Viral Load of the participants based on their neuropathy categorization.

The data were not normally distributed based on the boxplots, so a Wilcoxon-Mann-Whitney test was performed. No significant difference in Viral Load was found between the two groups (Z = -0.081346, p-value = 0.9372; CI = 0; 0).

Stavudine (D4t) exposure

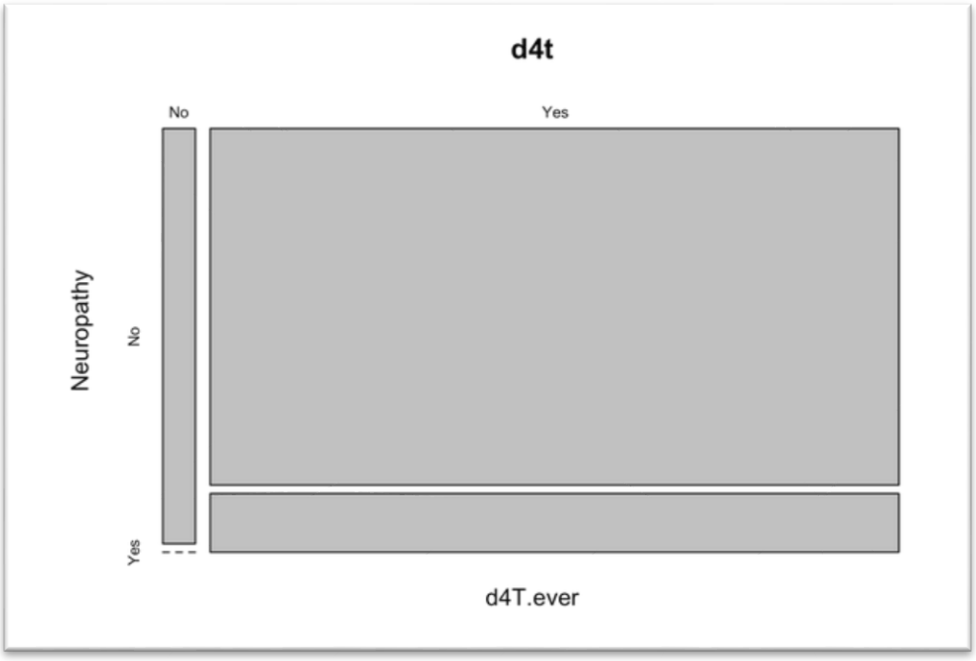


Figure 4.16 Graph of d4t exposure vs neuropathy status

Figure 4.16 above is a mosaic plot detailing the count of children who were exposed to d4t based on their neuropathy categorization. A chi-square test was performed to determine if there is any association between d4t and neuropathy, and the results suggested that there was no association. Chi-squared = 0.9835, p-value = 0.5971.

Years on ART

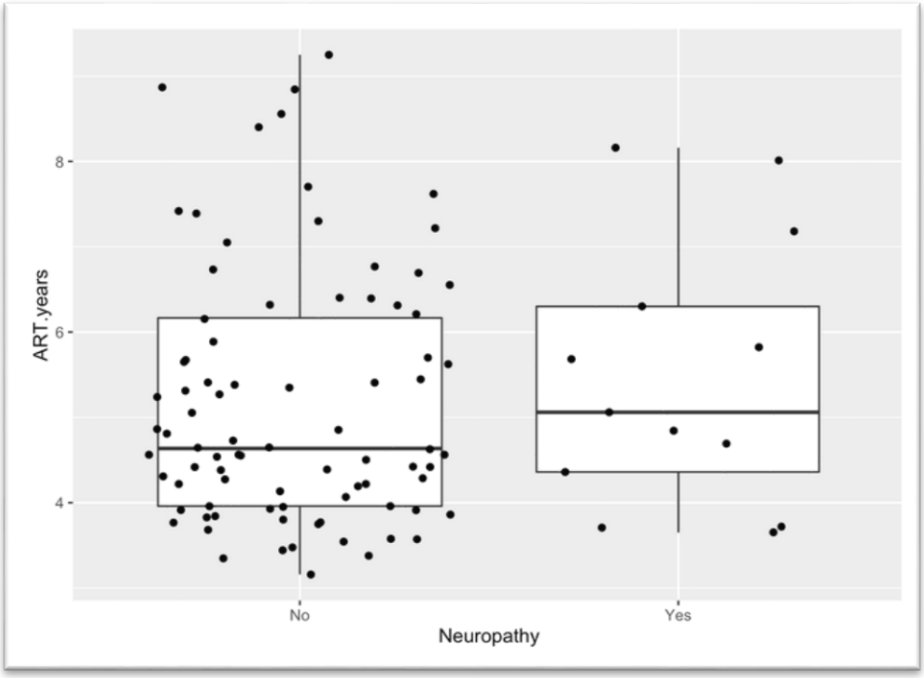


Figure 4.17 Graph showing time on ART versus neuropathy status

Figure 4.17 is a boxplot of the distribution of the Years on ART of the participants based on their neuropathy categorization.

The data were not normally distributed based on the boxplots, so a Wilcoxon-Mann-Whitney test was performed. No significant difference in Years on ART was found between the two groups (Z = -0.68833, p-value = 0.4973; CI = -1.19; 0.55).

As seen, there were no associative factors identified that could impact (causative or worsening the signs and symptoms) on the development of HIV-SN.

4.9.4 HIV-SN and quality of life

For the PedsQL™, 133 parent and 114 child questionnaires were completed these were all included in the analysis. The main descriptive statistics investigated here are: Mean (95% CI), Median and Standard Deviation.

PedsQL™ Total score

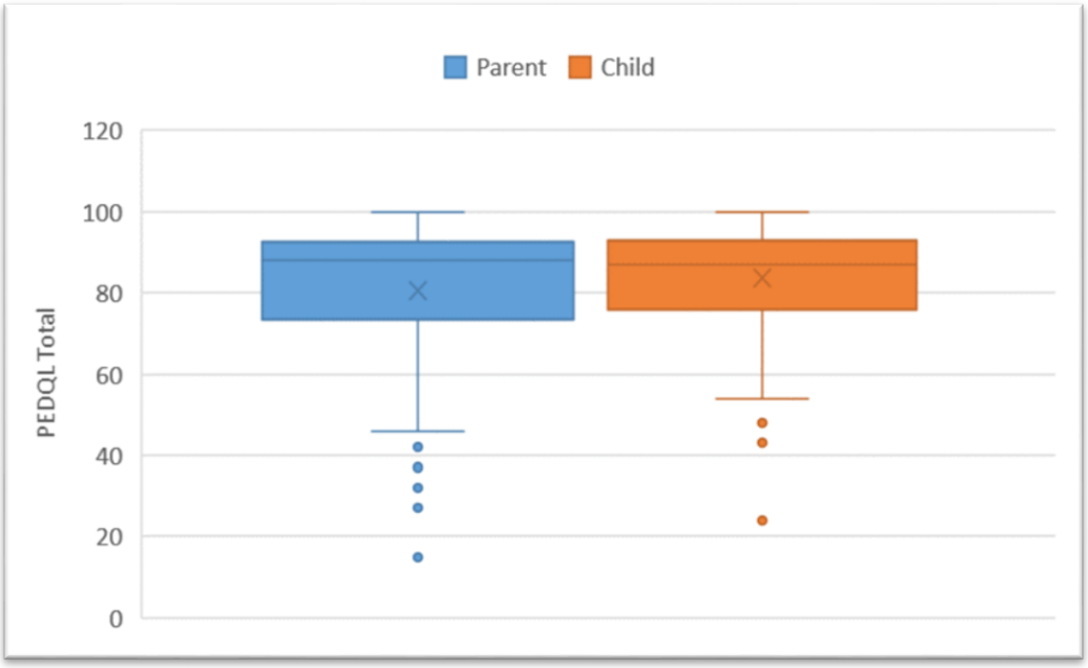


Figure 4.18 Graph comparing parent and child **Total scores** of the PedsQL™

Figure 4.18 above is a boxplot detailing the distribution of the PEDQL total scores between parent and child for the total sample. The mean score was 79.6 % with a CI = 75.9; 83.3 and a SD of 19.5. The median was 88.5.

PedsQL™ Psychosocial score

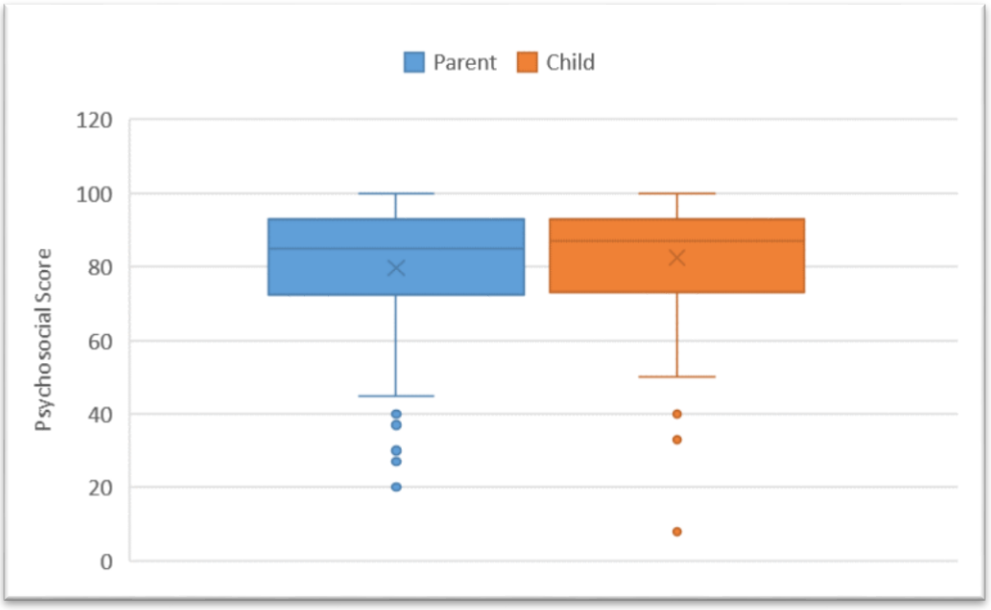


Figure 4.19 Graph comparing parent and child **Psychosocial scores** of the PedsQL™

Figure 4.19 above is a boxplot detailing the distribution of the PEDQL psychosocial scores between parent and child for the total sample. The mean score was 78.9 % with a CI = 75.3; 82.4 and a SD of 18.9. The median was 86.

PedsQL™ Physical score

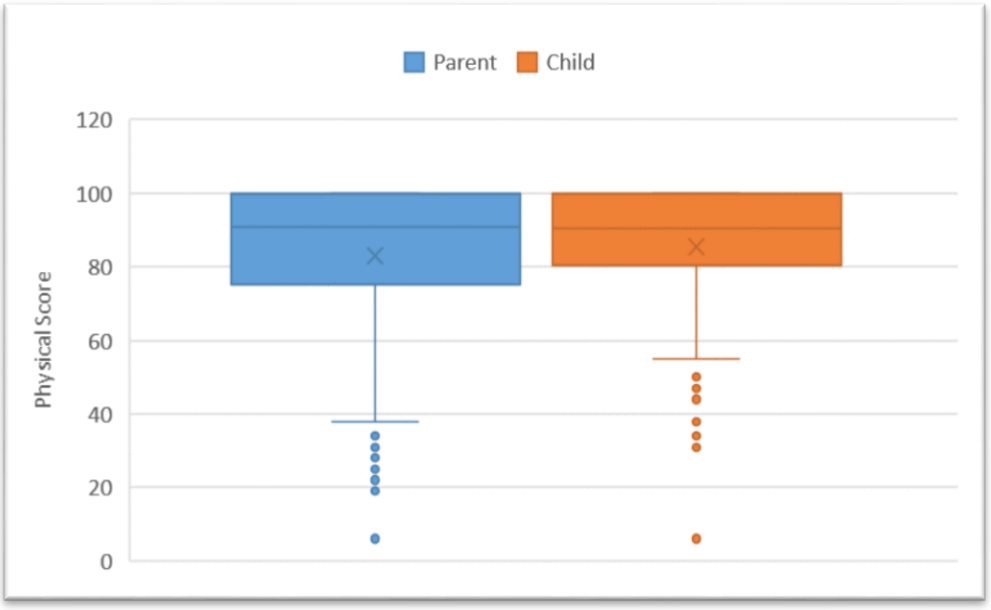


Figure 4.20 Graph comparing parent and child **Physical scores** of the PedsQL™

Figure 4.20 above is a boxplot detailing the distribution of the PEDQL physical scores between parent and child for the total sample. The mean score was 81.4 % with a CI = 76.9; 85.9 and a SD of 23.6. The median was 88.

Comparison of PedsQL™ based on neuropathy status

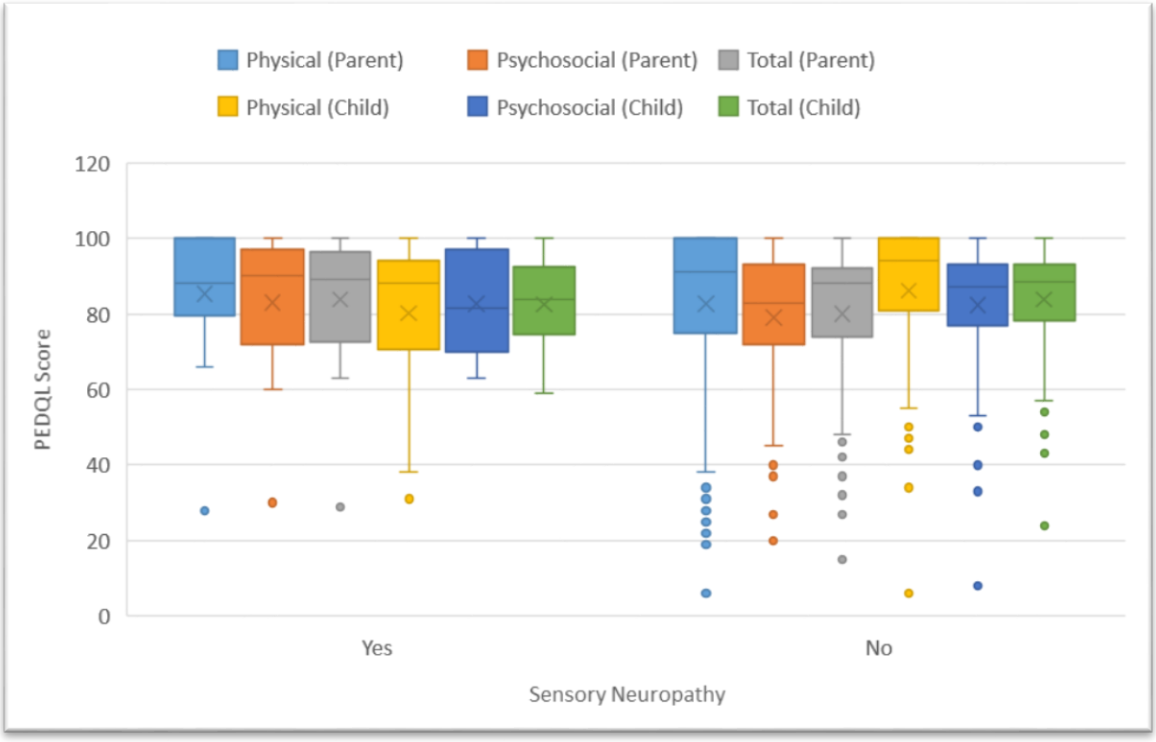


Figure 4.21 Graph of PedsQL™ domain and total scores vs neuropathy status

Figure 4.21 above is a boxplot detailing the distribution between SN groups, as well as the physical, psychosocial, and total PedsQL™ scores. There are no significant differences between the two groups, with all scores being well above 60%.

Table 4.5 below shows the results of comparisons of quality of life scores between the groups for parent and child scores.

Table 4.5Test Statistics[a] to compare PedsQL™ scores and neuropathy status

PedsQL™	Parent			Child		
Domain	Physical	Psychosocial	Total	Physical	Psychosocial	Total
Mann-Whitney U	1024.000	834.000	885.000	618.500	769.000	696.500
Wilcoxon W	7694.000	7504.000	7555.000	754.500	905.000	832.500
Z	-.075	-1.324	-.988	-1.382	-.123	-.715
Asymp. Sig. (2-tailed)	.941	.185	.323	.167	.902	.475

a. Grouping Variable: Neuropathy

Mann-Whitney-U tests were performed to determine if there was any difference between PedsQL™ scores and neuropathy groups. No significant results were found both parent and child choices, suggesting that there was no QoL difference between the two groups. Note: If Sig. is less than 0.05, the result is statistically significant.

QoL vs MABC Zones

Table 4.6 Test Statistics[a,b] comparing the PedsQL™ to the M-ABC zones

PedsQL™	Parent			Child		
Domain	Physical	Psychosocial	Total	Physical	Psychosocial	Total
Chi-Square	1.903	3.646	4.599	.314	.795	.666
df	2	2	2	2	2	2
Asymp. Sig.	.386	.162	.100	.855	.672	.717

a. Kruskal Wallis Test

b. Grouping Variable: MABC.zone

From the above analysis we can see that there was no significant difference in PEDQL scores based on the MABC zones, suggesting that M-ABC categorization did not affect the QoL of the sample. Note: If Sig. is less than 0.05, the result is statistically significant.

4.9.5 HIV-SN and Motor Development

MABC Manual dexterity domain

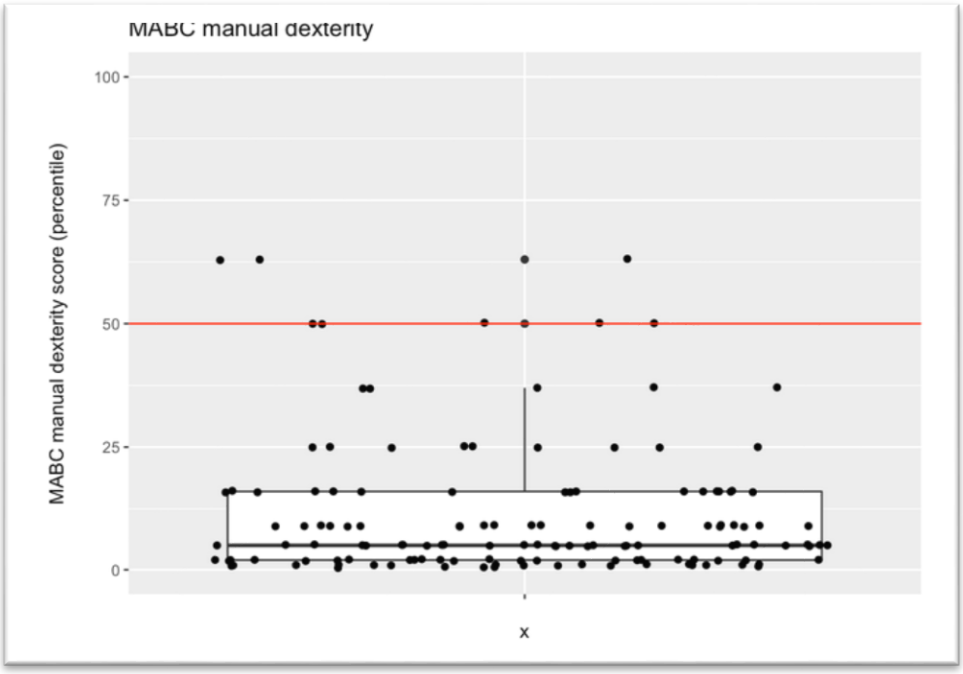


Figure 4.22 Graph showing the MABC manual dexterity percentiles

In figure 4.22 above, the boxplot details the distribution of the MABC manual dexterity percentiles for the total sample (N=135). We can see that most of the participants fall below the 25th percentile.

The first quartile (Q25) = 2

Median = 5

Third quartile (Q75) = 16

The 50th percentile is the same as the median (middle most) value. How we can interpret this is as follows: If someone scored 16 (CI 16; 23) they would score better than 75 percent of the sample. If someone scored 50 (CI 46; 71) they would score better than 95 percent of the sample. (This interpretation is applicable for the sections below as well).

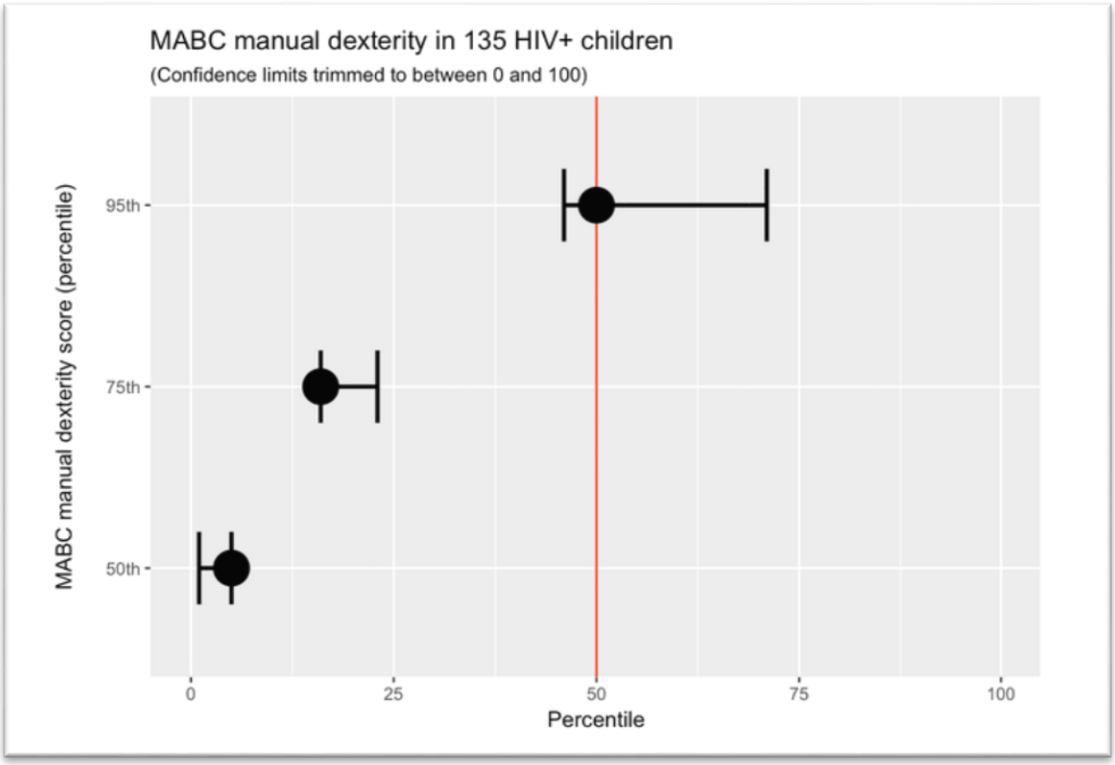


Figure 4.23 Graph showing MABC manual dexterity percentiles

Figure 4.23 above, is a ggplot which illustrates the percentile values and confidence intervals. For the total cohort, many participants scored within the 50th percentile for manual dexterity. Only a small number scored below the 25th percentile.

MABC Balance domain

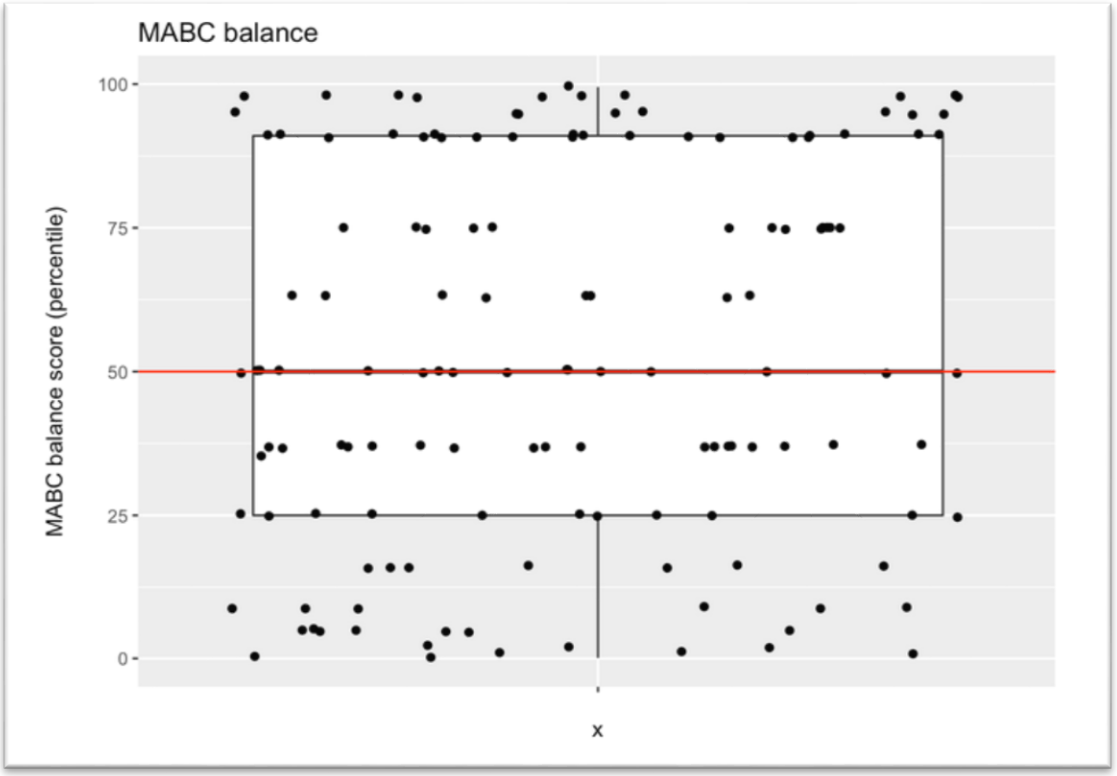


Figure 4.24 Graph showing MABC balance percentiles

Figure 4.24 above is a boxplot that illustrates the distribution of the MABC balance percentile scores for the sample.

The first quartile (Q25) = 25

Median = 50

Third quartile (Q75) = 91

Figure 4.25 is a ggplot which illustrates the percentile values and the confidence intervals.

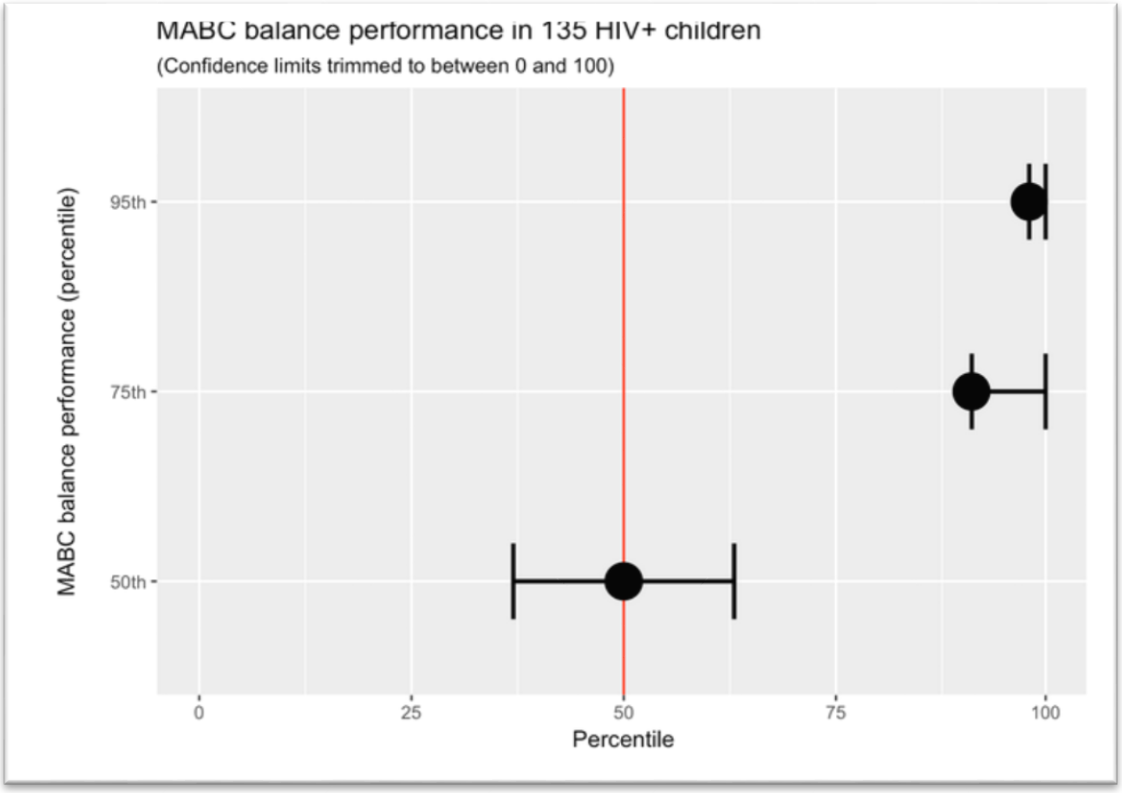


Figure 4.25 Graph showing MABC balance percentiles

As seen in figure 4.25, for balance scores, the largest average percentile was 50, indicating average balance skills. It has an equal range in both the positive and negative directions. However, this range is larger than the range at the 95th percentile. A smaller number fell into the 95th percentile indicating good balance skills

Throwing

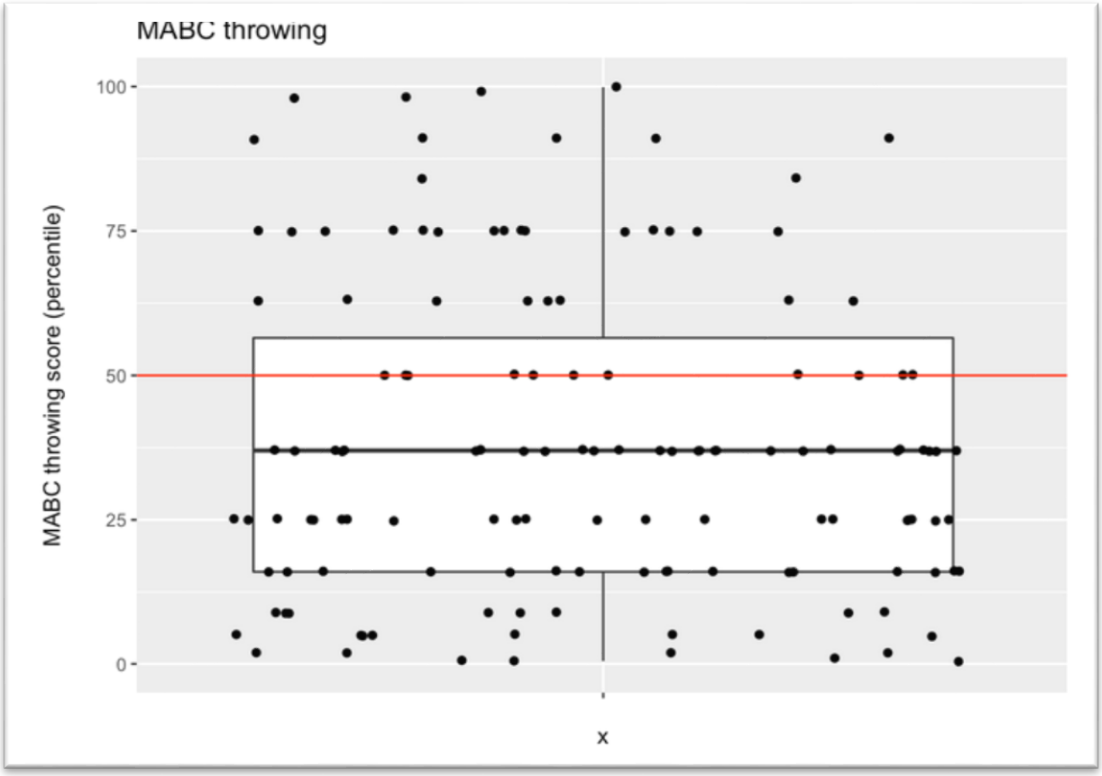


Figure 4.26 Graph showing MABC throwing percentiles

Figure 4.26 above is a boxplot plot illustrating the distribution of the MABC throwing percentile scores for the sample.

The first quartile (Q25) = 16

Median = 37

Third quartile (Q75) = 56.5

Figure 4.27 is a ggplot which illustrates the percentile values and the confidence intervals

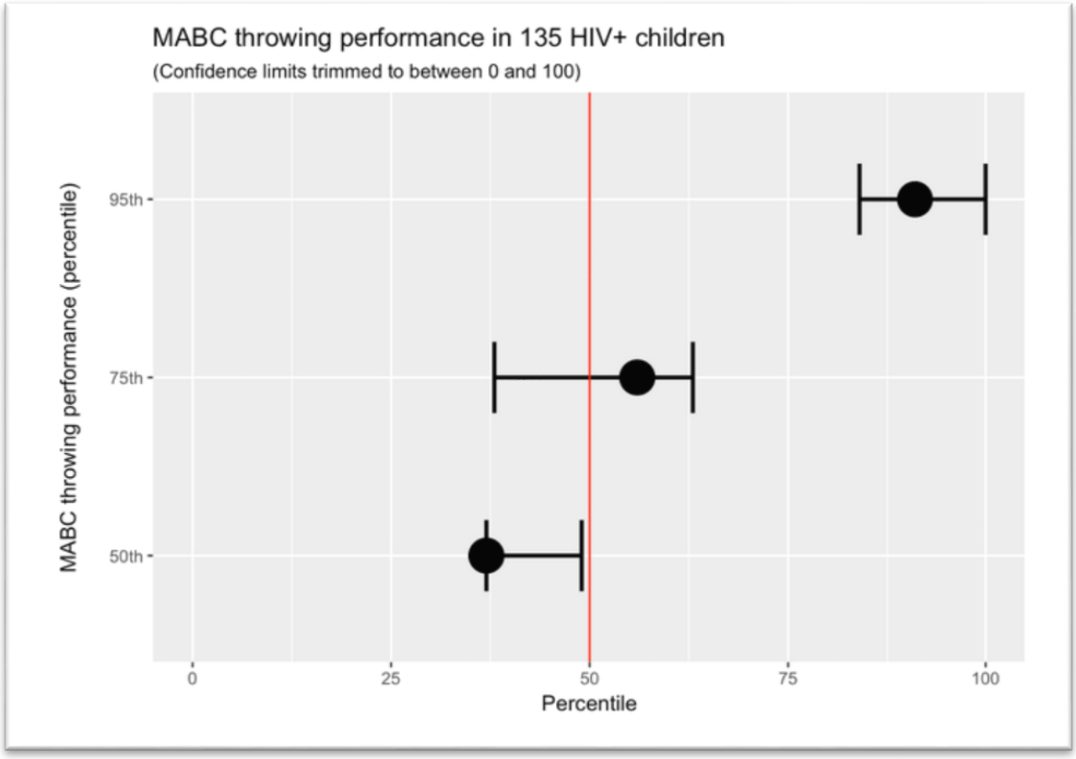


Figure 4.27 Graph showing MABC aiming and catching percentiles

As seen in figure 4.27 above, for aiming and catching most participants fell in the 75th percentile within a large range but most tending towards the lower scores. Those who scored lower than the 50th percentile tended to range towards the positive.

Overall performance

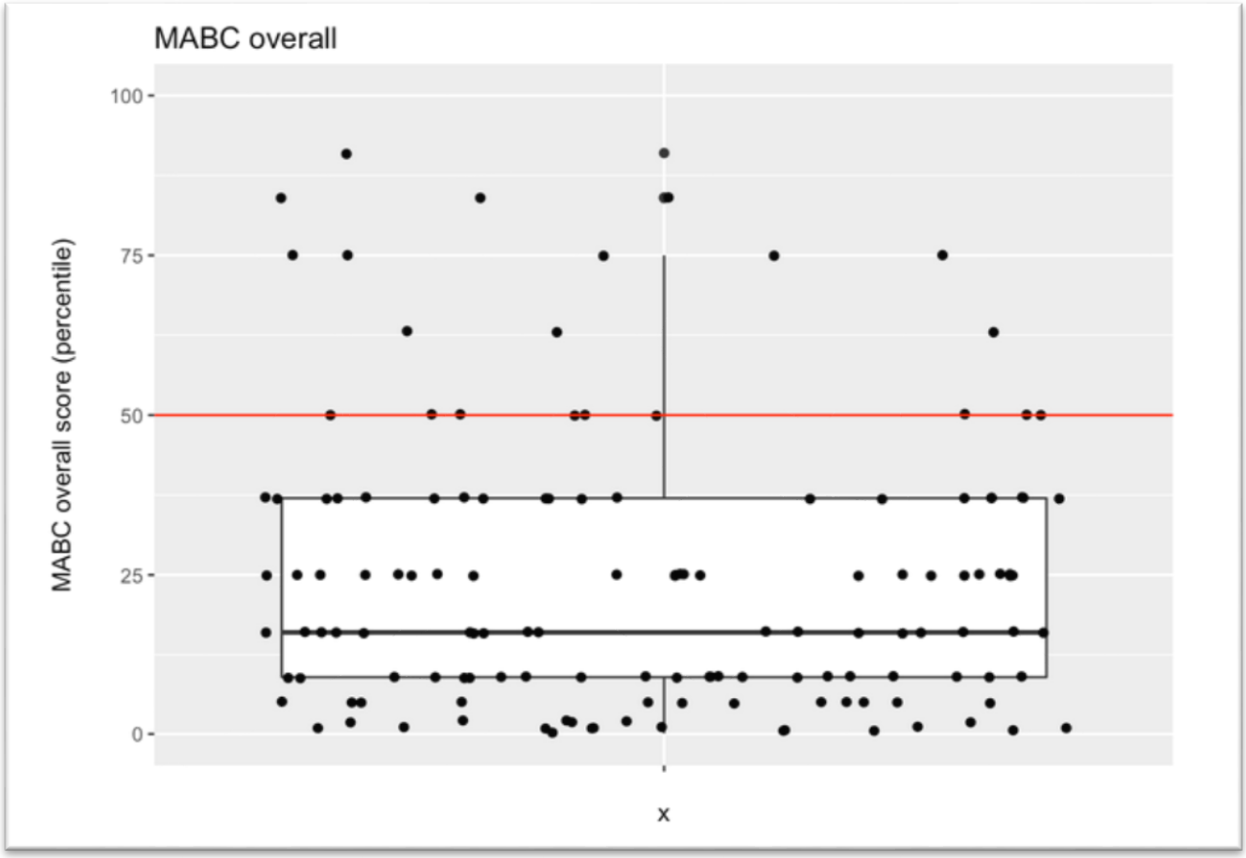


Figure 4.28 Graph showing MABC total percentiles

Figure 4.28 above is a boxplot of the distribution of the overall MABC performance (in percentiles). We can see that, overall, most of the participants are in the lower percentiles.

The first quartile (Q25) = 25

Median = 16

Third quartile (Q75) = 37

Figure 2.29 is a ggplot which illustrates the percentile values + the confidence intervals that were shown in the previous table.

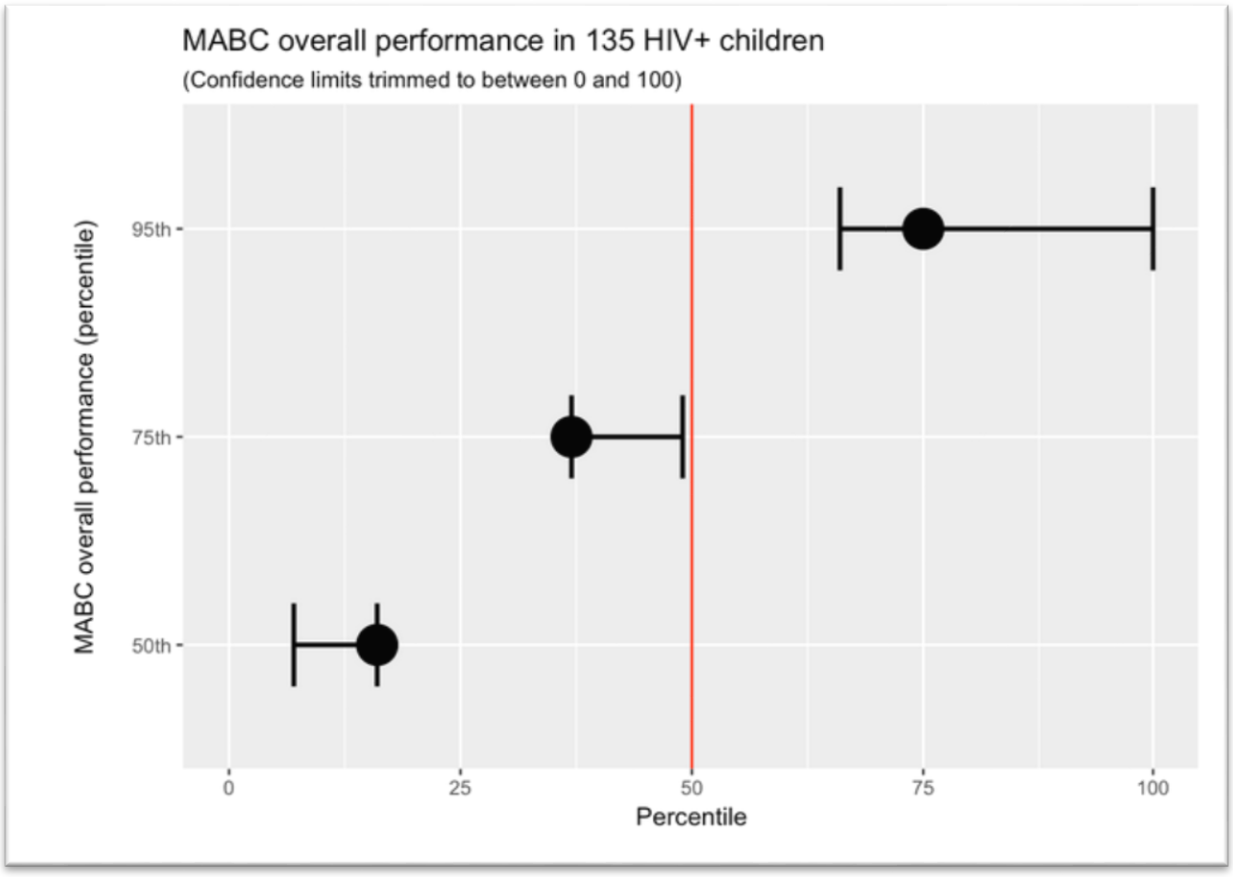


Figure 4.29 Graph showing MABC total percentiles

As seen in figure 4.29 above, large number of the participants fell within the 75th percentile for overall performance but it again showed a large range, tending towards the positive and thus, higher scores. A small number fell below the 25th percentile, tending towards lower overall scores and indicating poorer overall performance.

Traffic Light

The traffic light system provides a colour to distinguish the participants motor function where green shows no motor dysfunction, amber is minor dysfunction, requiring monitoring of function and red requires intervention for gross motor deficits.

As depicted in Figure 4.29, for the total sample, 65 were Green, 39 participants were Amber, and 31 were Red.

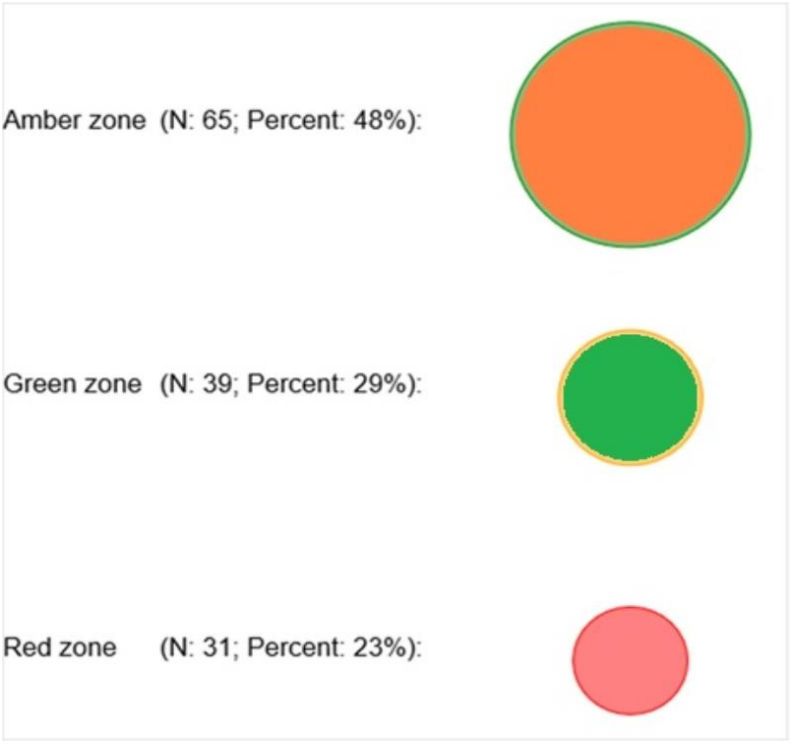


Figure 4.30 Traffic light depiction of the overall M-ABC2 results

Figure 4.30 indicates that just over half (n= 70) of the entire participant cohort (n=135) fell with the ‘at risk’ category (i.e. amber or red zone) which would require either close monitoring or intervention for gross motor dysfunction.

Risk factors for motor dysfunction

Risk for symptomatic SN were not explored because of the small sample size of HIV-SN.

Below is a graphical representation which contrasts the Q25, median, and Q75 percentile scores of the different MABC variables between the sample categories based on neuropathy status.

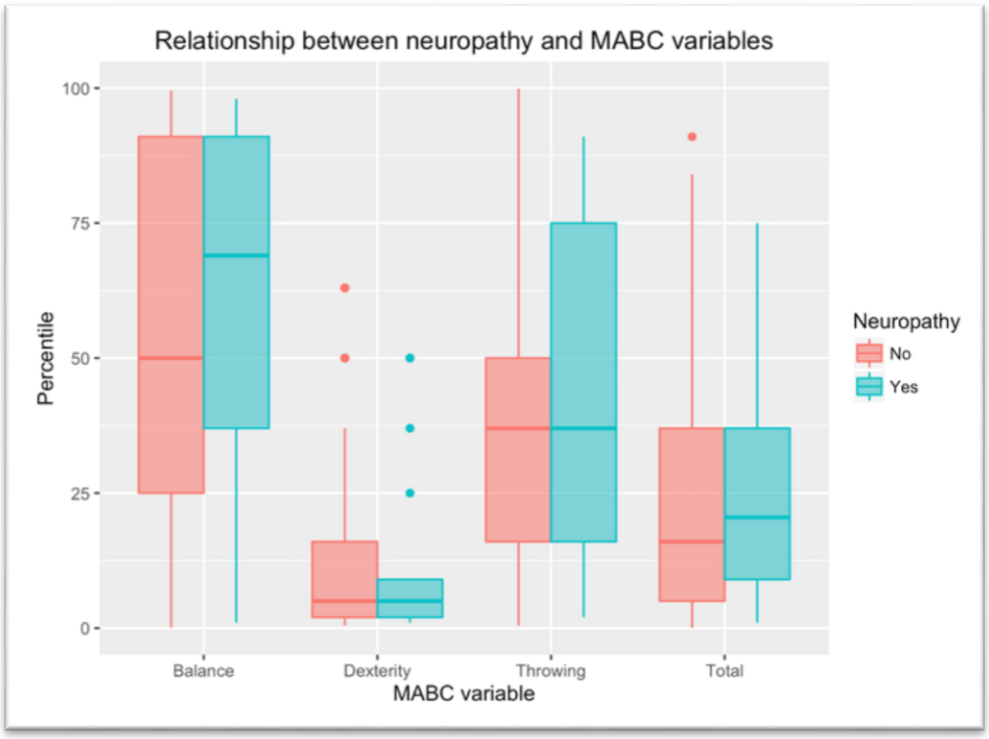


Figure 4.31 Graphical illustration comparing the different percentiles based on neuropathy status.

It can be seen in figure 4.31 that for balance the two groups, the SN negative group scored on average poorer and had a wider range of scores some being as low as the 25th percentile. For dexterity both groups performed poorly, below the 25th percentile. Interestingly, SN positive children performed equally well on the aiming and catching but also had a wide range, tending toward the 75th percentile. For the total score, those with SN had a better average score.

The following sections are testing statistical significance between the groups based on neuropathy status.

MABC Balance domain and neuropathy status

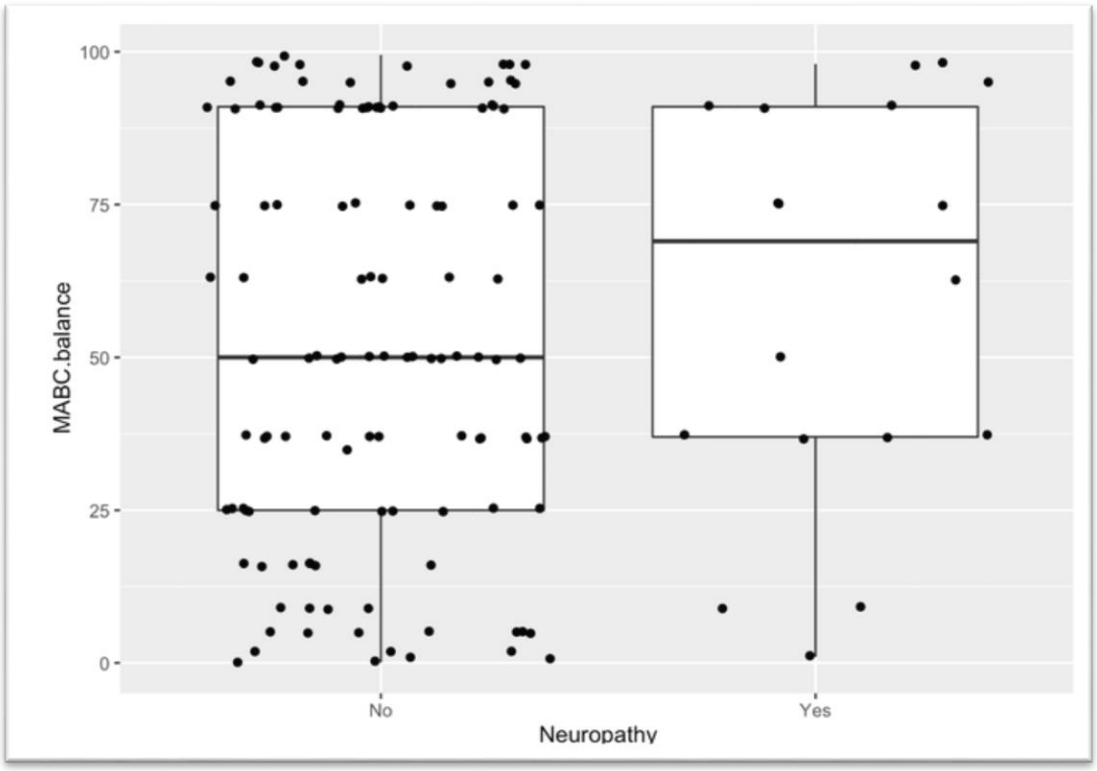


Figure 4.32 Graph of Balance scores vs neuropathy status

In figure 4.32 above is a boxplot looking at the MABC balance score distribution between the two neuropathy groups. From this boxplot we can see that the two groups are not normally distributed, so a non-parametric test was performed. After running the Wilcoxon-Mann-Whitney test, we can conclude that there is no significant difference in balance scores between the participants (Z = -0.81008, p-value = 0.422; CI = -25; 7).

MABC Dexterity domain and neuropathy status

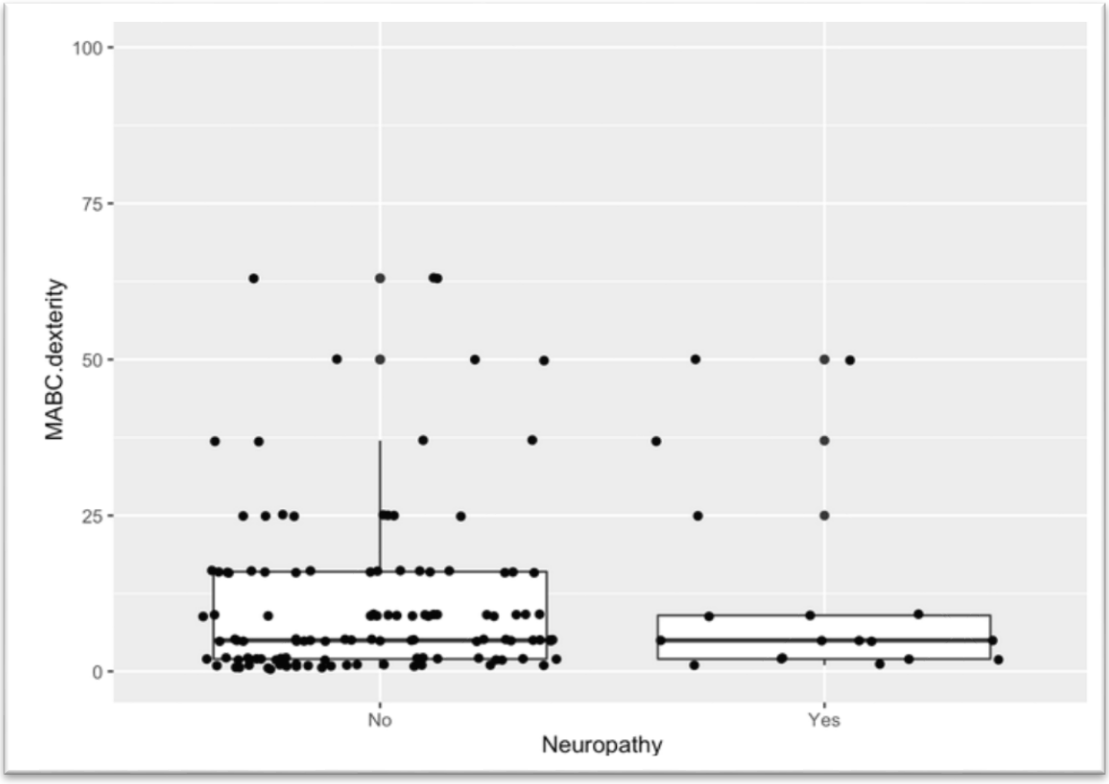


Figure 4.33 Graph of Manual dexterity scores vs neuropathy status

In figure 4.33 above is a boxplot looking at the MABC dexterity score distribution between the two neuropathy groups. From this boxplot we can see that the two groups are not normally distributed, so a non-parametric test was performed. After running the Wilcoxon-Mann-Whitney test, we can conclude that there is no significant difference in dexterity scores between the two groups (Z = 0.0032753, p-value = 0.9985; CI = -3; 4).

MABC Aiming and catching domain and neuropathy status

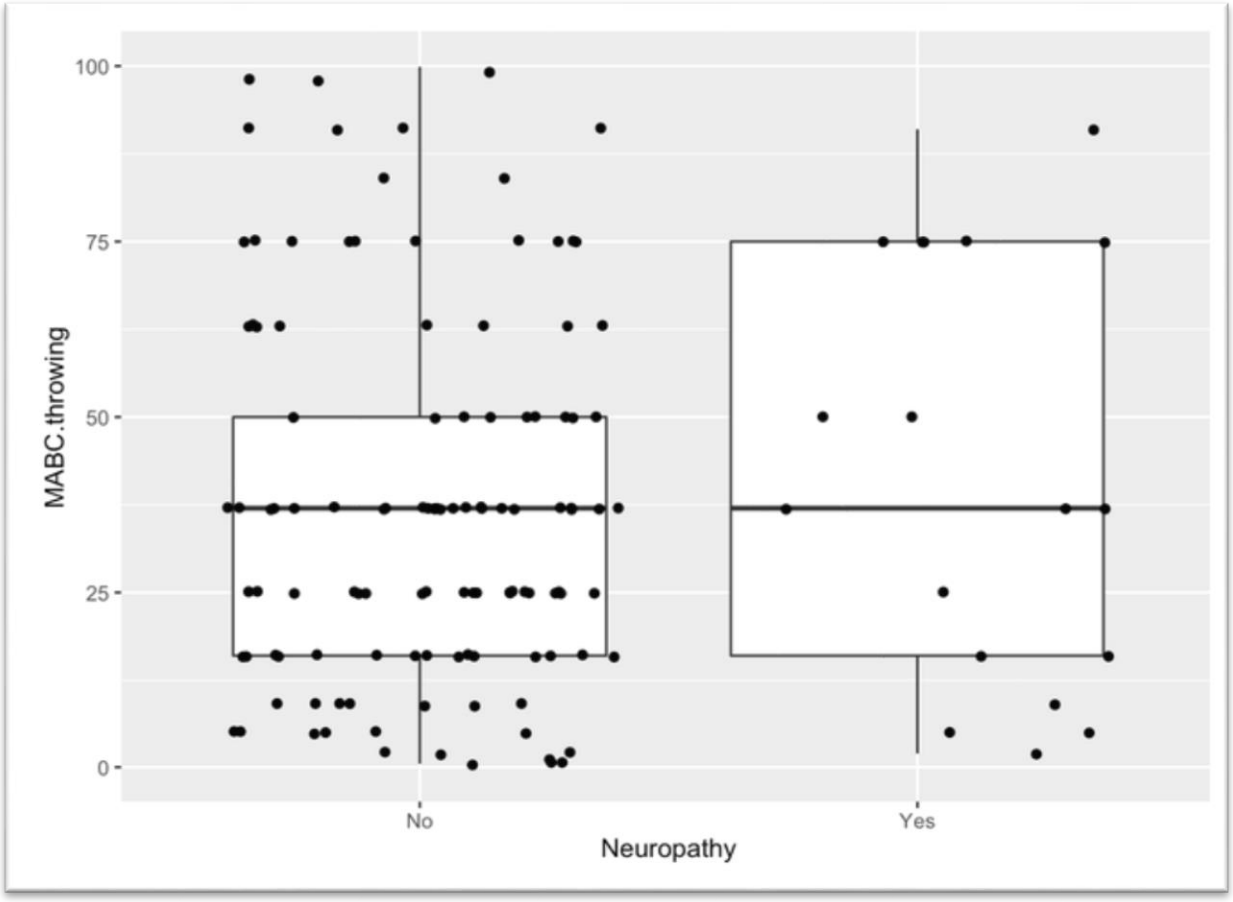


Figure 4.34 Graph of Aiming and catching scores vs neuropathy status

In figure 4.34 above is a boxplot looking at the MABC throwing score distribution between the two neuropathy groups. From this boxplot we can see that the two groups are not normally distributed, so a non-parametric test was performed. After running the Wilcoxon-Mann-Whitney test, we can conclude that there is no significant difference in throwing scores between the two groups (Z = -0.53215, p-value = 0.5986; CI= -21; 11).

MABC Total score and neuropathy status

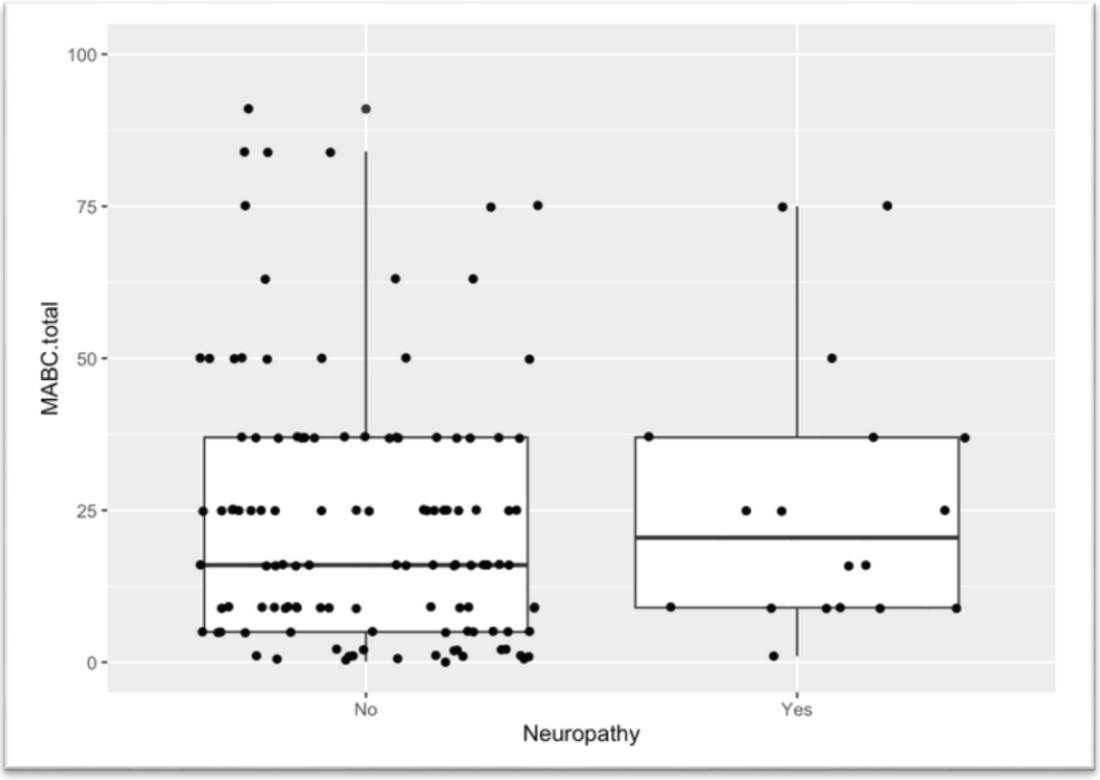


Figure 4.35 Graph of total MABC scores vs neuropathy status

Figure 4.35 above, is a boxplot looking at the MABC total score distribution between the two neuropathy groups. From this boxplot we can see that the two groups are not normally distributed, so a non-parametric test was performed. After running the Wilcoxon-Mann-Whitney test, we can conclude that there is no significant difference in total MABC scores between the two groups (Z = -0.68523, p-value = 0.4974; CI= -11; 7).

Other disease-related factors influence motor development

- No influence of SN on motor function, therefore collapsed across SN groups.
- Assessed the effect of weight for age, CD4 T-cell count, and viral load
- Effect of each ‘Other’ variable assessed against all MABC variables.
- If bivariate plot (continuous variables) showed no relationship, no correlation performed.

When comparing weight for age z-scores with the MABC balance, manual dexterity, aiming and catching and total scores respectively, there was no clear relationship between the variables.

When comparing CD4 counts with the MABC balance, manual dexterity, aiming and catching and total scores respectively, there was no clear relationship between the variables.

When comparing viral load with the MABC balance, manual dexterity, aiming and catching and total scores respectively, there was no clear relationship between the variables.

4.10 Summary

Statistical analysis revealed a frequency rate of 25.9% for HIV sensory neuropathy in a population of 135 children living with HIV. The most common presenting symptom was pain. No associated risk factors (age, sex, medication) for developing the condition could be isolated. Upon further statistical analysis it was found that there was also no correlation between quality of life and neuropathy status figure 4.19 and the same was established for gross motor development and neuropathy status (figure 4.29), even though manual dexterity was most severely affected, as depicted in figure 4.20. Most participants scored well in the balance domain which improved their total scores.

The frequency of HIV-SN was high in this paediatric population, was mostly symptomatic but not painful, and was largely undiagnosed prior to this assessment. Prior to this study, the frequency of HIV-SN in children was relatively unknown. A frequency rate of 25.9% is clinically important as the children are not routinely assessed. Using a standardised test that takes less than five minutes to conduct the assessment greatly assisted in identifying these individuals, thus ensuring that timely intervention can be done. A study with a larger population to determine the risk factors associated with the frequency of HIV-SN in children would contribute to the holistic approach at the management and prevention of HIV-SN in children.

Larger studies are needed to establish the true prevalence of HIS-SN in this population therefore the results of the present study cannot be generalised to the wider paediatric population living with HIV. Possible threats to external validity of this study are:

A) Selection bias as the children are attending a clinic where they receive counselling and are compensated for attending
B) 'Real world' versus 'experimental world' where resources (both human, time and funding) continues to be an issue.

There are no threats to internal validity as no manipulation of variables took place.

With HIV-SN having such high frequency in this population, the next step was taken to develop an intervention to manage the condition that will be tested in the final phase of the study.

Chapter 5: Methodology and Results Study Two: Literature Review and Delphi Study

Introduction: This chapter gives an outline of research methods that were followed in study two. It provides information on the methods for literature searching, the process of article inclusion and the methods used to assess the literature. A summary of the findings is provided at the end of the section.

In part two it provides information on the participants, that is, the criteria for inclusion in the study, who the participants were and how they were sampled. The researcher describes the research design that was chosen for this study and the reasons for this choice. The instrument that was used for data collection is also described and the procedures that were followed to carry out this study are included. The researcher also discusses the methods used to analyse the data. Lastly, the ethical issues that were followed in the process are also discussed.

5.1 Objective/s

Study two addressed objective six: To develop a physiotherapy intervention programme to manage SN using a questionnaire and a Delphi survey.

This chapter will assist in determining the current management of HIV-SN according to the literature. The second part of the chapter reports on the Delphi survey which was used to compile the intervention programme.

5.2 Study Design

5.2.1 Part one: Literature Review

A review was conducted of both local and international literature to address the research objective. The articles reviewed were systematically collected and reported in a narrative form. The information was collated using a standardised template (Appendix 14).

The aim for this phase was:

- To determine what medical and/ or physiotherapy technique(s) are used to prevent or treat HIV-SN

5.2.1.1 Inclusion criteria

a) Written in English only.
b) All articles until September 2015 (end of review).
c) International (outside of SA) and national (South African).
d) All types of peripheral/sensory neuropathy management.
e) Relevant trials to compare physiotherapy intervention(s) with no intervention or with each other.
f) Interventions need to be administered more than once to the participants.
g) Physiotherapy intervention(s) to prevent or treat peripheral neuropathy.
h) Alternative, non-medical interventions used to manage peripheral neuropathy and its related complications.

5.2.1.2 Exclusion criteria

a) Pilot studies
b) Proposals

5.2.3 Data collection process and data management

The articles selected were then critiqued according to Population, Intervention, Comparison, Outcome, Type of question being asked (therapy, diagnosis, prognosis, harm, etc.) and the best Type of study design for that particular question (PICOTT) (Table 5.1) to improve the relevance of search results (Schardt *et al.*, 2007)

Table 5.1 PICOTT criteria for the management of HIV-SN

Headings	Criteria
Population	All patients with peripheral neuropathy
Intervention	• Physiotherapy intervention • Physiotherapy intervention for SN • Physiotherapy intervention for SN pain • Intervention for SN • Alternative intervention for SN • Exercise intervention for SN
Comparison	• No intervention • Education • Another intervention
Outcome	Self-reported and/or measurable outcome in: • Quality of life • Balance • Pain • General movement • Sensation
Type of Question	• Does Physiotherapy intervention improve the patient's condition? • Does Exercise intervention improve the patient's condition? • Does Physiotherapy intervention improve the patient's Quality of life?
Types of Studies	• Randomised controlled trails • Cohort Studies • Quasi –experimental studies • Case studies • Case reports

The databases used to conduct the search were MEDLINE, CINAHL, Cochrane library, and PEDro, as suggested by van de Wees and Mead (2004). The Science Direct database was also used to broaden the search, while grey literature was searched using PubMed, online conference proceedings from the World Confederation for Physical Therapy (WCPT), and the use of the snowball method where the references of the articles selected for review were searched (Giustin, 2012) as well as electronic citations tracking. The use of the CINAHL database was also considered as searching for grey literature (Giustin, 2012).

The review included articles that were published in English prior to and including June 2015 (end of literature review search), articles being identified based on the research questions. Search terms

were selected based on the research question, and Boolean words as well as truncation were used as part of the search strategy. Keywords used were: HIV; peripheral neuropathy; sensory neuropathy; p?diatrics; management. The strategy is depicted in Figure 5.1 below:

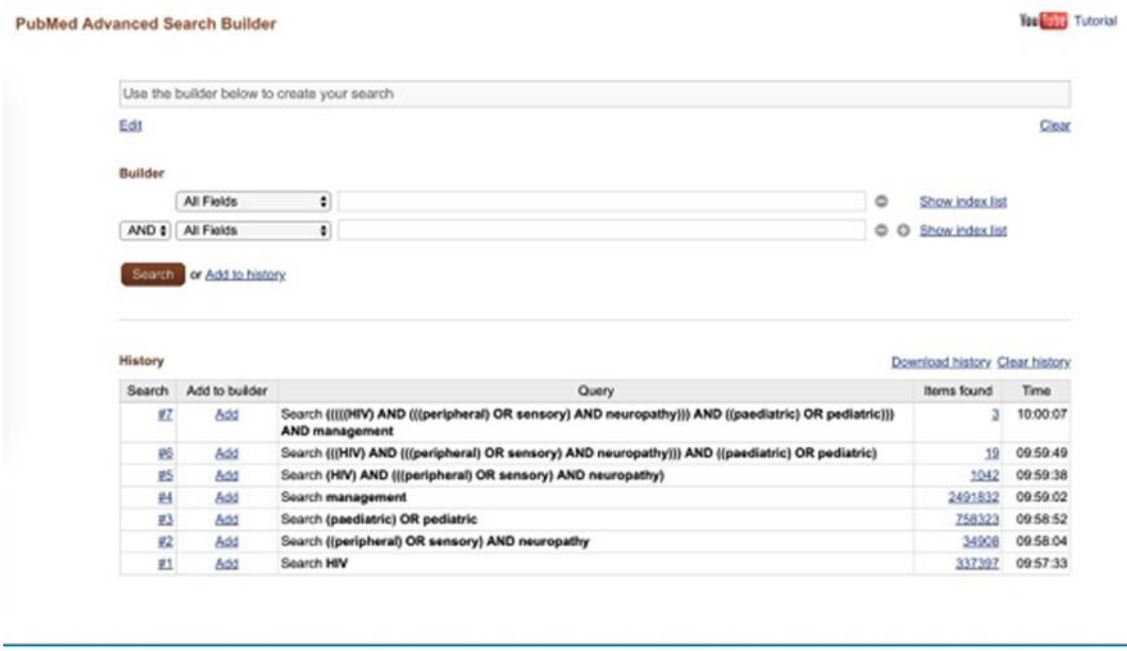


Figure 5.1 Example of literature search using PubMed

For paediatric HIV there were only two hits; one article only focused on assessment and the second was an historical review. The keywords HIV sensory neuropathy management yielded 47 hits. Of these 12 titles were eliminated for the following reasons:

- Two studies investigated ocular neuropathy
- Two studies focused on neurocognitive behaviour
- Five articles used cannabis as an intervention
- Two studies were done on animals
- One article investigated bladder dysfunction

The articles selected were critiqued according to the PICOTT criteria (Table 5.1). While RCT's remains the most rigorous method to evaluate interventions (Lindegger, 2009), the paucity of research in this field led the researcher to include cohort study designs, quasi-experimental study

designs, case studies and case reports. The search was conducted independently by the researcher and a research assistant, with no discrepancies being noted in the exclusion of articles. Figure 5.1- represents the screening process for the paediatric HIV and HIV sensory neuropathy using an adapted version of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram (Liberati *et al.*, 2009). A total of 23 articles were suitable for review.

5.2.4 Data processing

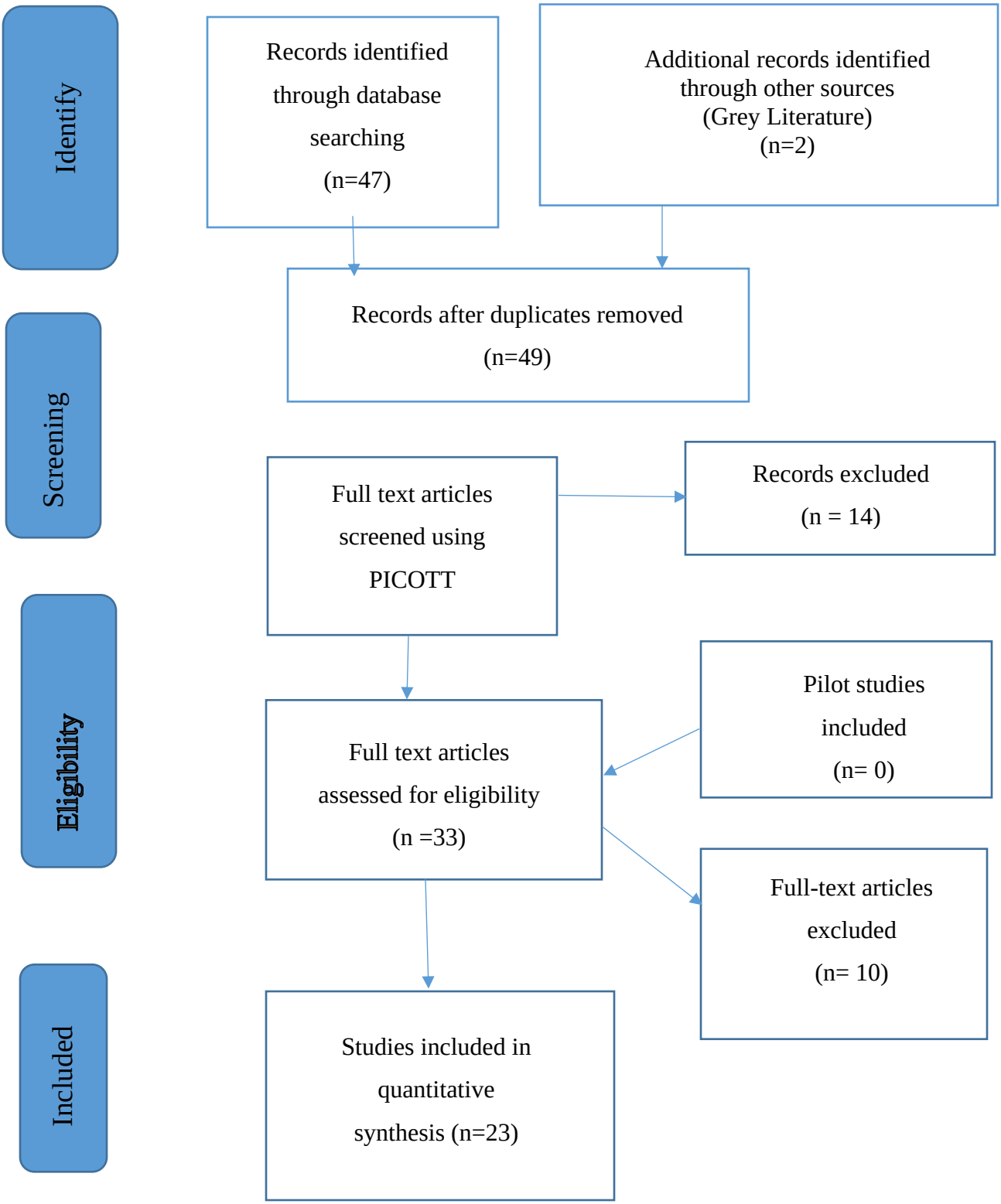


Figure 5.2 PRISMA flow diagram for article retrieval for HIV sensory neuropathy

The selected studies that fulfilled the requirements were then scored for methodological quality by two independent reviewers, using the PEDro scale for randomised controlled trials (Verhagen et al., 1998). The PEDro scale is a reliable tool and provides a score out of 10 (Maher, Sherrington, Herbert, Moseley & Elkins, 2003), while studies that attain a PEDro score of 4 or less are considered "poor quality", those that score five or six are considered "moderate quality" and studies scoring 7 or greater are considered "high quality" in terms of study methods and susceptibility to bias (Harvey, Herbert & Crosbie, 2002). Discrepancies between the scoring were discussed verbally until consensus was reached between the two reviewers, with the scoring being adjusted accordingly (Table 5.2). The studies selected were of varying methodological quality from which the data were then extracted and is presented in Appendix 14.

Table 5.2: Example of how scoring of articles using the PEDro scale was done

Scoring criteria	Included articles*	
	Mueller et al (USA)	Quigley et al (USA)
Score /10	10	10
Eligibility criteria specified**	Y	Y
Randomization	Y	Y
Allocation concealed	Y	Y
Baseline similarity	Y	Y
Blinding of subjects	Y	N
Blinding of researchers	Y	Y
Blinding of assessors	Y	Y
>85% of subjects were measured for at least one key outcome	Y	Y
Outcomes measured for Treatment or control groups were received as allocated	Y	Y
Between group statistical comparison	Y	Y
Point measures and measures of variability for at least one outcome	Y	Y

* Scored as per the PEDro scale Yes = Y; No = N

** Not considered as part of the scoring.

A data extraction sheet was designed to identify relevant information in the study, such as author, date of publication, country, population (sample size, age and gender), the type of interventions and outcome measures used, the results, and the conclusions from the studies; this is represented in Appendix 14

5.2.5 Summary of literature review

The Educational Resources Information Centre (1982, p. 85) defines a literature review as an "information analysis and synthesis, focusing on findings and not simply bibliographic citations, summarizing the substance of the literature and drawing conclusions from it". This type of research is important in assist practitioners in making informed clinical decisions (de Vet, 1997).

The purpose of the literature review was to examine research about the management strategies for HIV-SN or sensory neuropathy irrespective of the cause. Following the process, very few randomised controlled trials were available to inform the review. Literature reviews of trials provided more information. The most common intervention strategies identified were exercise (White, Pritchard and Turner-Stokes, 2004; Katherine I. Ites *et al.*, 2011; Salsabili *et al.*, 2011; Song *et al.*, 2011; Mohammad Akbari *et al.*, 2012; Sartor *et al.*, 2012, 2014; Knauf and Koltyn, 2014; Quigley *et al.*, 2014; Streckmann *et al.*, 2014). Less common articles investigated electrical modalities (K Pieber, Herceg and Paternostro-Sluga, 2010; Smith *et al.*, 2010; V. Bril *et al.*, 2011) and physical techniques (Gale, 2003). These findings were compared to strategies identified in Round one of the Delphi survey and used to design the questionnaire for Round two. The Delphi survey is discussed further in the next section.

The literature review was to identify treatment techniques for managing neuropathies irrespective of aetiology. The systematic review yielded 23 articles that could be considered for review. Articles included varying strategies of intervention and ranged from case studies, randomised controlled trials to literature reviews. Nine articles showed that exercise could be used to improve symptoms associated with neuropathy. Some only focused on pharmacotherapeutic agents which are not relevant in the current setting. Of importance to note is that all the identified studies were done for adult patients and literature for the management of neuropathy in children is scarce, highlighting the importance of the current study.

5.3 Part two: Delphi survey

The Delphi method is a well-recognised research tool for solving problems in the health care setting (Fink, Kosecoff, Chassin & Brook, 1991). Specific to this research, the Delphi technique was selected to address the incomplete state of knowledge in this area (Delbecq, van de Ven & Gustason, 1975) though the pooling of expert opinion in this area that would not have been possible because of the geographical spread of the experts (Hsu & Sandford, 2007). The Delphi technique comprises several rounds, with each round informing the next. The initial round begins with an open-ended questionnaire that serves to extract specific information about the desired field from the participants (Hsu & Sandford, 2007). The researcher then collates the information into a structured questionnaire for the subsequent rounds, where the participants are requested to rate or rank the statement, usually using the Likert Scale (Hsu & Sandford, 2007; Stitt-Gohdes & Crews, 2004). Two rounds were used to collect the information for this study as two or three rounds are preferred for a Delphi (Green, Jones, Hughes & Williams, 1999; Proctor & Hunt 1994), because too many rounds may cause sample fatigue and tax resources (Schmidt, 1997).

The Delphi method provides an opportunity for experts to share opinions, knowledge and experience anonymously on a topic. It provides an opportunity to see how their evaluation and experience of the issue aligns with others. Delphi studies have the potential to provide valuable information and is often utilised in clinical research.

5.3.1 Study population

Literature has suggested that a panel of 10 – 15 participants is sufficient to obtain consensus in a homogeneous group of participants (Hsu & Sandford, 2007). The researcher purposively selected 20 physiotherapists who would be considered ‘experts’ in the field. The selected group was initially approached telephonically (n=6), via appointment (n=3) or via email (n=11). Only eight physiotherapists in total responded and agreed to be panel members.

5.3.2 Inclusion criteria

a) Experts in the field of paediatric physiotherapy

5.3.3 Exclusion criteria

a) Physiotherapists not managing children

5.3.4 Data collection process and data management

The Delphi consisted of two rounds, which were conducted in several steps, with the information from round one used as a basis for round two. Figure 5.2 indicates the flow of the Delphi study.

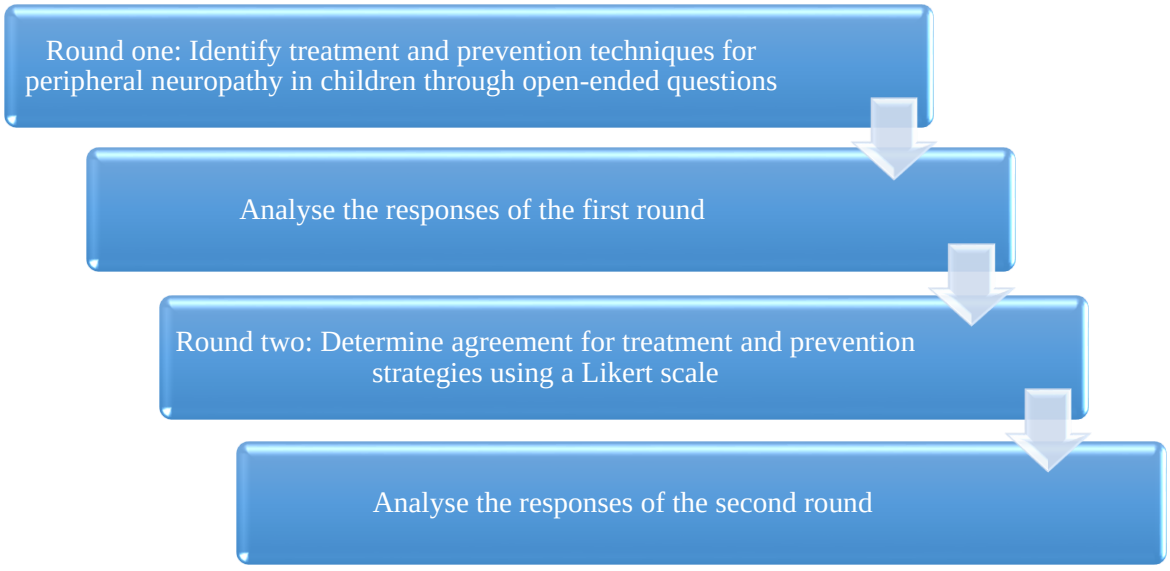


Figure 5.3 Flow diagram of the steps taken in the Delphi survey

The process will be explained below:

a. <u>Round one:</u>

The first round sought to determine treatment techniques or strategies related to treating or preventing complications identified in study one using an open-ended questionnaire. The aim of this round was to obtain a list of the common treatment techniques or strategies identified and then rank them in round two. Questions used in this round was derived from the findings (signs and symptoms) of study one. For each finding, the participant was asked to give a recommended treatment and prevention strategy choice and to state whether the decision was made based on clinical experience or research evidence.

The questionnaire was piloted for content and face validity by four physiotherapists (academic physiotherapists n=2; public physiotherapists n=2) who were not included in the study. Feedback received included minimal grammatical corrections, which were amended on the questionnaire. No other comments were made.

A purposive sample of twenty physiotherapists were selected, based on clinical experience and post-graduate qualification in the field of paediatric physiotherapy. The first questionnaire was designed and created on Google Drive™ using the results of Study one of the research project and included a section for basic demographics of participants. The survey comprised a mixture of multiple choice questions and open-ended questions. The questions took ≤ 30 minutes to complete and were divided into two sections:

- Section A: demographics (multiple choice) and qualification (open-ended)
- Section B: Complications associated with HIV and ARV's in children (open-ended) he second section asked for specific intervention and prevention strategies in the management of the paediatric patient presenting with peripheral neuropathy.

Since this is such a novel area of intervention, the questions were posed such that strategies could be mentioned irrespective of the cause of the neuropathy.

The survey commenced with the researcher sending out an electronic invitation with the study details, to participants. If the recipient selected to participate in the survey, they were requested to provide online consent within the survey created on Google Drive™ (Appendix 15). Participants were only linked to the survey once individual online consent was provided.

This round lasted for four weeks, during which the researcher sent out five reminders. The responses were collated and presented in round two for ranking.

b. <u>Round two</u>

The second phase used a Delphi format and the same participants of the first questionnaire participated in the second round. The collated information from round one was presented to the panel (round two) using a Likert scale (Hartley, 2014) to measure the level of agreement about which management strategy the panel were most likely to use and why (Appendix 16). The complications found in study one of the research were presented verbatim as per round one, with treatment and modality options for the panel to select.

The Likert scale used in this study comprised of: 1 representing 'very unlikely', 2 representing 'unlikely', 3 representing 'neutral', 4 representing 'likely', and 5 representing 'very likely'. A balanced scale with a 'midpoint' was preferred with equal favourable and

unfavourable responses (Friedman & Amoo, 1999). The midpoint of the scale usually 'neutral' is important as its absence could result in distortion of the results (Garland, 1991). The scale items were rated from low to high with the negative items on the left and positive on the right (Hartley, 2014). In this round, the panel members were exposed to the other panel members' input and could select how 'likely' they were to use that specific modality to treat the complication presented, while still retaining anonymity (Hsu & Sandford, 2007).

5.3.5 Data analysis of Delphi results

For Delphi round 1, the researcher collated the responses (modalities and treatment techniques) by grouping them quantitatively. In Delphi round 2 the raw data were captured and cleaned on Excel. All data were exported to R (v3.3.3) R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria (URL http://www.R-project.org) for analysis.

Analysis was done using descriptive statistics (Holey et al., 2007). Although all central tendencies are favoured when interpreting the results, the use of the median (Jacobs, 1996) and mode (Ludwig, 1994) are generally preferred. The reasoning is simply that the median "best reflects the convergence of opinion" compared to the mean, whereas the mode is useful when there is convergence at two or more points, as the mean and median could be misleading in this situation (Ludwig, 1994). Percentages, mean, median and mode were used to determine consensus among the panellists. The percentage used was the level of agreement, which was determined by adding the 'likely' and 'very likely' scores. Percentage of agreement was set at 80% despite the dearth of literature on the topic. Convergence and the level of agreement was used to determine how favoured the treatment option was.

5.4 Summary of Delphi survey results

Twenty paediatric physiotherapists from across South Africa were invited to participate in the Delphi survey. Of these, only eight participated in both rounds of the survey.

The socio-demographic and education profile of the survey participants are given in the table below:

5.4.1 Round one

Section 1 of the questionnaire required that participants provide their demographic details, the results are provided in the table below:

Table 5.3 Sociodemographic details of survey participants (n=8)

Socio-demographic information	Categories	Total n=8 (%)
Age	<30 years	1 (12,5)
	30 – 40 years	7 (87,5)
	41 - 50 years	0 (0)
	>50 years	0 (0)
Residing province	Gauteng	5 (62,5)
	Limpopo	1 (12,5)
	Western Cape	2 (25)
Postgraduate qualification in paediatrics	Yes	2 (25)
	No	6 (75)
Postgraduate courses in paediatrics	Yes	8 (100)
	No	0 (0)
Years of experience	1 – 5 years	1 (12,5)
	6 – 10 years	6 (75)
	11 – 15 years	1 (12,5)
	16 – 20 years	0 (0)
	>20 years	0 (0)

In table 5.3 it is shown that most of the participants reside in Gauteng and have between six and ten years' experience in the field of paediatric physiotherapy. All participants had undertaken postgraduate paediatrics courses, but only two had a formal postgraduate qualification.

General management of HIV–SN

Figure 5.4 below provides details of specific intervention strategies for managing HIV-SN.

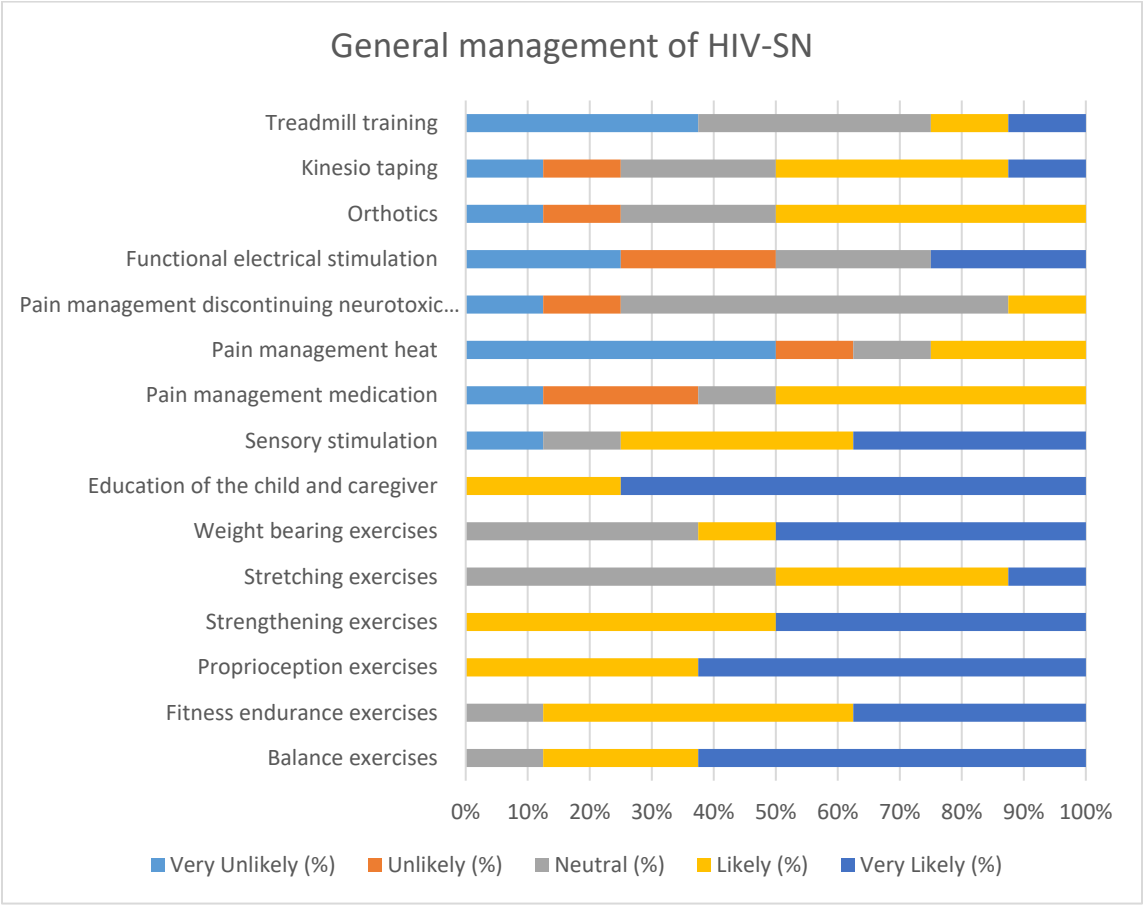


Figure 5.4 Management strategies for HIV-SN

In figure 5.4 it shows that most participants favoured the use of different exercise strategies for the management of HIV-SN, with strengthening and proprioceptive exercise reaching 100% consensus for inclusion.

Prevention strategies for HIV-SN

Figure 5.5 below provides details of specific strategies for preventing HIV-SN.

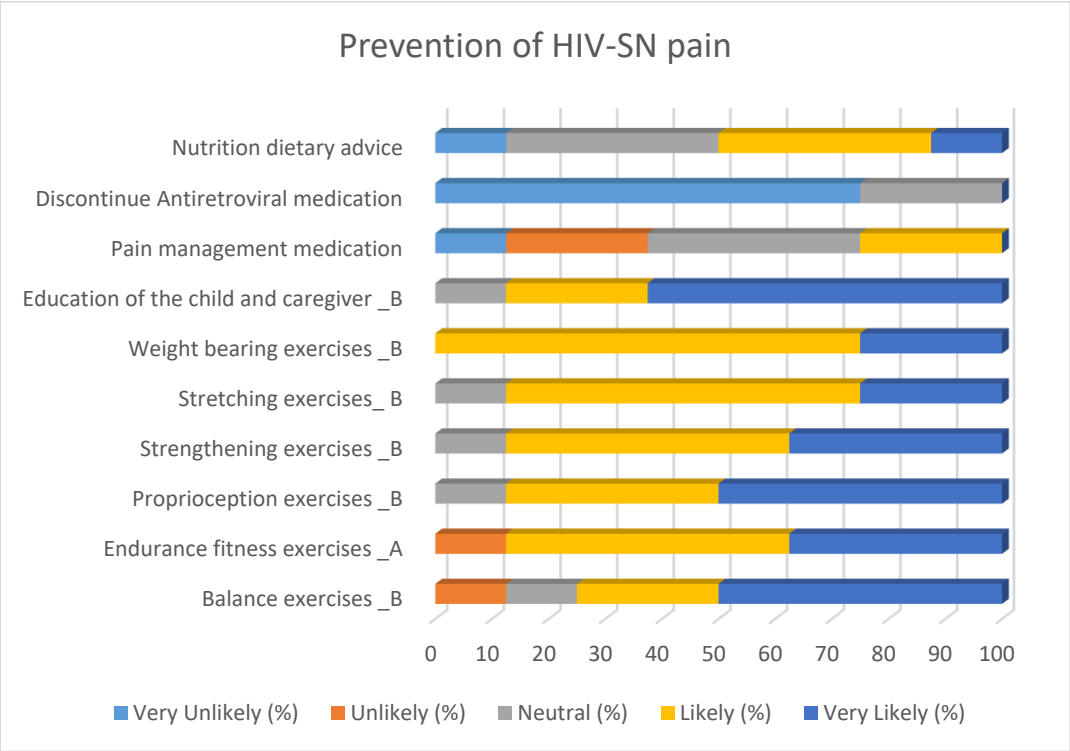


Figure 5.5 Prevention strategies for HIV-SN

Figure 5.5 above shows that most participants favoured the use of different exercise strategies for the prevention of HIV-SN, with weight-bearing exercise reaching 100% consensus for inclusion in the programme.

HIV-SN pain management

Figure 5.6 below provides details of specific intervention strategies for managing HIV-SN related pain.

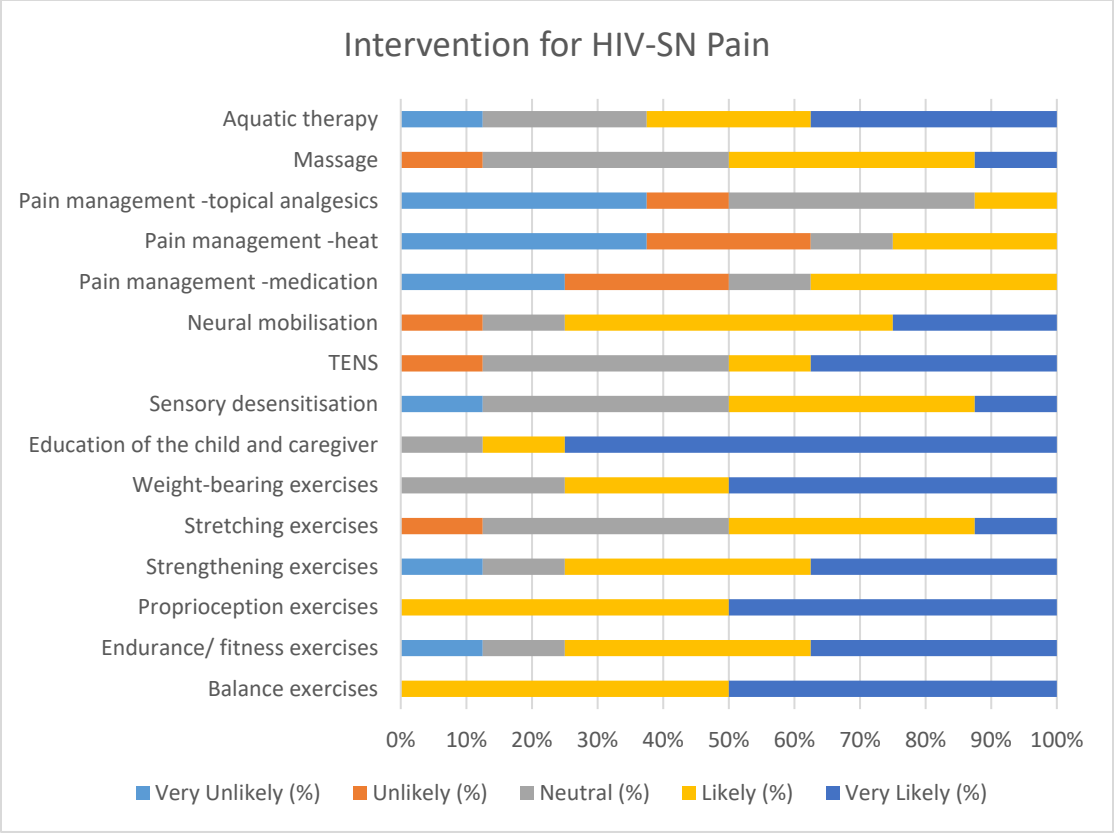


Figure 5.6 Intervention strategies for HIV-SN pain

In figure 5.6 above, it shows that for pain-related symptoms the most common strategies are education of the child and caregiver as well as exercise with proprioception and balance exercises reaching the highest level of consensus at 100%.

Figure 5.7 below provides details of specific prevention strategies for managing HIV-SN related pain

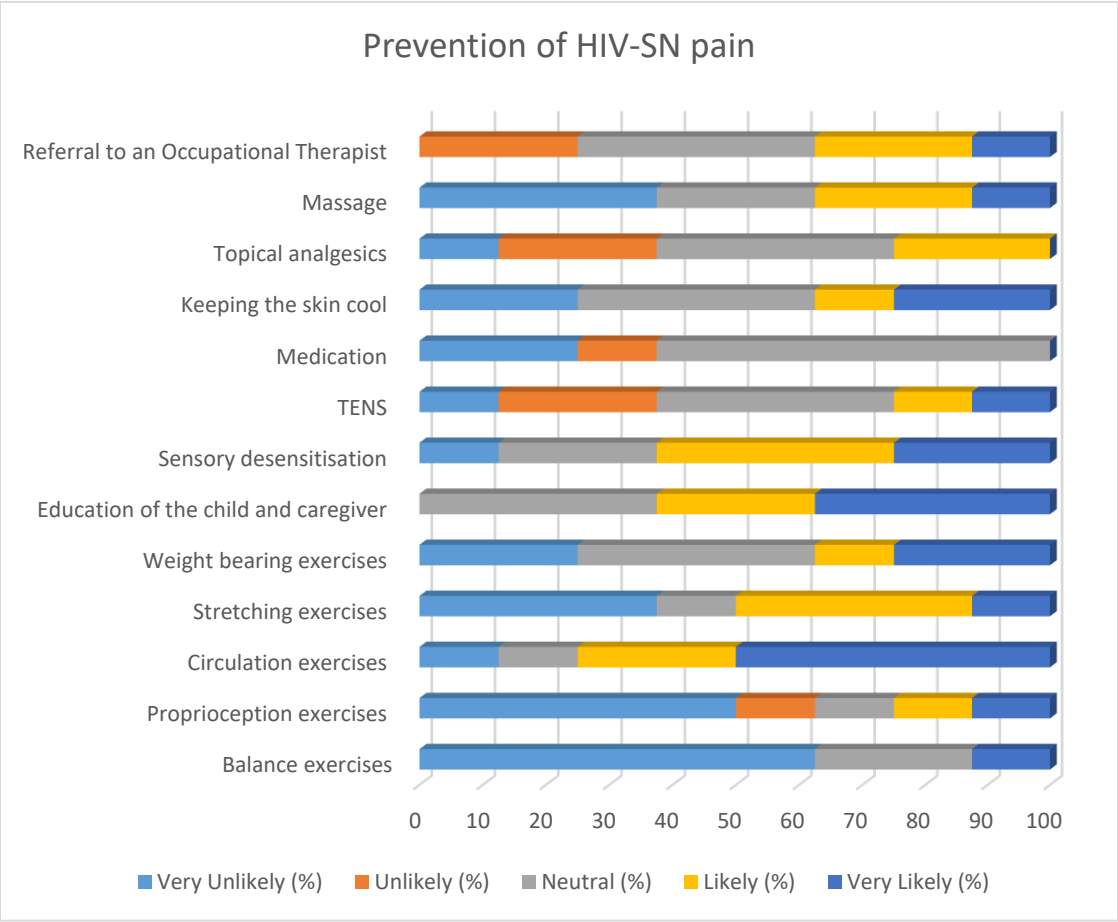


Figure 5.7 Prevention strategies for HIV-SN pain

In figure 5.7 above, it is shown that the most commonly identified strategies are education of the child and caregiver and exercise, scoring their choice as likely or very likely. Over 70% of respondents do not advocate discontinuation of ARV medication.

HIV-SN itching management

Figure 5.8 below provides details of specific intervention strategies for managing HIV-SN itching

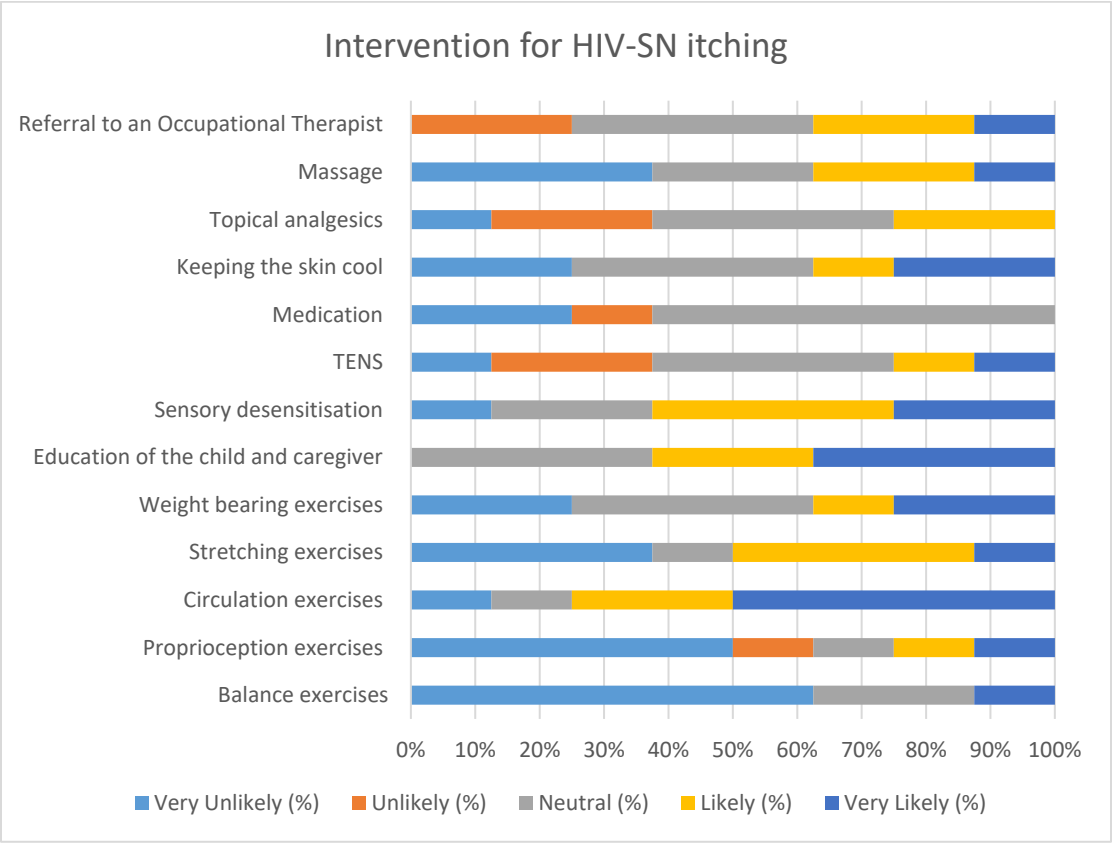


Figure 5.8 Intervention strategies to manage HIV-SN related itching

In figure 5.8 it shows that the consensus for management was mainly sensory desensitisation, education of the child and caregiver as well as circulation exercises.

Figure 5.9 below provides details of specific prevention strategies for managing HIV-SN itching.

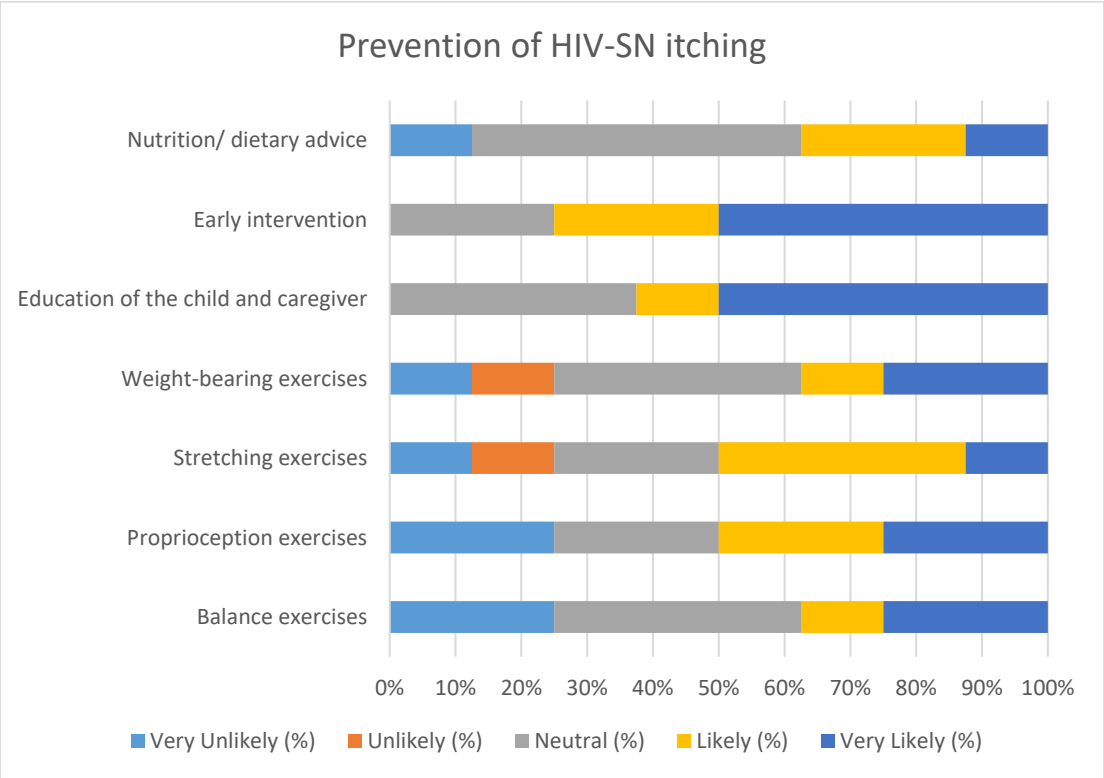


Figure 5.9 Prevention strategies for management of HIV-SN related itching

As seen in Figure 5.9, early intervention and education of the child and caregiver were the most common strategies identified by the study participants.

HIV-SN numbness management

Figure 5.10 below provides details of specific intervention strategies for managing HIV-SN numbness:

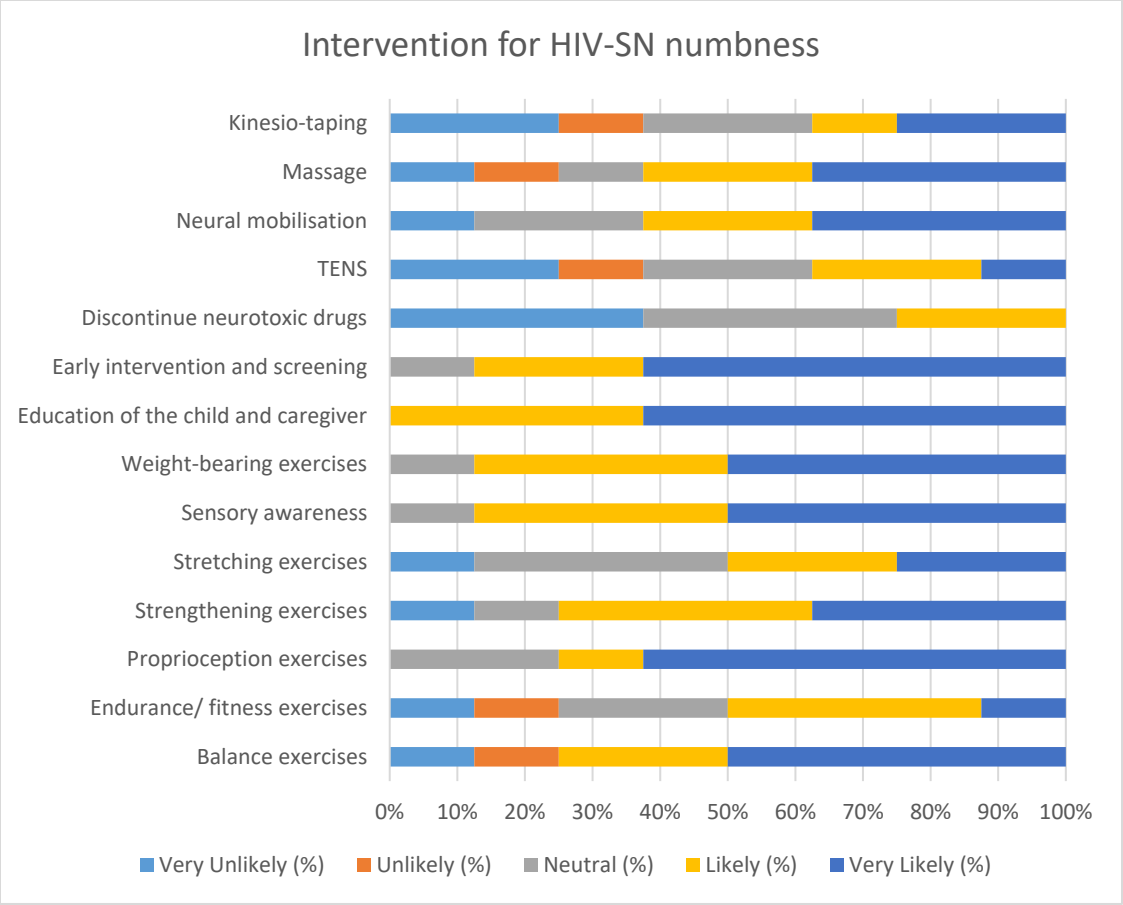


Figure 5.10 Intervention strategies for the management of HIV-SN related numbness

In figure 5.10 it shows that the strategies with the highest consensus includes early intervention and screening; education of the child and caregiver; weight-bearing exercises and improving sensory awareness.

Figure 5.11 below provides details of specific prevention strategies for managing HIV-SN numbness

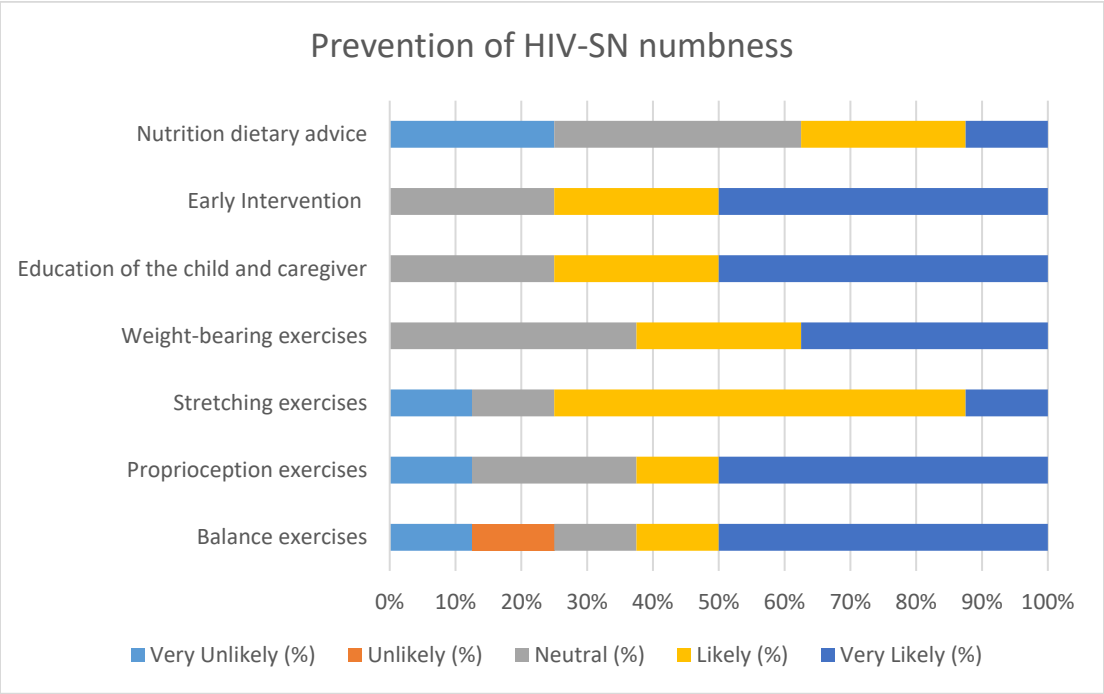


Figure 5.11 Prevention strategies for HIV-SN related numbness

Figure 5.11 shows that the most common identified strategies for the prevention of HIV-SN related numbness were early intervention (75%), education of the child and caregiver (75%) and stretching exercises (75%) as shown in figure 5.10 above.

HIV-SN pins and needles management

Figure 5.12 below provides details of specific intervention strategies for managing HIV-SN pins and needles

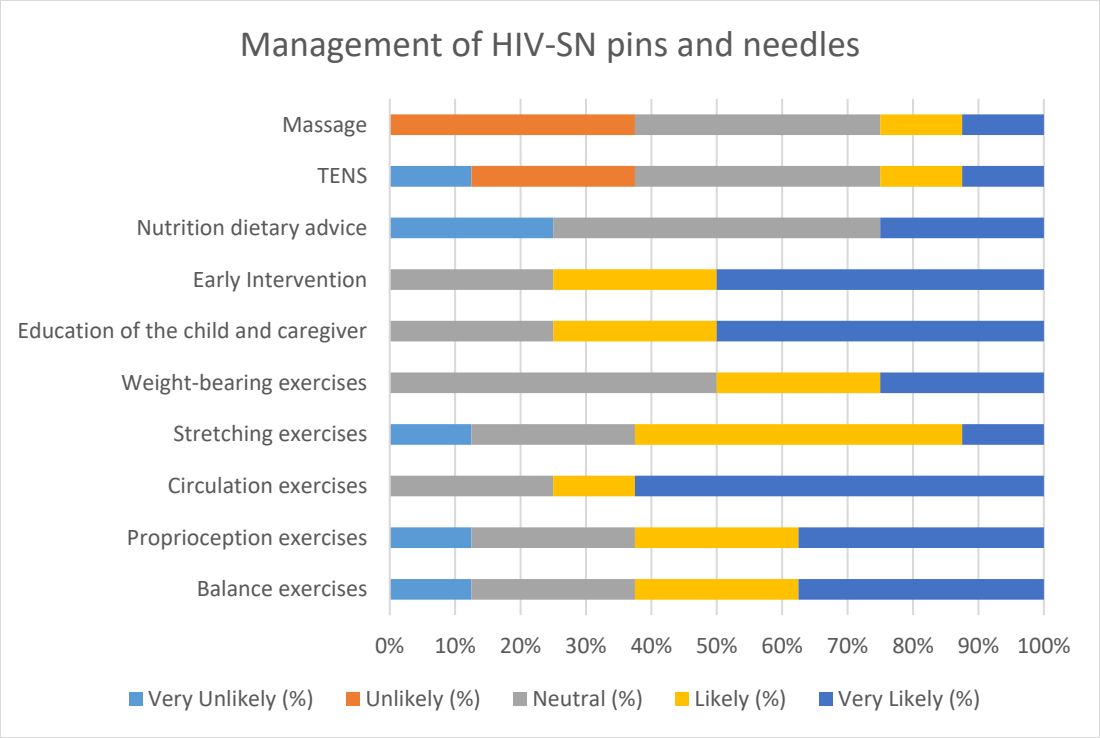


Figure 5.12 Intervention strategies for the management of HIV-SN related pins and needles

Strategies with the highest consensus in the management of HIV-SN pins and needles were early intervention, education of the child and caregiver as well as circulation exercises as shown in figure 5.12 above.

Figure 5.13 below provides details of specific prevention strategies for managing HIV-SN pins and needles

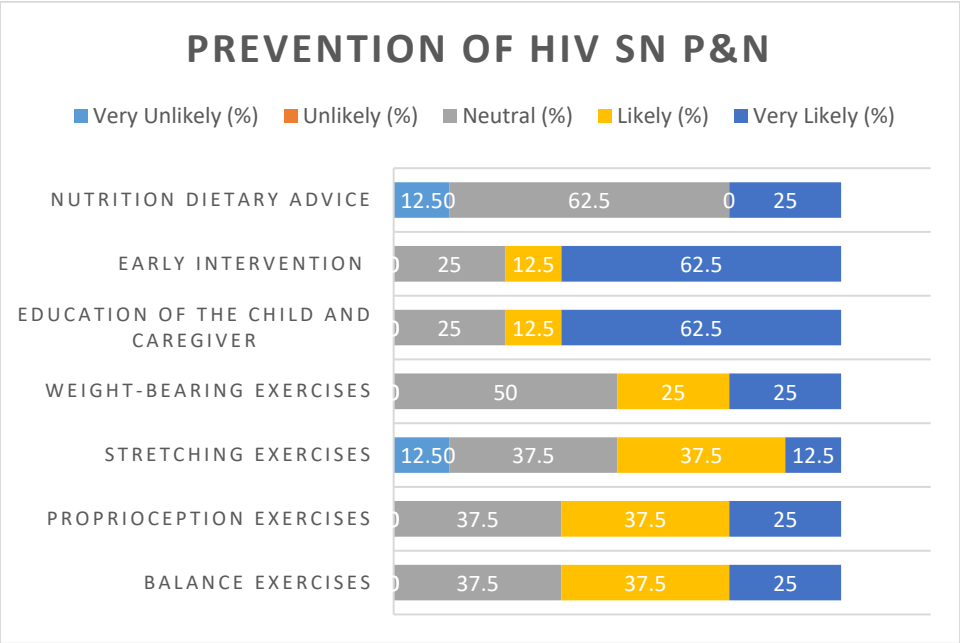


Figure 5.13 Prevention strategies for HIV-SN pins and needles

Figure 5.13 shows the consensus for this aspect of HIV-SN varied with the highest tally being 75% for early intervention and education of the child and caregiver. There was a 50% split for weight-bearing and stretching exercises, with slightly more totals at 62.5% for proprioception and balance exercises.

Manual dexterity management

Figure 5.14 below provides details of specific intervention strategies for managing poor manual dexterity

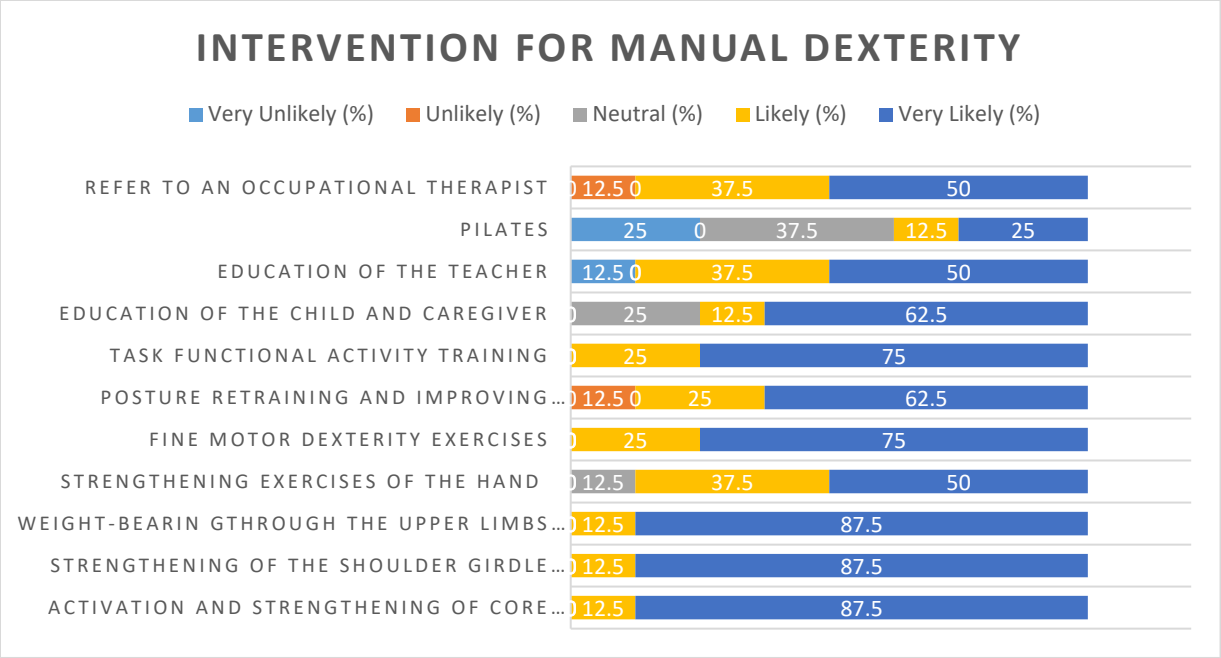


Figure 5.14 Intervention strategies for managing poor manual dexterity

In this category figure 5.14 shows that the consensus was highest (100%) for task functional activity training and fine motor dexterity exercises, static and mobile weight-bearing through the upper limb, strengthening of the hand and activation and strengthening of the core muscles. The lowest score was for Pilates at 32.5%.

Aiming and catching ability

Figure 5.15 below provides details of specific intervention strategies for managing poor aiming and catching ability

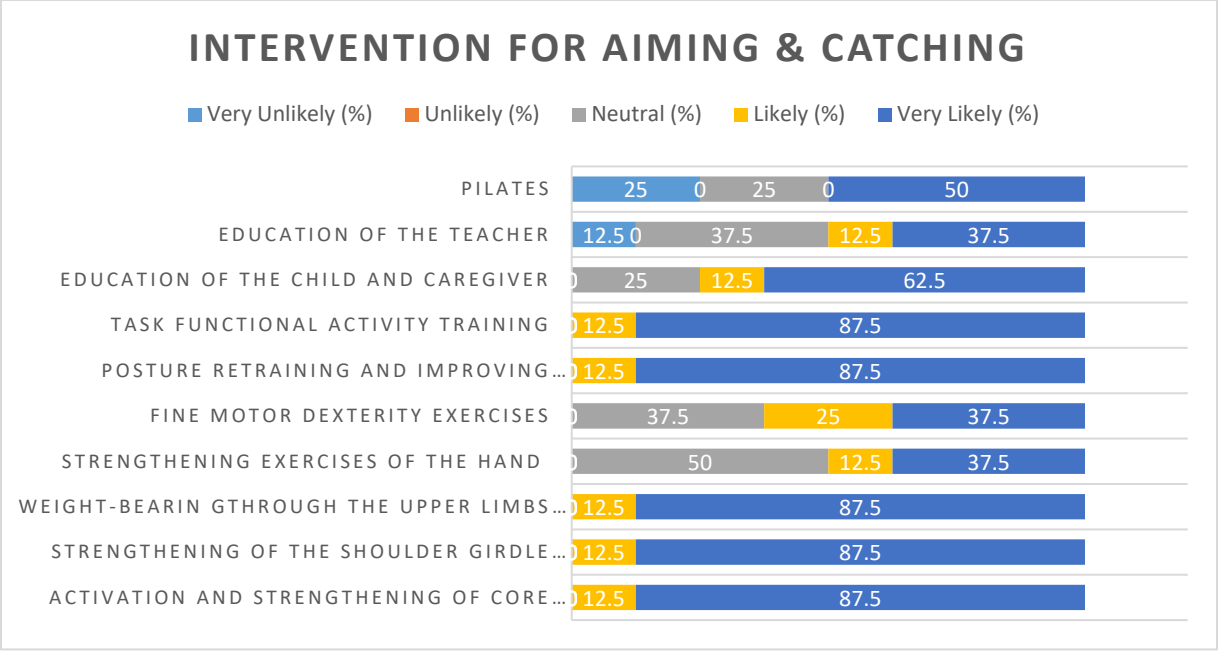


Figure 5.15 Intervention strategies for improving aiming and catching skills

In this case figure 5.15 shows, the consensus was the same (100%) as that for intervention strategies recommended for improving manual dexterity with weight-bearing through the upper limb, strengthening exercise of the hand, activation of core muscles, posture retraining and task functional activity training. The lowest scores were Pilates and education of the teacher at 50%.

Balance

Figure 5.16 below provides details of specific intervention strategies for managing poor balance.

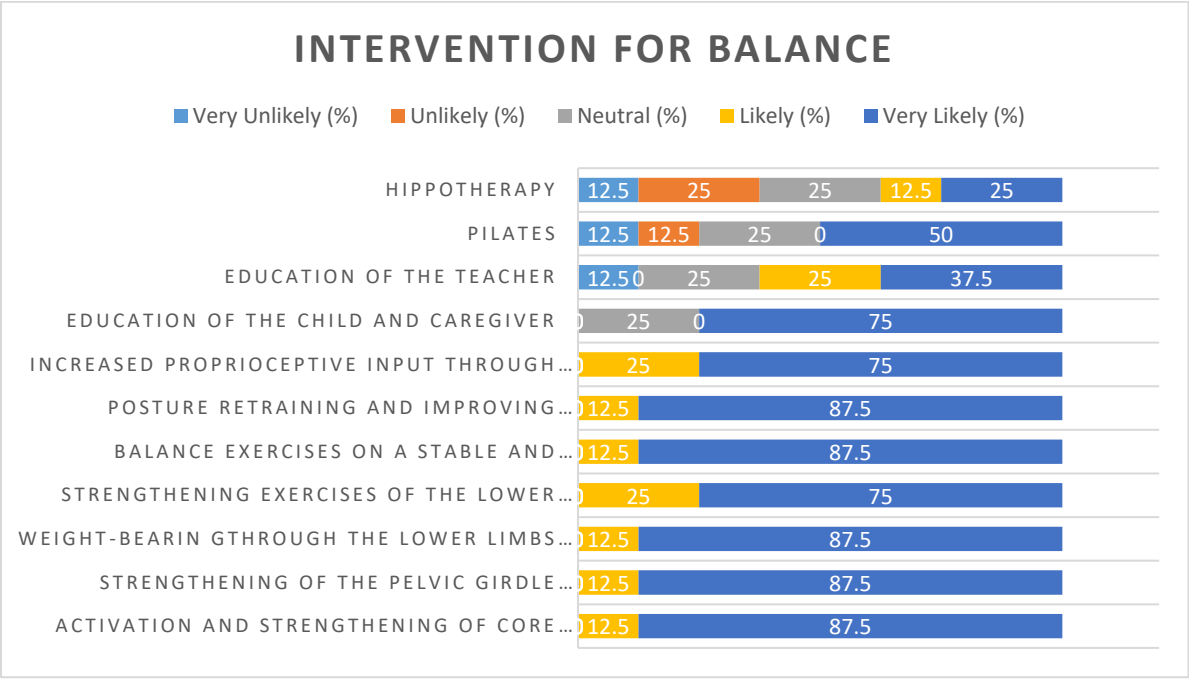


Figure 5.16 Intervention strategies for improving balance

In figure 5.16 the highest consensus was reached for posture re-training, balance exercises, weight bearing exercises, strengthening of the pelvic complex and activation and strengthening of the core muscles. This was closely followed by education of the child and caregiver, increased proprioceptive input and strengthening exercises of the lower limb.

Quality of life

Figure 5.17 below provides details of specific intervention strategies for managing poor quality of life.

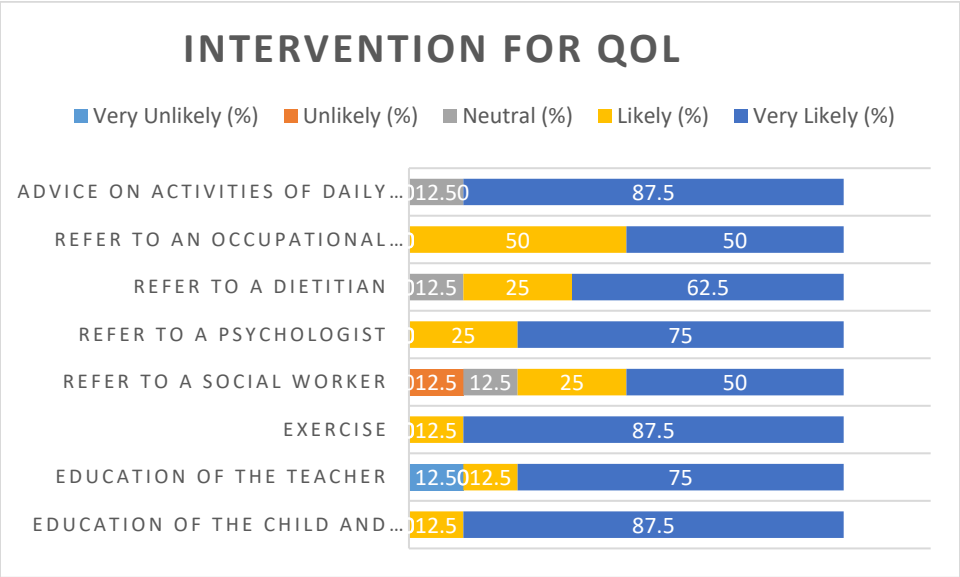


Figure 5.17 Intervention strategies for improving quality of life

For intervention for improving quality of life, the highest consensus was reached for advice on activities of daily living, exercise and education of the child and caregiver as well as the teachers. This is closely followed by referral to an occupational therapist and a psychologist and lastly, referral to a dietician.

5.4.2 Round two

For the second part of the Delphi survey, the responses for round one were collated and strategies that were selected as being likely and very likely were tabulated. Respondents were requested to vote on the strategy that they would most likely use in practice for inclusion in the exercise programme. Consensus was determined to be at 80% per strategy. The 80% is constituted of the likely and very likely selection combined. The frequencies are depicted in table 5._ below, with the highlighted sections showing the highest consensus.

Table 5.4 Consensus tabulation for each strategy

	Frequency Respondents for neutral, likely and very likely	Neutral	Likely	Very likely	Consensus Percent for inclusion	Total percent
Balance exercises	8	12.5	25	62.5	87.5	100
Endurance exercises	8	12.5	50	37.5	87.5	100
Proprioception exercises	8	0	37.5	62.5	100	100
Strengthening exercises	8	0	50	50	100	100
Stretching exercises	8	50	37.5	12.5	50	100
Weight bearing exercises	8	37.5	12.5	50	65.5	100
Education	8	0	25	75	100	100
Sensory stimulation	7	12.5	37.5	37.5	75	100
Medication	5	12.5	50	0	50	100
Heat	3	12.5	25	0	25	100
Discontinuing neurotoxic medication	6	62.5	12.5	0	12.5	100
Functional electrical stimulation	4	25	0	25	50	100
Orthotics	6	25	50	0	75	100
Kinesiotaping	6	25	37.5	12.5	50	100
Treadmill training	5	37.5	12.5	12.5	25	100

5.5 Summary

Twenty paediatric physiotherapists from across South Africa were invited to participate in the Delphi survey. Of these, only eight participated in both rounds of the survey, yielding a poor response rate. Of those invited, there were fourteen that responded to the email. Four of the respondents cited insufficient experience in managing this condition as their reason for not

participating. Two respondents only completed Round one, resulting in only eight completing the full survey. A possibility for the poor response rate may be the length of the questionnaire and the time needed to complete it. Most of the therapists invited to participate are in private practice and thus may not have had sufficient time.

For part one, strategies with the highest consensus (100%) were exercise, education of the child and caregiver as well as referral to both an occupational therapist and/or a psychologist. The types of exercise with the most consensus was proprioception, balance and strengthening, followed by circulatory, weight-bearing and endurance exercise. The least popular selection was stretching. Most of the choices were based on clinical experience rather than research evidence, with only two participants consistently citing this as the reason for their selection. Education of the child and caregiver was a consistent selection with very high consensus.
For part two, the highest consensus was for exercise and education.

Based on this information and supported by the literature findings, the following intervention programme and information booklet were designed. Bearing in mind that exercises needed to be simple, safe and easy to follow within the home environment of participants. The programme was emailed to participants for final comments, the response rate remained the same as for part two, n=8, with no further input recommended. The programme is presented below:

Intervention strategy

The exercise programme included

1. **Warm-up:**
   - Marching on the spot – two repetitions of 2 minutes each;
   - Spinning arms in small circles – two repetitions of 1 minute each.
2. **Stretching:**
   - Touching toes – two repetitions of 30 seconds each;
   - Pull arm across body – two repetitions of 30 seconds each side;
   - Pull hand up in front of body using other hand – one repetition of 30 seconds;
   - Reaching up – two repetitions of 30 seconds each;

- Ankle exercise, writing the alphabet with your big toe – two repetitions of "A" through to "Z".

3. **Aerobic Exercises:**

- Jumping jacks – two repetitions of 20 each;
- Skipping – one repetition of 30 seconds;
- Running with high knees for 20m – two repetitions;
- Walking with heels to the bottom for 20m – two repetitions;
- Sideways skipping for side 20m – one repetition for each side.

4. **Strengthening Exercises:**

- Sit ups – two repetitions of 20 each;
- Push ups – two repetitions of 20 each;
- Squats – two repetitions of 20 each;
- Air cycling – two repetitions of 20 each.

5. **Balance Exercises:**

- Standing on one leg for 30 seconds with eyes open – one repetition on each leg
- Standing on one leg for 30 seconds with eyes closed – one repetition for each leg;
- Hopping on one leg with eyes open – one repetition of 10 seconds on each leg.

6. **Cool Down:**

- Walking for 5 minutes at a slow and comfortable pace.

7. **Massage:**

- Massage using a hand-held vibrating massager (Figure 6.1, Portable Massager, DQUIP). The device was issued to the participants for use at home. The procedure of the massage was as follows: Starting at the toes, the massager was held on the toes for a few seconds. Then slow circular movements on the sole of the foot from the ball of the foot to the heel. Then the dorsum of the foot, up the anterior aspect of the lower leg. The same direction on the posterior aspect, until the entire lower leg was covered, and no pain was felt.



Figure 5.18 Photo of the hand-held massager issued to participants

8. <u>Diary</u>

- A diary was issued to each participant containing the information sheet and diagrams of the exercises as a reminder and for recording exercises done (Appendix 19).

Strategies with evidence but excluded in the programme:

Strategies such as kinesio-tape (KT), functional electrical stimulation (FES), nutritional advice, sensory desensitisation, medication or neural mobilisation were omitted from this programme as there was insufficient consensus. Though the evidence for the use of FES exists, it was omitted based on the fact that it requires application by a qualified person and is therefore not suitable for a home programme.

Chapter 6: Methodology and Results Study Three: Case Control Study

Introduction

This chapter gives an outline of research methods that were followed in study three. It provides information on the participants, that is, the criteria for inclusion in the study, who the participants were and how they were sampled. The researcher describes the research design that was chosen for this study and the reasons for this choice. The instrument that was used for data collection is also described and the procedures that were followed to carry out this study are included. The researcher also discusses the methods used to analyse the data. Lastly, the ethical issues that were followed in the process are also discussed.

6.1 Objective

Study three addressed objective seven

To determine the outcome of this intervention programme on the gross motor function, mobility and the quality of life.

6.2 Study Design

Due to the small sample size (n=28) available to assess the intervention and the novelty of the intervention programme, a case series study design was selected.

6.3 Inclusion criteria

a) Children who tested positive for HIV-SN in study one of the research project, and who were willing to participate in the exercise programme.

6.4 Exclusion criteria

a) All HIV-positive children who do not have symptomatic HIV-SN;
b) All HIV-positive children who tested positive for HIV-SN and who were unable to participate in the exercise programme.

6.5 Data collection process and data management

All participants from study one that tested positive for HIV-SN (n=34) and that presented with gross motor difficulties, i.e. they fell within the amber or red categories for the M-ABC-2®, were invited to participate in the study. Twenty-eight participants agreed to participate and were reassessed at the start of the intervention. The assessment followed that same procedures used in study one, and included the BPNS, M-ABC® and PedsQL™. For most participants more than 12 months had passed since the initial assessment and therefore fell into a different age band of the M-ABC-2® requiring reassessment. For consistency of the baseline data, all participants were reassessed. Further, possible changes in the status of the neuropathy over time (either improving or getting worse), warranted a reassessment. The RA, who was also a physiotherapist was briefed on the exercise programme and massage protocol prior to the study commencing.

For the intervention, participants were issued with the programme (see end of Chapter 5), the RA explained and demonstrated how exercises were done, and the participants showed whether they understood the instruction by demonstrating the movements. The programme was run over a four-month period, with reassessments every six weeks (three assessments for each participant). During the intervention period, participants received weekly short message system (SMS) reminders to do the exercises and record it in the booklet. The same system was used to remind them of appointments for follow-up assessments. During the reassessment visits, the BPNS, PedsQL™ and MABC-2® were repeated.

Due to participants going away on holiday over the traditional Southern Hemisphere summer school break (December to January) and the researcher being hospitalised, not all participants could be assessed during the second follow up visit, thus affecting the total number of participants for that period.

The programme started with a sample of 28 participants, of which 24 completed all three assessments (BPNS, M-ABC-2® and PedsQL™) at baseline. There was a total of five drop-outs from the first assessment to the final assessment. Some of the participants moved provinces or withdrew from the intervention (n = 4) and were no longer able to attend and five (n = 5) did not arrive for the final assessment. The diagram below shows the attrition more clearly. This is total of n=9 dropouts.

It is important to note that for the baseline assessment 28 children arrived for assessment, of these all completed the BPNS and PedsQL™ but only 24 completed the M-ABC-2®. Due to the physical nature of the test, one was unable to complete it as he had just had surgery (circumcision), and the remaining two refused to comply.

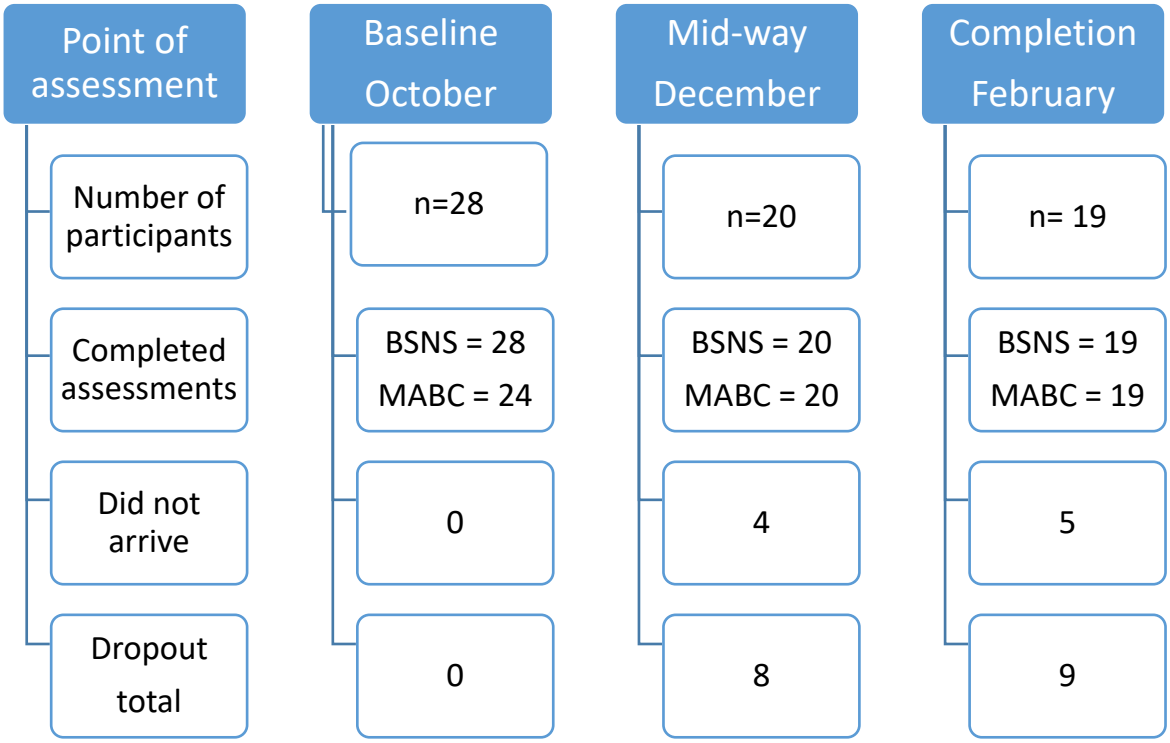


Figure 6.1 Flowchart of attrition

The intervention was well adhered to with the participants eager to show they had received their stars for doing so. Most reported that the exercises were easy enough to incorporate into their activities of daily living, thus improving adherence. It may have been wise to incorporate more aerobic and strengthening exercises as in the adult studies, since it shows improvement in aerobic capacity which would improve participation in physical activity and thus, gross motor function (Hand *et al.*, 2008b; Neto *et al.*, 2015).

6.6 Data analysis

Data are reported as mean (standard deviation) if parametric continuous data, median (IQR) if non-parametric continuous data, and counts and percentages were used for categorical data. Mixed model regression was used for repeated categorical variables with subject ID included as a random intercept and the time periods as a fixed effect. Linear regression models (using the Enter method) were used for continuous dependent variables with the time periods coded as dummy variables acting as the predictor variables, with the first-time period of testing (October) being the reference point. Homoscedasticity and multicollinearity were tested prior to performing the regression analyses. The threshold for statistical significance was set at 0.05.

6.7 Results

6.7.1 Demographics

Table 6.1 Demographics of the participants

Demographics	
N (total)	28
Sex	50% female
Age (years)	Mean 8.6 (±1.6)
ART start age months/years?	0.27; (range 0-2)
Years on ART	Mean = 5.2; (range 3.16 - 9.25)
HIV clinical status	
CD4 Cell Count	Mean = 1213 (range 111 - 2808)
Viral Load	Mean = 1.709 (range 1.301 – 4.863)

Table 6.1 depicts the total number of participants n=28, where 50% (n=14) were female. The mean age of the children was 8.6 years (SD = 1.7). The youngest child was 6.6 years and the oldest was 12.1 years. The average age of commencing ART was 27 months, while the average time of being on the treatment was 7.2 years (86 months).

6.7.2 M-ABC2 scores

Table 6.2 Results according to the colour zones

Zone	October 2015 (n)	December 2015 (n)	February 2016 (n)
Red	8 (33.3%)	3 (15%)	2 (10.5%)
Amber	3 (12.5%)	3 (15%)	1 (5.3%)
Green	13 (54.2%)	14 (70%)	16 (84.2%)
Total	24 (100%)	20 (100%)	19 (100%)

Of the completed assessments there was an improvement according to the zoning. The intervention started with 11 participants (45.8%) being classified as being 'at risk' (red and amber zones) to only three (15.8%) on completion. Most of the participants moved into the Green zone. With the final group of participants, one in the red zone and one in the amber zone moved over to an older age category. One participant, who was still positive on the BPNS for HIV-SN remained in the red zone from the previous assessment.

In October, there were n=8 participants who were classified as "red". In December, n=3 of these participants were classified as "green"; n=4 of the participants did not attend the December follow-up session; n=1 of the participants maintained the "red" classification. This participant was classified as "green" in February – i.e., not at risk. Only n=1 participant who was "red" in October maintained that classification in February.

A linear regression was run to determine whether a difference in MABC zones was evident over the three different time periods. The data was simplified into 'at risk' (red and amber) and 'not at risk' (green) for simplification of analysis as dichotomous dependent variables. No significant association between MABC zones and time was found, F (2) = 0 .830, p = 0 .441.

M-ABC total test score

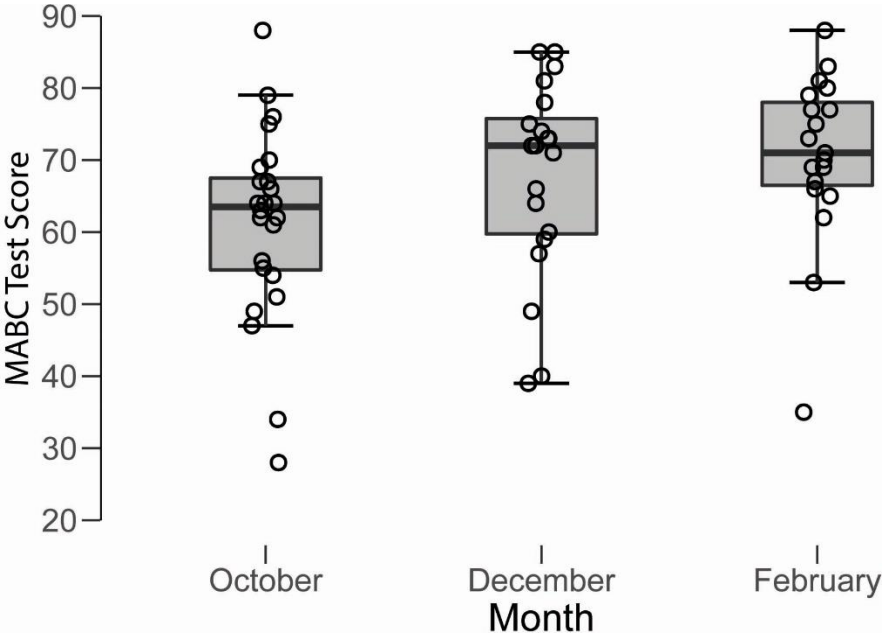


Figure 6.2 Box plot for MABC total scores

A linear regression (enter method) model with the first-time period (October) as the reference was used to determine if the month of scoring predicted MABC score. The model was not statistically significant, $F(2) = 2.9$, $p = 0.063$, with an adjusted R-square value of 0.058. While the overall model was not significant, February was found to be a significant predictor of increased MABC score, $\beta = .318$, $t = 2.31$, $p = .024$.

M-ABC components

Manual dexterity

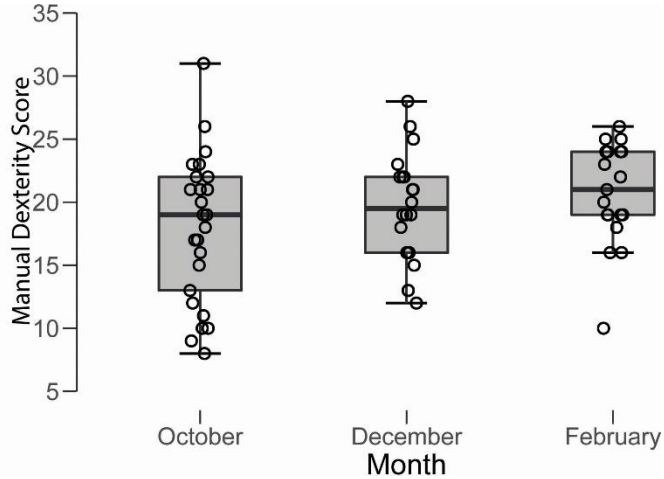


Figure 6.3 Box plot for Manual dexterity scores

A linear regression (enter method) model with the first-time period (October) as the reference was used to determine if the month of scoring predicted of composite manual dexterity score. The regression model was not statistically significant, F (2) = 1.802, p = 0.174.

Aiming and catching

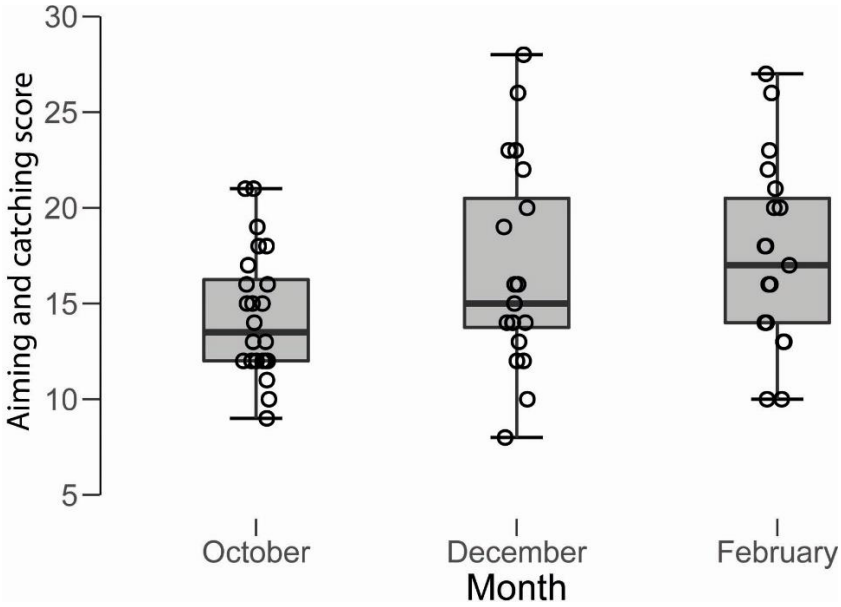


Figure 6.4 Box plot for aiming and catching scores

A linear regression (enter method) model with the first-time period (October) as the reference was used to determine if the month of scoring predicted was a significant predictor of aiming and catching score. The regression model was not statistically significant, F (2) = 2.773, p =.071, with an adjusted R-square value of 0.054. While the overall model was not significant, February was found to be a significant predictor of increased aiming and catching score, β = .307, t = 2. 23, p = .03.

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Balance

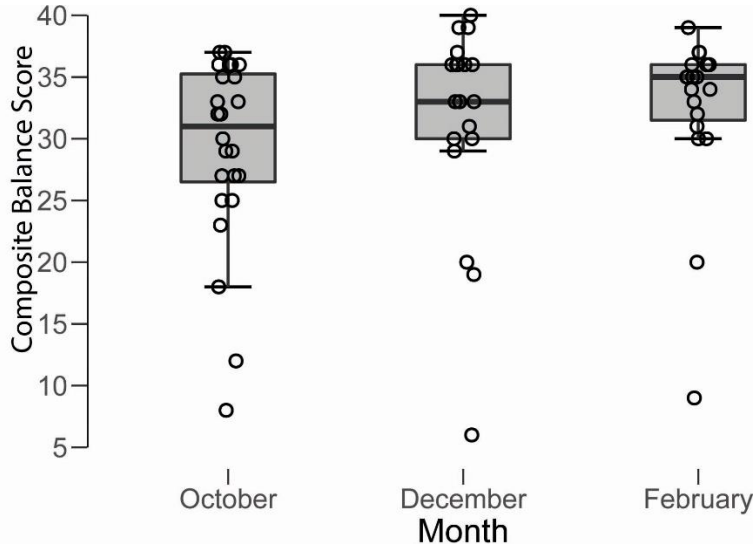


Figure 6.5 Box plot for Balance scores

A linear regression (enter method) model with the first-time period (October) as the reference was used to determine if the month of scoring predicted composite balance score. The regression model was not statistically significant, F (2) = 1.081, p = 0.346

6.7.3 PedsQL™ scores

The results for the quality of life questionnaires is given below.

Physical domain

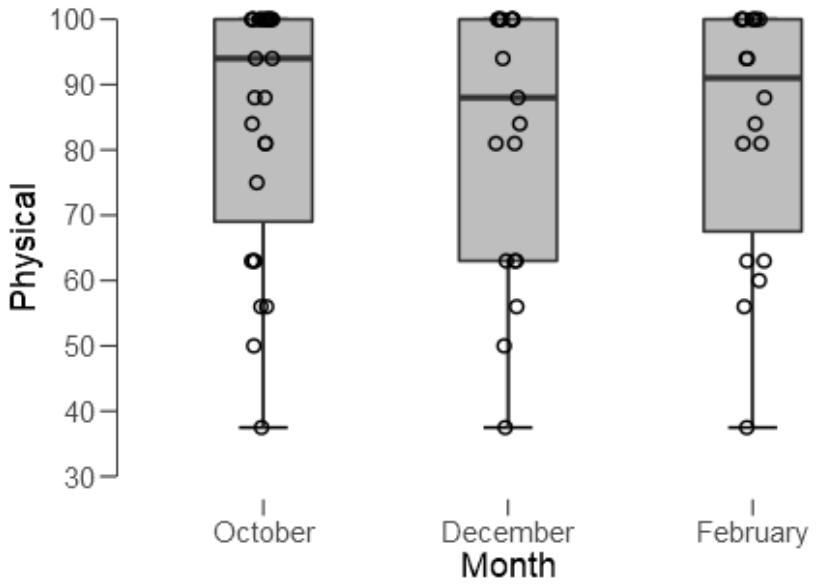


Figure 6.6 Boxplot for Physical component of PedsQL™

A linear regression (enter method) model with the first-time period (October) as the reference was used to determine if the month of scoring predicted the physical component of the PedsQL™ score. The regression model was not statistically significant, F (2) = 0.062, p = 0.940.

Psychosocial domain

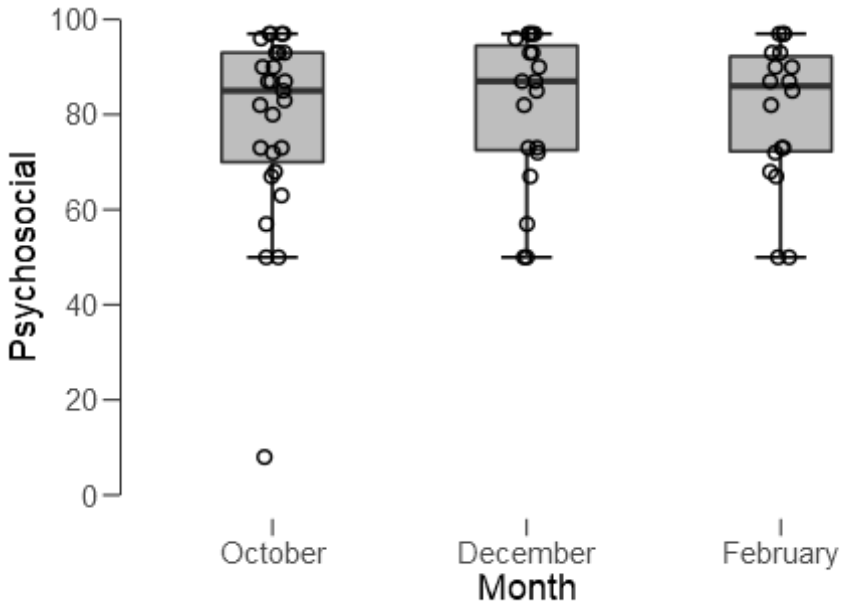


Figure 6.7 Boxplot for psychosocial component of PedsQL™

A linear regression (enter method) model with the first-time period (October) as the reference was used to determine if the month of scoring predicted of the psychosocial component of the PedsQL™ score. The regression model was not statistically significant, F (2) = 0.174, p = 0.841.

6.7. 4 Neuropathy signs and symptoms

BPNS status

At baseline 12 of the 28* children tested positive for HIV-SN, which is 51.8 % frequency. At the second assessment only 4 of 20* participants tested positive which is a 20% frequency rate. At the final assessment 7 of 19* participants tested positive which is a frequency of 36.8 %.

A linear regression was run to determine whether a difference in BPNS status was evident over the three different time periods. No significant association between BPNS status and time was found, F (2) = 1.537, p = 0.223.

6.8 Summary

In summary, for the M-ABC, there was a statistically significant change in the total score between periods one (start of the intervention) and two (mid-way through intervention) where $p = 0.023$. When looking at the zoning of Green, Amber and Red, there was an overall improvement of 30% in motor ability. The overall test score and the aiming and catching scores showed a statistically significance where $p = 0.023$ and $p = 0.024$, respectively, indicating an improvement over the intervention period.

For the PedsQL™ values remained relatively unchanged and could not be assessed for significance. There was no significant association for BPNS status over the twelve-week period. Generalisability of these results are limited due to the small sample size.

Larger studies are needed to establish the effects of exercise on HIV-SN, in this population therefore the results of the present study cannot be generalised to the wider paediatric population living with HIV.

Possible threats to external validity of this study are:

A) Selection bias as the children are attending a clinic where they receive counselling and are compensated for attending
B) 'Real world' versus 'experimental world' where children and caregivers may not accurately have performed exercises or recording of sessions were possibly manipulated to appear compliant.

There are no threats to internal validity as no manipulation of variables took place.

Discussion of these results are done in the following chapter.

Chapter 7: Discussion

For this study the initial question posed was as follows: ‘How does peripheral neuropathy impact on gross motor function (GMF) of children infected with HIV and can physiotherapy intervention make a positive difference in managing the condition?’
To begin, the frequency of HIV-SN was established along with the gross motor function of children living with HIV, an exercise programme was then developed and tested. In this chapter, the findings of each study are discussed and related to the literature available on the topic.

7.1 Study one

In study one the frequency of HIV-SN was established in children living with HIV (CLWHIV) as well as the impact it had on their quality of life and overall gross motor function. The objectives of the study were to determine the frequency of HIV-SN and factors associated with it. It also looked at gross motor function of children who develop HIV-SN and how it influenced their quality of life.

Frequency of HIV-SN in CLWHIV

The frequency of HIV-SN in this population was established to be 26%, which is just under one-third as found by Araújo et al in their study investigating neuropathy in children living with HIV over the age of five years (Araujo *et al.*, 2000). It is slightly more than the findings of Peters and colleagues who had an overall frequency rate of 24%.

In this study 135 participants consented to be assessed, which is slightly less than the study by Peters et al (2014) that included 174 children and much larger than the groups evaluated by Araújo et al (2000) and Sankhyan et al (2014) who only included 39 and 40 children, respectively in their studies (Araujo *et al.*, 2000; Peters *et al.*, 2014). The mean age of participants in this study was just under seven (6.8) years, where the youngest was three years and the oldest was ten years. In the Araújo et al (2000) study the children were an average of eight years old, in the Peters study they were average age of nine years and the Sankhyan participants were average age 11 years. All participants in the various studies were on ART’s. Since the populations for each of these studies are comparable and the clinical testing was similar except for Sankhyan and colleagues that used

electrophysiological criteria as well (Sankhyan *et al.*, 2014).The results of each will be discussed and compared to the present study.

Anthropometry

A short explanation of z-scores is provided: a child that has a z score of zero is at the average, or 50th percentile, for their age and gender in any growth measurement. If a child grows along a given percentile, changes in z scores over time are zero. For example, a height z-score of minus one indicates, that a child's height is one standard deviation less than the age- and gender-specific median height for the normal population.

Growth in children living with HIV has been widely studied (Arpadi, 2000; Bruck *et al.*, 2001; Baar *et al.*, 2008; Baillieu and Potterton, 2008; Ferguson *et al.*, 2009; Isanaka, Duggan and Fawzi, 2009; Potterton *et al.*, 2009; Whitehead, Potterton and Coovadia, 2014; Potterton, Hilburn and Strehlau, 2016a) and the effects of HIV on growth have been well described. Prior to the ART era, most studies reported stunting as a major effect (McKinney Jr. *et al.*, 1993; Arpadi, 2000). This failure in growth is still persisting despite being on controlled on ART's (Foster *et al.*, 2006; Isanaka, Duggan and Fawzi, 2009; Govender *et al.*, 2011; Sutcliffe *et al.*, 2011; Lowenthal *et al.*, 2014; Sherr *et al.*, 2014; Skeen *et al.*, 2014; Potterton, Hilburn and Strehlau, 2016; Ramteke *et al.*, 2017). It is important to note that this failure to grow has improved since the advent of ART.

Positive change was seen as early as 2005 in the Nachman study where at baseline, children infected with HIV were significantly shorter than uninfected children (mean z score, −0.57; 95% confidence interval, −0.73 to −0.41; $P < 0.001$). Administration of ART led to an increase in mean weight z scores to normal values (mean z score increase, from −0.16 to >0) and an increase in mean height z scores of 72% toward normal values (mean z score increase, from −0.57 to −0.16). The younger children gained height more quickly ($P < 0.001$), and children with higher baseline viral loads gained weight more rapidly ($P < 0.001$) (Nachman *et al.*, 2005).

A more recent study by Sutcliffe and colleagues conducted in Zambia had a group of children of a similar age to those in this study. They established that both weight and height scores improved with the initiation of ARTs. Their findings were that the children's weight increased steadily (from

-2.4 to -1.3) during the first six months on ART but then plateaued. It is noteworthy that these children were a lot more underweight when compared to the children in the Arpadi study done eleven years previously. This could be related to the different socio-economic circumstances for each study and thus the nutritional status of the children (New York – Arpadi [2000] versus Zambia – Sutcliffe [2011]). When the researchers compared the height findings, the children improved from -3.5 at initiation of treatment to -2.1 at completion of the study. Again these are a lot lower than the findings of Arpadi at -2.2, reflecting back to the socio-economic circumstances and therefore nutritional status of the study participants (Sutcliffe *et al.*, 2011).

Participants for this study were from the same cohort as those in the Ramteke and Potterton, Hilburn and Strehlau studies and yielded similar results for weight (-0.79 vs -0.7 vs <-2) and height (-1.32 vs -1.1 vs < -2) thus concurring that the children are lighter and shorter than children that are exposed but uninfected (Isanaka, Duggan and Fawzi, 2009) as well as children that are unexposed and uninfected (Ramteke *et al.*, 2017). These results are better than the values reported by Arpadi, Sutcliffe and Nachman. For height, the Arpadi finding was -2.2 and the weight was -1.4 (Arpadi, 2000). It is important to note that the Arpadi study was conducted prior to the rollout of early initiation of ART and the Nachman study only five years later, showing overall growth improvements. It thus shows that the early initiation has made a difference in growth of children living with HIV but also that family involvement in adherence and control of the ART is important (Hazra, Siberry and Mofenson, 2010; Shariat *et al.*, 2017).

Viral load distribution and CD4 count:

The average viral load of the study population was 1.709, which falls well below the recommended <50. This means the children are doing well clinically by maintaining a suppressed viral load (National Department of Health , 2010*). The average CD4 cell count for this study population was 1213, with a range from 111 to 2808. This is slightly lower than the figures (1.311) reported in the study by Benki-Nugent et al that investigated the development of infants (Benki-Nugent *et al.*, no date). This was a much younger cohort of children and concurs with the findings of Lindsey et al and Nachman et al where young children improve more on ART than their older peers. (Nachman *et al.*, 2005; Lindsey *et al.*, 2007).

*http://www.mic.uct.ac.za/sites/default/files/image_tool/images/51/Children 2016.pdf

Frequency of HIV-SN:

The following case definition for HIV-SN was used in this study: at least one bilateral sign (reduced/absent vibration sense, absent ankle jerk reflexes and reduced pin-prick sensation). A total of 25.9% (n=36) children in the sample met this definition of SN, with 24.1% having previous symptoms, and 7.8% having current symptoms. This in keeping with previous findings of Peters et al that reported 24% (Peters *et al.*, 2014), Arajuo et al reported 34% (Araujo *et al.*, 2000), but is a lot more than the 5% estimate made by Govender et al (Govender *et al.*, 2011) and the 10% reported by Sankhyan et al (Sankhyan *et al.*, 2014). Peters and colleagues had a sample of 174 children and used the neuropathy disability score (NDS) and the neuropathy symptom score (NSS) to assess for the presence of neuropathy. The Neuropathy disability score tests the same elements of vibration sense, pin-prick sensation and ankle reflexes but also included temperature sensation (Peters *et al.*, 2014). Arajuo et al used a clinical assessment protocol consisting of tendon reflexes, light touch, pain, temperature and vibration sense (128Hz). The present study used a revised version of the Brief peripheral neuropathy screen that included pin-prick sensation. The Govender study had a small sample size (n=78) and did not specify the neurological assessment components. They reported the peripheral neuropathy as being 'distal weakness' and therefore cannot be compared to the current study as the methods were not equally rigorous nor were the assessments aimed at specifically identifying neuropathy (Govender *et al.*, 2011). The Sankhyan study also had a very small sample size, targeted children specifically on stavudine therapy and utilised both neurological examination and nerve conduction studies in their assessments (Sankhyan *et al.*, 2014). The current study and the Peters study therefore have the larger samples with more specific assessments for neuropathy and are thus better comparisons. The Arajuo study included nerve conduction testing which is more accurate in diagnosing subclinical neuropathies, which explains the higher frequency rate of 34%. (Araujo *et al.*, 2000). This highlights the fact that more diagnoses of sensory neuropathy is being missed.

In this study most of the participants were under the age of eight years and had language barriers (English was not their first language) and the description of pin-prick sensation is often difficult, and the parent or caregiver was asked to provide a description of the sensation. However, problems with understanding an instruction of any outcome measure can result in incorrect information being provided and thus affect the results (Heyworth *et al.*, 2017). With this uncertainty as to

whether all the participants understood the instructions for pin-prick, this aspect was excluded in a secondary analysis to see the difference. The frequency of HIV-SN was reduced to 13.3% (n=18). The purpose of pin-prick testing for pain sensation is to assess the integrity of non-myelinated pain fibres and their input as part of the spinothalamic pathway, separate from dorsal column functions. The dorsal column conveys localized sensations of fine touch, vibration, two-point discrimination, and proprioception from the skin and joints. This highlights the importance of making the assessment more comprehensive by including the pin-prick sensation but ensuring that the participants understand the instructions well.

Presentation of HIV-SN

The results of this study showed that 13 participants were symptomatic. Of the thirteen symptomatic participants, all reported having previous pain, four had current pain, three had experienced painful cold, two had itching symptoms and one had numbness, cramping and pins and needles. Since the importance of inclusion of pin-prick sensation findings have been highlighted, these will be included in the discussion from this point.

Of the participants with HIV-SN, one child presented with absent reflexes and seventeen children presented with reduced or absent vibration sensation. This is very different to the findings of Arajuo et al who reported that distal paraesthesia, pain, diminished ankle reflexes and decreased vibration sense were most commonly affected. (Araujo *et al.*, 2000). Of the participants in this study the findings for diminished sensation did not follow a particular pattern. The difference in these groups can be attributed to the programme that the children of the current study are involved in, where they are closely monitored Administration of medication and thus adherence is carefully monitored, and caregivers are educated on the use of the medications as well as the importance of good nutrition.

The frequency is smaller compared to the 57% prevalence of HIV-SN in black South African adults exposed to Stavudine (Wadley *et al.*, 2011a). The symptoms reported in this study were mainly pain, followed by numbness and itching. The South African study by Peters and colleagues, reported burning, numbness and tingling as the common symptoms among children (Peters *et al.*, 2014). Pain symptoms reported in this study was similar to the primary symptom of

HIV-SN reported by black South African adults exposed to Stavudine, where the primary symptom of HIV-SN was pain(Wadley *et al.*, 2011a). This could possibly be explained by the children not always understanding the sensations they are experiencing except for pain, which is a distinctly uncomfortable sensation.

Extent of HIV-SN and factors associated with it

Many studies on HIV-SN in the adult population were able to identify factors associated with the severity of the neuropathy and the factors that predispose or worsen the condition (Simpson *et al.*, 2006; Smyth *et al.*, 2007; Antonia L. Wadley *et al.*, 2011a; Scott R Evans *et al.*, 2011; Ekenze, Nwosu and Ogunniyi, 2014). In this study, the Wilcoxon-Mann-Whitney test was performed to determine the significant difference between categorical variable of presence or absence of HIV-SN and continuous variables of age, weight, height, CD4 count, viral load and years of ART. The results showed that there was no significant difference between children with HIV-SN and children without HIV-SN ($p<0.05$). This is an important finding as all children living with HIV have an equal risk of developing HIV-SN. In the Peters study they found that smaller height was only a crude risk factor for HIV-SN (Peters *et al.*, 2014).
There was no significant association between presence/absence of sensory neuropathy and gender. Predictors for HIV-SN were not explored in the current study due to the small sample size.

With further analysis, this study showed no association between clinical measures (CD4 count and viral load), years on ART, demographics (age and gender) and anthropometric measures (weight and height). The participants in this study were slightly shorter and but were on par for weight for their age when compared to the WHO standards. The findings of stunting correlate with studies that investigated growth in children that are living with HIV (Lowenthal *et al.*, 2014, Sher *et al*, 2014) where it appears that it is the one aspect in terms of growth that persists despite being on controlled ART.

In adults with HIV-SN in South Africa, height and weight were independently associated with HIV-SN but they are not predictors of HIV-SN (Antonia L. Wadley *et al.*, 2011a). There is a strong multicollinearity between weight and height resulting in unstable parameter estimates which makes it very difficult to assess the effect of independent variables on dependent variables, in this

case HIV-SN. However, the study showed that people aged 38 years and above reported a higher prevalence of HIV-SN when compared to the people below the age of 38 years (Wadley et al., 2011). This can be explained by aging of the nervous system and thus vulnerability to metabolic stress and toxic substances such as some ART's. This is not surprising due to the distribution of HIV prevalence in South Africa and its association with long term use of ARTs as well as the debilitating effect of the disease. Research has shown a link between the length of time patients are on ART, co-morbidities such as hepatitis C and some combinations of ART as well as tobacco use. (Antonia L. Wadley *et al.*, 2011a; Cherry, Wadley and Kamerman, 2012; Luiza Areal Corrêa de Sá Benevides *et al.*, 2017) .

It is estimated that HIV prevalence is higher in Black African women aged 20-35 and black African men aged 25-49 years. There is a dearth of literature on the risk factors associated with HIV-SN in children. Only one study reported the association between malnutrition and Distal Symmetric Polyneuropathy (Esteban et al., 2008). Kamerman et al. (2012) summarised the risk factors associated with HIV-SN in adults into demographic and genetic factors. Older age (Maritz et al., 2010; Evans et al., 2011; Anziska et al., 2012), female sex (Mehta et al., 2011) and exposure to stavudine (Cherry et al., 2005; Forna et al., 2007; Wright et al., 2008) were reported to be at risk for HIV-SN. Luiza Areal Corrêa de Sá Benevides et al (2017) in their study on adults with HIV reported older age and higher CD4 levels as associated factors as well (Luiza Areal Corrêa de Sá Benevides *et al.*, 2017). This indicates a possible different pathological process when compared to children.

In this study there was no significant relationship between HIV-SN and socio-demographics, history of ART and clinical outcomes. In the adult population, the pathophysiology of HIV-SN is associated with the progression of HIV and the side-effects of ART use, most especially Stavudine (Antonia L. Wadley *et al.*, 2011a; Centner, Bateman and Heckmann, 2013). However, Peters *et. al.*, reported that the participants in their study developed symptoms soon after initiating ART but no list of medication or time frame for developing symptoms was provided (Peters *et al.*, 2014). In this study all the children were exposed to stavudine with 13 still being on it. With the introduction of newer medications in 2010 and thus changes in combinations (National Department of Health, 2010), most participants were on a new combination of 3TC, ABC and EFV which have fewer neurotoxic side effects. Even with the small study size, the Sankhyan study

specifically investigated children who were on stavudine (individuals tested positive for neuropathy), but the association between time of initiation and onset of symptoms could not be established. This could indicate a link to the actual disease process in conjunction with medication side-effects and warrants further investigation to optimise management of HIV in children. A study with a larger population to determine the risk factors associated with the prevalence of HIV-SN in children would contribute to the holistic approach in the management and prevention of HIV-SN in children.

Quality of life in CLWHIV who develop HIV-SN

For this study both caregivers and participants completed the PEDsQL. The most striking result to emerge from the data is that the scores were consistently similar between the two, thus the scores are not differentiated in this discussion. Previous studies, including the developers of the PEDsQL used the same tool to assess quality of life and are used for comparison to our results (Varni, Limbers and Burwinkle, 2007; Bomba *et al.*, 2010; Punpanich, Gorbach and Detels, 2012). Comparisons between patients with chronic health conditions with healthy children's PedsQL™ scores assist in understanding the impact of HIV and HIV-SN on QoL when compared to other chronic health conditions.

The average total score for the PEDsQL in this study was 79.6% which is high (> 50%), indicating a better QoL according to the scoring guidelines of the outcome measure (Varni and Limbers, 2009). The psychosocial scores (78.9%) were considerably higher than the findings of Bomba et al (2010) and Punpanich et al (2012) that yielded results above 69% for this domain. For the physical domain the participant average score was 81.4% which was higher than both the previous studies at 78% (Bomba *et al.*, 2010) and 75% (Punpanich, Gorbach and Detels, 2012). The study by Varni in 2007 examined the quality of life in children with chronic diseases such as diabetes, gastrointestinal conditions, cardiac conditions, asthma, obesity, end stage renal disease, psychiatric disorders, cancer, rheumatologic conditions, and cerebral palsy and compared them to healthy counterparts.(Varni, Limbers and Burwinkle, 2007). Scores for the healthy children were: total score 83.8%; psychosocial score 81.5% and physical score 83.5%.

This is a four percent difference in the total score when compared to the current study. When comparing the scores for the other conditions in the Varni study, the current study scored lower

than the diabetes group but better than the remaining conditions [as listed above] (Varni, Limbers and Burwinkle, 2007). This can be attributed to the fact that services for the management of HIV and diabetes are more readily available especially in the public-sector hospitals. It results in better adherence and therefore improved overall outcomes.

The finding for psychosocial health in this study is consistent with findings of Varni, which reported significantly lower overall psychosocial health across the disease clusters in comparison to healthy children (Varni, Limbers and Burwinkle, 2007). Varni also found that except for the diabetes cluster, the other groups reported lower physical health in comparison to healthy children. This score was 85.8% for the diabetes group, which is higher than the score of 81.4% as reported by the participants of this study. However, these scores are still higher than the remaining groups in the Varni study (Varni, Limbers and Burwinkle, 2007).

The Mann-Whitney-U tests revealed no significant differences between the results of quality of life of the children with no HIV-SN when compared to those who did have HIV-SN. What is interesting in this data is that there were no differences in the perceived quality of life for children who develop HIV-SN, despite pain being their main complaint. The studies by Bomba and Punpanich only evaluated and reported quality of life in one group of participants and did not compare to another group. The study by Bomba et al (2010) looked at validity and reliability of the tool and a second study by Vatsa compared the quality of life of children living with HIV to the QoL of children diagnosed with cystic fibrosis. The latter study found that children living with HIV reported overall better QoL (Vatsa *et al.*, 2010). It is important to note that the Vatsa et al study had a very small sample size and the results therefore cannot be generalised.

Gross motor function in CLWHIV who develop HIV-SN

Gross motor skills are important to enable children to perform every day functions, such as walking and running, playground skills (e.g. climbing) and sporting skills (e.g. catching, throwing and hitting a ball with a bat). However, these are crucial for everyday self-care skills like dressing (where you need to be able to stand on one leg to put your leg into a pant leg without falling over) and climbing into and out of a bath or even getting into and out of bed. Gross motor skills are attained and matured through practice at primary school level. These skills are an integral

part of cognitive functions such as learning (Lopes *et al.*, 2013). The gross motor function of the children in this study will be discussed next.

The Movement-ABC uses the traffic light system to categorise motor function where green shows no motor dysfunction, amber is minor dysfunction and red requires intervention (Henderson, Sugden and Barnett, 2007). In this study 29% and 23% of participants fell in the amber and red zones respectively, equating to more than half of the study group. This is an important finding as it suggests that many of the children living with HIV present with motor difficulties that need either monitoring or intervention. Current management does not include routine screening for motor dysfunction thus children with these difficulties are being missed. Gross motor function is an area where physiotherapy intervention can have a huge impact.

This study is the first of its kind to evaluate the gross motor development of children older than five and that used the Movement-ABC as an assessment tool. Previous studies on gross motor function included infants and young children younger (< 5 years) and used the Bayley scales of infant development or the Griffiths Mental Development Scales (Foster *et al.*, 2006; Lindsey *et al.*, 2007; Smith, Adnams and Eley, 2008; Ferguson and Jelsma, 2009; Lowick, Sawry and Meyers, 2012; Whitehead, Potterton and Coovadia, 2014; Potterton, Hilburn and Strehlau, 2016). However, these are standardised tools that assess the same aspects in a different age range and the results are therefore relevant. These studies all found delayed development and when looking at the results of the present study, it appears that motor difficulties persist in at least of half of the children living with HIV irrespective of being healthy and well controlled on ART.

When the groups, HIV-SN versus HIV with no SN were compared, no significant differences were found for the total scores as well as the individual domains of manual dexterity, aiming and catching and balance. There is currently no literature to compare these finding to.

The limitation of using an outcome measure such as the M-ABC is that it is not readily available within the context of public hospitals in South Africa. It has also not been validated in this context. However, the components of the test are easily replicated, using similar activities.

Summary

The frequency of HIV-SN was high in this paediatric population, was mostly symptomatic but not painful, and was largely undiagnosed prior to this study. Prior to this study, the frequency of HIV-SN in children was relatively unknown. A frequency rate of 25.2% is clinically important as the children are not routinely assessed. Using a standardised test (BPNS), that takes less than five minutes to conduct, greatly assisted in identifying these individuals, thus ensuring that timely intervention can be instituted. A study with a larger population to determine the risk factors associated with the frequency of HIV-SN in children would contribute to the holistic approach at the management and prevention of HIV-SN in children.

7.2 Study two

The purpose of study two was to find evidence for exercise and provide clinical expert input for management strategies in neuropathies. The author then designed an exercise programme based on existing literature and confirmed exercise inclusion through a Delphi survey. The exercise programme was tested in study three.

This discussion includes both: (i) the literature review findings and (ii) the Delphi survey.

Neurophysiology of exercise

As described in literature on chemotherapy induced neuropathy, neurotoxic agents cause damage through mitochondrial and vascular dysfunction (Bennett, 2010; Moore and Groninger, 2013). In their study on mitotoxicity in chemotherapy-induced-; diabetic- and, HIV-associated neuropathy, Bennett et al confirmed that the mechanisms of these neuropathies are similar although they present differently (Bennett, Doyle and Salvemini, 2014). Damage to the mitochondria leads to a loss of energy generating capability (generation of adenosine triphosphate) and vascular impairment deprives muscle and nerve cells of oxygen rich nutrients, further impairing neuronal function (Tofthagen, Visovsky and Berry, 2012; Pitceathly, Robert D.S., Hanna, Michael G., Reilly, 2018).

Few studies on exercise in adults showed that it stimulates endothelium-dependent vasodilation and vascular endothelial growth factor (VEGF) expression, this improves endoneurial blood flow

and energy generating capacity through mitochondrial protein synthesis and glycolysis (Gustafsson *et al.*, 1999; Ojala *et al.*, 2001). Exercises aimed at improving strength and balance, as well as aerobic exercise, may increase blood supply, oxygen and glucose to mitochondria, improving its ability to produce energy in the form of ATP. The increase in efficiency of mitochondrial energy and the increased blood supply to peripheral nerves could lead to fewer neuropathic symptoms, increased strength and balance, and better quality of life (Tofthagen, Visovsky and Berry, 2012). The latter study also involved adults exclusively. This provides physiological evidence for the inclusion of exercise in an intervention programme for HIV-SN and supports the findings of a hospital –based exercise intervention study conducted by Miller and colleagues. They did a follow up of patients that were given a home exercise programme and found that they maintained the positive changes in fitness, strength and lean body mass. (Miller *et al.*, 2010).

Paediatric physiotherapy

The area of paediatric physiotherapy in South Africa is a well-established field of interest, supporting the anticipation of a wide range of experience, which was represented in the results. In terms of the impact on this study, the results provided a slightly wider than expected variety of techniques with the "less experienced" physiotherapists more likely to suggest techniques based on a combination of courses attended, undergraduate training, clinical experience or evidence-based studies reported in the literature that, albeit not specific to this group, was specific to the complication being treated. There has been increased emphasis on the teaching skills needed to implement evidence-based research in practice in short courses and at an undergraduate level in the profession (Jette *et al.*, 2003). This, combined with younger physiotherapists being more confident with computer skills, and searching for on-line journal articles, suggests that if adequately trained, younger physiotherapists do incorporate evidence-based methods (Jette *et al.*, 2003).

The results obtained from the first round of the Delphi survey showed that several techniques were suggested by the panel members that could be used to treat or prevent the complications presented from Phase 1 of the study. The second round of the Delphi survey assisted in determining which

of those treatment techniques or modalities would be most appropriate to manage sensory neuropathy by means of consensus and level of agreement, which is discussed below.

Pain management

Children identified with HIV-SN in phase one of this study that were symptomatic mostly reported having pain, numbness and itching. Those that were asymptomatic frequently reported having had previous pain. Pain symptoms are consistent with the finding in adults with HIV-SN (Gonzalez-Duarte, Cikurel and Simpson, 2006; Smyth *et al.*, 2007; Antonia L. Wadley *et al.*, 2011a; Kaku and Simpson, 2014; Cherry, Wadley and Kamerman, 2016b). However, in this population emphasis would be on prevention of pain.

Management of HIV-SN

The consensus for both management and prevention of HIV-SN (all signs and symptoms) was that the child and caregiver need to be educated about the condition, that exercise was essential, and that sensory stimulation should be used as treatment modalities.

- Exercise

There is sufficient evidence for exercise in the management of neuropathy in the adult population (Katherine I Ites *et al.*, 2011; Salsabili *et al.*, 2011; M Akbari *et al.*, 2012; Mueller *et al.*, 2013; Knauf and Koltyn, 2014; Quigley *et al.*, 2014; Streckmann *et al.*, 2014). The evidence shows improved balance and gait outcomes (Quigley *et al.*, 2014) but is best documented for patients with diabetic peripheral neuropathy.(DSN). The systematic review by Streckmann and colleagues provide evidence that balance training is the most effective exercise intervention. Further to this, they found that exercises focused on strength, or a combination of endurance and strength, had smaller impact (Streckmann *et al.*, 2014). One of the recommendations by the South African Department of Health in the management of children living with HIV is to encourage exercise (Ministry of Health and Social Welfare, 2015). A small study (n=42) was conducted in Potchefstroom, South Africa (Botha and Pienaar, 2008), also recommended exercise to improve gross motor skills. The focus of the study was to determine the growth of children living with HIV. Their findings emphasised that motor ability in children with HIV was poorer when compared to

uninfected peers. They therefore made the recommendation for the inclusion of exercise in intervention programmes.

- Kinesiotaping and orthotics

An interesting point to note was that kinesio taping and orthotics both had a 50% consensus. Studies relating to the use of taping have focussed on the upper limb (Kaya, Zinnuroglu and Tugcu, 2011; Lemos *et al.*, 2015; Mansiz Kaplan *et al.*, 2018), treatment of sports-related injuries (Nunes *et al.*, 2015; Pyšný, Pyšná and Petrů, 2015; Harmanci *et al.*, 2016; Seo *et al.*, 2016) and pain management (Artioli and Bertolini, 2014). As stated earlier, the participants of this study did not complain mainly of pain, therefore this strategy was excluded.

Unfortunately, few studies have been carried out on the use of orthotics in the management of peripheral neuropathy without pain. A case study by Croarkin et al investigated the changes induced by the use of orthotics in a patient with chemotherapy induced neuropathy and found improved outcomes in ability to stand unassisted and gait (Croarkin *et al.*, 2015). The participants of the present study did not present with such severe impairment, thus making this form of intervention null.

- Functional electrical stimulation

Only 20% of participants rated the use of functional electrical stimulation (FES) as 'very likely' despite evidence in support of this modality for the management of pain (Karin Pieber, Herceg and Paternostro-Sluga, 2010; V Bril *et al.*, 2011) with good results. The review by Bril et al found one randomised controlled trial that reported an improvement of pain by 42% on the visual analogue scale. One study showed no improvement and another only a small change in pain but with the concomitant use of amitriptyline (V Bril *et al.*, 2011). The review findings of Pieber et al had varying outcomes, with larger studies emphasising prolonged use of FES for pain management and smaller studies showing no effects. They recommended that more randomized, double-blind, placebo- controlled studies with larger numbers of participants that have a longer duration of treatment, and longer follow-up assessments are needed (Karin Pieber, Herceg and Paternostro-Sluga, 2010). The outcomes were again focused on the reduction of pain symptoms and was therefore not relevant to this study population.

- Massage

Massage was also highlighted as an intervention strategy for treating pain and sensory difficulties. Evidence in support of this technique is sparse and mostly based on case studies (Gale, 2003; Benjamin and Jelsma, 2014). More recent reviews (Cheng and Huang, 2014) of existing literature found many methodological flaws in studies conducted and the results were only moderately supportive of massage as a technique to relieve pain (Cheng and Huang, 2014). It is important to note that the study focus was on musculoskeletal pain and not neurological. The authors highlighted the need for more robust studies comparing massage to other intervention strategies (Cheng and Huang, 2014). More studies investigating the effects of massage on neurological pain are therefore also warranted.

Soft tissue mobilisation induces mechanical and physiological changes including increased venous return and thus removal of metabolites, improved nutrient delivery to targeted tissue and improved extensibility of connective tissue (Goats, 1994; Gale, 2003). In 1994 Goats stated: "Massaged muscle fibres display less spasm, an increased force of contraction and enhanced endurance compared with muscle simply rested" (Goats, 1994, page 153, paragraph 6). This is supported in a recent review of massage as a therapeutic technique by Field who further concluded that the effects may be as a result of stimulation of pressure receptors leading to enhanced vagal activity and decreased cortisol levels (Field, 2016).

In the intervention used by Gale, both petrissage and effleurage were applied to the limit of patient tolerance, working from distal to proximal. However, this is a very specific, hands-on technique used by qualified physiotherapists and is thus not suitable for inclusion in a home programme. Benjamin and Jelsma (2014) utilised a vibromat as a massage technique. This can easily be implemented using commercially available massagers and was thus included in the intervention.

Due to the high level of consensus for exercise, a programme was developed that incorporated mostly cardiovascular, strength and balance exercises. This inclusion is supported by the recommendation of Tofthagen to include strength and balance training for its effects on physical performance, overall improvement of independence and its positive effects on health related

quality of life (Tofthagen, Visovsky and Berry, 2012). Educational advice on the condition and the importance of adherence to exercises were also emphasised. See Appendix 18.

7.3 Study three

Study three was aimed at testing the exercise intervention programme and to determine the effects it would have on children who present with HIV-SN in terms of gross motor development and overall quality of life. Due to the small sample a case series design was selected. Kooistra et al (2006), stated that: "The primary purpose of a case series should be the generation of hypotheses that subsequently can be tested in studies of greater methodological rigor", and as such, case series provide a means of reporting novel treatment strategy outcomes.

At this point, it is important to emphasise that the participants in this study only reported a marginally lower quality of life when compared to their non-HIV infected peers.

This is the first study that the researcher knows of that involves exercise intervention for the management of HIV-SN in children living with HIV. Participants in this study were selected for inclusion based on their diagnosis of HIV-SN and were therefore a percentage of study one sample. A case series design was used to test the intervention programme as it was a very small sample size (n =28).

When looking at the traffic light system of the M-ABC results, there was an improvement in gross motor function from 33% being in the red zone pre-intervention to only 10.5% on completion of the study. This improvement is reflected in the statistically significant difference ($p = 0.023$) between the start and completion results. The most improvement occurred in the aiming and catching ($p = 0.024$) domain. In 2010, Miller and colleagues conducted an intervention trial of a structured exercise programme to assess the effect on fitness, strength and lean body mass in children infected with HIV between the ages of six and 15 years. These components were not tested in the present study, but the research findings point towards improved motor outcomes as fitness and strength are incorporated in gross motor activities. The Miller study was conducted in a very different setting when compared to the present study and the sample was smaller 17 versus 28 in the current study (Miller *et al.*, 2010).

However, when looking at the adult literature, positive changes in overall health, balance and strength as well as a decrease in pain has been noted (Nicholas *et al.*, 2007; Hand *et al.*, 2008a; Jaggers *et al.*, 2013; Knauf and Koltyn, 2014; Pullen *et al.*, 2014; Quigley *et al.*, 2014; Mkandla, Myezwa and Musenge, 2016). The mentioned studies used a variety of exercise intervention strategies and had different outcome measures that included pain (Knauf and Koltyn, 2014) balance, strength (Hand *et al.*, 2008a; Neto *et al.*, 2015), physical status (Jaggers *et al.*, 2013; Neto *et al.*, 2015) and quality of life (Mkandla, Myezwa and Musenge, 2016). The most common intervention used was combined aerobic and resistance exercise over a minimum of six weeks. In her thesis, Parker investigated the effects of a six week group exercise and education intervention in reducing pain intensity and interference and increasing self-efficacy and quality of life in women living with HIV .The study yielded positive results with improvement in all assessed domains (Parker, 2013).

Results for the PEDsQL were the same as that for study one, with all participant consistently scoring well above 50% for all domains. Although scores were the same, some participants qualitatively reported improvements. The mother of one participant is quoted: “Wow, the results are amazing, she has lost so much weight, is looking healthy and doing better at school. Please can I do the exercises too?” A second participant reported improved participation levels in school sporting activities: “I can now play a full game of soccer without getting tired”.

Many of the participants verbally reported improvement in concentration in the classroom and thus better scholastic results. This was not recorded but concurs with evidence that improved gross motor function leads to improved learning ability (Westendorp *et al.*, 2014).

The PEDsQL only provides quantitative values for analysis of quality of life and the possibility of participants being uncertain about answering some questions exist. The psycho-social component of the PEDsQL asks about missing school because of seeing a doctor but does not specify if it is for a health check or whether the participant is ill. Since the participants of this study are living with a chronic condition that requires frequent visits to the clinic, they always score lower in this domain. This is a limitation of using the PEDsQL. A qualitative component which included individual interviews may have yielded more in depth, richer data.

The intervention was well adhered to with the participants eager to show they had received their stars for doing so. Most reported that the exercises were easy enough to incorporate into their activities of daily living, thus improving adherence. It may have been wise to incorporate more aerobic and strengthening exercises as in the adult studies, since it shows improvement in aerobic capacity which would improve participation in physical activity and thus, gross motor function.(Hand *et al.*, 2008b; Neto *et al.*, 2015).

7.4 Conclusion

In summary, the participants in this study displayed a high asymptomatic frequency of HIV-SN, but no correlations between medication, time on ART, age, sex or anthropometry data could be made. This finding is supported by the sparse existing paediatric data (Araujo *et al.*, 2000; Govender *et al.*, 2011; Donald *et al.*, 2012b; Peters *et al.*, 2014) and is slightly less than reported in the adult population (Verma and Simpson, 2007; S R Evans *et al.*, 2011; Kamerman, Wadley and Cherry, 2012; Gabbai, Castelo and Oliveira, 2013). We thus conclude that children living with HIV are at risk of developing HIV-SN and that they should be monitored regularly for signs and be educated about the condition so that they can recognise and report any symptoms.

The results of the literature review on intervention for the management of peripheral neuropathy show that a combination of exercise (Tuttle, Hastings and Mueller, 2012; Streckmann *et al.*, 2014; Neto *et al.*, 2015), education, massage (Gale, 2003; Benjamin and Jelsma, 2014) and FES (K Pieber, Herceg and Paternostro-Sluga, 2010; V. Bril *et al.*, 2011) have positive effects. Since FES cannot be included in a home programme, only exercise and massage were included in the final programme. Education about the condition, symptoms associated with it and the emphasis on good adherence was given at the clinic visit and in an information sheet.

When testing the programme, it was found that the most change was seen in the first six weeks of the intervention with participants then reaching a plateau. This is in keeping with literature (Hand *et al.*, 2008b; Streckmann *et al.*, 2014; Neto *et al.*, 2015). Even thought there were no significant changes in the reported quality of life, the participants showed improvement in their overall gross

motor function, with most moving over to the ‘Green’ category of the M-ABC-2® traffic light system. We thus deduce that the programme was successful, but that six weeks will be sufficient to see positive change.

7.5 Limitations of the study

The following limitations are noted with respect to the study:

1. The PEDsQL relied on the participants' ability to recall information, which they may not always have been able to do.
2. Children may not have completely understood instructions for the clinical evaluation of HIV-SN especially younger children.
3. Caution should be taken in generalising the results of the study to all children living with HIV as this study had a relatively small sample size and was conducted at a single urban site.
4. A larger sample size is recommended to establish more accurate frequency rates.
5. A randomised controlled trial with larger numbers are needed to better test the efficacy of the exercise programme in the management of HIV-SN in children
6. The Delphi survey could have included more participants by including physiotherapists who manage adults with HIV-SN, as well as sensory neuropathy due to other causes.

7.6 Implications of the study

The information generated in this study could assist in improving the lives of children living with HIV and is an important step forward in this field for the physiotherapy profession. The importance of continually screening children living with HIV for complications of the virus and the medication taken to manage HIV is highlighted in the fact that many of the participants presented with previously undiagnosed HIV-SN. Clinical reasoning cannot be excluded when managing a patient, but the information generated in this study equips physiotherapists with knowledge and will guide their treatment choices.

This study assists the physiotherapy profession by confirming the role of physiotherapists in the multidisciplinary management of children living with HIV. This area of physiotherapy has the potential for growth and development and students should be exposed to the impact of HIV on gross motor development from an undergraduate level which will stimulate interest and promote

research in this field. Furthermore, this will have positive long-term implications by improving the quality of care offered to patients, which can be subsequently monitored and evaluated. The importance of including physiotherapists in the management of people living with HIV is also supported in the literature (Pullen *et al.*, 2014)

7.7 Recommendations

This study has highlighted gaps that need to be addressed to improve the quality of care offered to children living with HIV:

Future research

- Research into the complications of HIV in children of all ages should be encouraged, promoted, and supported
- 'Larger studies and randomized controlled trials to investigate the long-term benefits of exercise in children.
- Longitudinal studies to monitor gross motor development and the changes experienced due to complications such as HIV-SN
- The impact of HIV in other areas of development such as fine motor skills and cognition and mental health should be investigated.

Clinical

- Management of children living with HIV should include routine screening for HIV-SN and development, including gross motor abilities.
- Children and their caregivers should be educated about the complications that they may develop. This would ensure better reporting of symptoms and thus prevent the condition worsening.
- Postgraduate courses need to incorporate evidence-based practice with clinical training, which will encourage qualified physiotherapists to use evidence-based techniques and improve clinical behaviour.

Chapter 8: Conclusion

"Education is the most powerful weapon which you can use to change the world" – Nelson Mandela

To improve the quality of care offered to people in our health care system, they need to be managed comprehensively and holistically, which can only be achieved through knowledge in an area. The inclusion of physiotherapy intervention for children living with HIV has the potential to improve their overall participation in their families, communities and in society.

8.1 Summary of the study

In study one we aimed to establish the frequency of HIV-SN in children and identify specific developmental or gross motor function problems in which physiotherapy intervention is needed. Due to the small sample size, only the frequency could be established. It was determined that there is a high frequency of HIV-SN (25,9%) in children living with HIV and the importance of including a brief neurological assessment in the routine management was highlighted. Additionally, we found that most of the children living with HIV presented with gross motor deficits, irrespective of whether they developed neuropathy. Interestingly, most of the participants in this study reported a satisfactory quality of life.

In study two we developed a home programme comprising of education and exercise with massage as an intervention by interrogating the existing literature and inviting experts in the field of paediatric physiotherapy to share their knowledge and expertise. There is evidence to support the inclusion of exercise in management programmes with the emphasis on resistance and aerobic exercises for an initial period of six weeks. The programme consisted of education of the child and caregiver on the signs and symptoms of sensory neuropathy and the importance of exercise to improve mobility and function. The exercise programme comprised of a warm up, stretching, aerobic exercises, balance exercises and strengthening exercise followed by a cool-down and massage using a small hand-held vibrating massager. These exercises were demonstrated to the participants and caregivers by the research assistant to ensure that they understood the pictures and

that they did the exercises correctly. Children were issued with a diary in which they recorded how often they completed the exercises each week for the duration of the intervention period, which was 12 weeks. For each completed week they received a star. Caregivers received weekly short messages on their cellular phones to remind them of the exercises and one week before the reassessments.

In study three this programme was tested in a case series over a 12-week period, which yielded positive results in terms of HIV-SN signs and symptoms diminishing and the outcomes of gross motor function improving within the first six weeks. Quantitatively, the scores for the quality of life questionnaire remained unchanged but qualitatively many participants expressed an improved ability to concentrate, improved scholastic achievement and an overall improvement in well-being.

This thesis has provided information which will remedy the dearth of literature in this area both nationally and internationally. The information generated can be used to improve services provided to children living with HIV. We hope that these results will ensure that all HIV positive children will be screened for neuropathy. As therapists we need to advocate that this service is provided to all children living with HIV. Furthermore, that those who present with SN will receive early intervention aimed at reducing the severity of existing signs and symptoms and preventing further neuropathy from developing. The results of this study contribute to the body of knowledge in the management of children infected with HIV. This is aligned with the National Strategic Plan of South Africa 2017-2022 (South African National Department of Health, 2017).

Appendices

APPENDIX 1: PhD Proposal

Research Proposal

Name: Natalie Alice Benjamin (MSc, Wits)

Supervisors: Dr Joanne Potterton (PhD, Wits)

Prof Peter Kamerman (PhD, Wits)

Title: An investigation of peripheral neuropathy in children who are infected with HIV

Introduction

Background

In sub-Saharan Africa, where many new HIV infections continue to occur, an estimated 1.8 million people became infected in 2009; considerably lower than the estimated 2.2 million people in sub-Saharan Africa newly infected with HIV in 2001. This trend reflects a combination of factors, including the impact of HIV prevention efforts and the natural course of HIV epidemics (UNAIDS, 2010)

In southern Africa, the number of children under 15 who became newly infected with HIV fell from 190 000 in 2004 to 130 000 in 2009—a 32% reduction (UNAIDS, 2010)

In a national survey of prevalence and incidence of HIV conducted in 2008, the estimate of HIV prevalence among South Africans of all age groups was found to be 10.6%. It was estimated that in 2008 about 5.2 million people of the total population was HIV-positive. However, with provincial estimates, it was noted that KwaZulu Natal had a 4.1% increase in prevalence from 2002 (11.7%) to 2008 (15.8%) in all age groups, which remains the highest in the country. KwaZulu Natal had the highest reduction of HIV prevalence among children, decreasing from 7.9% in 2005 to 2.8% in 2008.

Peripheral neuropathy in HIV

Peripheral neuropathy (PN) may develop in five to 30% of human immunodeficiency virus – strain 1 (HIV-1) infected patients depending on their stage of disease (Kamerman et al, 2012; Maritz et al 2010). This figure is in excess of 50% in patients on stavudine-based antiretroviral therapy. (Wadley et al, 2011; Maritz et al, 2010)

Parasthesiae and pain are the most common presenting complaints, followed by weakness or loss of motor ability (Shankar et al, 2005)

The most common form of HIV-related neuropathy is distal sensory or axonal neuropathy, which is directly related to HIV-1 infection and often compounded by anti-retroviral therapy (Donald et al, 2011). However, the prevalence of PN in children is not well documented in the South African context even though HIV-related PN is known to be increasing with more children living longer in the Highly Active Anti-Retroviral Treatment (HAART) era.

Studies on HIV-related peripheral neuropathy, its impact on function and mobility as well as management, has been focused to the adult population (Wulff et al, 2000; Botes and Levay, 2004; Cherry et al, 2005; Gonzalez-Duarte et al, 2007; Ellis et al, 2010; Wadley et al, 2011). Very little has been done in the paediatric population, other than estimates of its prevalence (Araújo et al, 2000; Esteban et al, 2008; Donald et al, 2011; Govender et al, 2011 [the latter two studies having been conducted in the same Western Cape, South African hospitals]). The studies by Govender et al (2011) and Donald et al (2011) assessed the extent of neurological complications and neurobehavioural problems in a group of children attending infectious disease clinics in the Western Cape. The researchers established that HIV-associated neurologic complications are common and span a wide spectrum of disorders, but the focus remained on the central nervous system.

The developing nervous system

In a review by Hilburn et al (2010), the impact of HIV on the developing nervous system is discussed and related to factors such as mode of transmission, maternal viral load at time of birth, nutritional status and breast-feeding among others. HIV encephalopathy may occur very early in the course of HIV infection, and 88.1% of children who develop it do so within the first 2 years of life.

HIV related encephalopathy and HIV associated neurocognitive disorders (HANDS) have also been extensively investigated (Poneprasert B, 2002; Shankar et al, 2005; Wilmshurst et al, 2006; Van Rie et al, 2007; Smith et al, 2008; Donald et al, 2011; Govender et al, 2011), with emphasis on neurocognitive function. However, there is a lack of information on peripheral nervous system complications of HIV infection and its treatment in HIV-infected children.

Effect of HIV on motor development

In 2006, Foster and colleagues conducted a retrospective analysis on the motor development of 62 children under the age of three years. The study established that there were statistically significant increases in the prevalence of abnormal neurological signs and motor impairments in infants presenting with more advanced HIV-1 disease. This persisted despite immune reconstitution in HAART. (Foster et al, 2005). Jelsma et al (2011) conducted similar study in Cape Town, comparing the motor development of orphaned children with and without HIV infection. Participants in the study were of average age of four years and data collection was done between 2006 and 2007. The findings of the study were that the children infected with HIV were significantly delayed compared to their healthy counterparts. The study conducted by Govender et al (2011)

only used a screening tool for motor development and therefore could not make robust conclusions about gross motor development. There is a dearth of knowledge regarding the gross motor function of children infected with HIV that are older than three years of age.

Physiotherapy in patients infected with HIV

A systematic review on the effects of exercise on individuals with HIV disease was conducted by Kietrys and colleagues (2007) revealed that regular exercise has no detrimental effect on the immune system over time and that cardiovascular fitness improves. Again, this has been focused to the adult population and has not considered the impact of PN on gross motor development and function in children.

Maintenance of endurance, strength and range of joint movement (active and passive) are important components of any motor function treatment plan. Neuromuscular facilitation and inhibition, positioning and splinting are modalities used to influence tone where abnormal changes have occurred due to central nervous system involvement. Gait training, the use of assistive devices, training in motor planning, balance and endurance exercises are also included. (Kietrys and Galantino, 2007). Coates (1990) stated that with PN the physiotherapy indications and procedures employed should be no different in HIV than those utilised for similar lesions through other causes.

Significance and novelty of the study

Peripheral neuropathy is a known complication of HIV in adults but the prevalence of the condition in the paediatric population, the effects of the neuropathy on gross motor function and the quality of life of children with HIV-related PN is unknown. This study is novel in that research of this nature in the paediatric population has never been done before in South Africa, Africa or the world.

The study aims to establish the prevalence of HIV-PN in children and identify specific developmental or gross motor function problems in which physiotherapy intervention is needed, to ensure that HIV positive children who present with PN develop adequate motor skills so that they are able to function maximally at home, school, in their communities and thus, in society as a whole. The results of this study will make a significant contribution to the body of knowledge in the management of children infected with HIV. This is aligned with the National Strategic Plan of South Africa 2012 -2016.

Research question

How does peripheral neuropathy impact on gross motor function (GMF) of children infected with HIV and can physiotherapy intervention make a positive difference in managing the condition?

Aim

This study aims to determine the proportion of children infected with HIV that develop PN, the effect of the neuropathy on gross motor development/ function and how it impacts on their daily life. In addition to this the study will investigate the changes, if any, a structured physiotherapy programme can make to improve mobility and quality of life.

Objectives

Study One:

1. To determine the prevalence of HIV-related peripheral neuropathy in children attending Rahima Moosa Mother and Child Hospital.
2. To determine the extent of the PN.
3. To determine the factors associated with PN.
4. To assess whether PN affects the quality of life in children infected with HIV.
5. To describe the gross motor function of children infected with HIV, who develop peripheral neuropathy compared to those children who do not develop PN.

Study Two:

6. To develop a physiotherapy intervention programme, using the Nominal Group Technique to manage PN.
7. To determine the outcome of this intervention programme on the gross motor function, mobility and the quality of life

Methodology

Study One:

Objectives one to five will be addressed in Study One. A prospective cross-sectional cohort study (Mann CJ, 2003) will be conducted to ascertain the prevalence of PN in children infected with HIV that attend the Rahima Moosa Mother and Child Hospital outpatient clinic.

Following informed consent of caregivers and verbal assent of the participants, the hospital records will be accessed and information recorded. Information on basic socio-demographic details as well as medical information of first diagnosis, frequency of hospital visits, stage of disease, medication , CD4 and T-cell counts, as well as the current viral load of patients. Anthropometric data of age, height and weight will be taken as part of the routine follow-up at the clinic and recorded for the project.

Since patients are not routinely assessed for neuropathy, The BPNS [see Appendix 8, pg. 33] and the Pin-prick Sensitivity Test as per The Utah Early Neuropathy scale (Singleton et al, 2008) [see Appendix 8, pg. 36] will be used to ascertain whether participants present with PN and if so, the level and extent of the PN. For case ascertainment, subjects will be divided into groups, namely; No PN (no signs or symptoms of PN present); Asymptomatic PN (one or more positive signs but no symptoms present) and Symptomatic PN (two or more signs and symptoms present) Data will be captured manually, recorded and captured on SPSS version 19.

The PedsQL™ [see Appendix 8, pg. 32] will be administered to determine quality of life and level of pain experienced, if any, due to the PN

To determine objective five, a quasi-experimental study will be conducted to ascertain the levels of gross motor function of children infected with HIV and who develop PN. Participants will be divided into the three groups, as described above (par 2, pg. 7) The M-ABC-2® [see Appendix 8 pg. 31] will be conducted to determine the gross motor function levels of the participants at baseline, for all the above-mentioned groups

Inclusion Criteria:

b) All children between the age three and ten years attending the Rahima Moosa Mother and Child Hospital.

Exclusion Criteria:

d) Acute medical conditions that require admission to hospital
e) Tuberculosis of the Spine
f) Any neurological or musculoskeletal conditions that affect gross motor function adversely

Study Two:

Study two will address objectives six and seven. An extensive review of the literature based on the medical and physiotherapy management of peripheral neuropathy in children will be conducted. Once the information is collated, experts in the field of paediatric peripheral neuropathy, such as paediatric therapists (Physiotherapy and Occupational therapy), paediatricians who specialise in oncology, paediatric nurses and paediatric neurologists, will be invited to participate in face to face interviews and discussion, using the Nominal Group Technique [see Appendix 8, pg. 38] to find consensus on the most effective methods for intervention.

Findings of the discussion will be used to design an intervention programme which then will be implemented and tested in a randomised control trial.

The M-ABC-2® [see Appendix 8, pg.31] will be repeated for participants at three and six months post intervention to ascertain changes in the gross motor function levels.

Statistical considerations

Approximately children between the ages of six months and 18 years attend Rahima Moosa Mother and Child Hospital outpatient clinic. Some 800 children are suspected to fall within the age range of three to fifteen years. To determine the prevalence of PN a sample of 323 children will be screened to estimate the expected prevalence of 30% with 95% confidence, to an accuracy of within 5%.

Patients who are positively diagnosed with PN will be invited onto the study and randomly diagnosed negative will be invited to get two, more or less equal groups of expected size between 70 and 90, i.e. total sample of 140 – 180 patients. This sample

size will be adequate to address objectives 2, 4 and 5. Objective 2 requires 10 or more patients per expected risk factor, which should not exceed 8 and hence sample size is adequate.

Objective 4 and 5 have 5 and 3 subscales respectively. Study groups will be compared using Hotelling's T^2- test for the 5 x 1 (Q1, Q2, Q3, Q4, Q5) and #x 1 (F1, F2, F3) observations vectors respectively. By convention, when error degrees of freedom exceeds 30, which will be the case, sample size is regarded as adequate. For objective 7, the sample will also be adequate as now Hotelling's T^2-test for paired observations will be used to compare pre-to post intervention results of gross motor function.

To compile an 'ideal' physiotherapy intervention programme, an expert group will be invited to participate in the Nominal Group Technique approach. A further approach to design such a programme will be to model pairwise rations of an importance between items/actions/elements and the geometric mean method will be applied, a well established procedure in multi-criteria decision analysis (Hennessy et al, 2006 and Becker et al, 2009)

Ethics

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee, Clearance number: M 120767. I will request permission from the hospital manager at Rahima Moosa Hospital, as well as the Gauteng Department of Health to conduct the research at the selected site.

It would be important to obtain (signed) consent from Parents/ Guardians/ Caregivers (written if they are literate or verbal, if they are not) of the participants after explaining the purpose and procedure of the study as well as that the risks involved (in their home language and with the assistance of a translator, if needed). I would emphasise that declining to participate will not affect their access to the same healthcare services as other patients and that they have the right to withdraw at any time.(See Appendix 4,5, and 7)

Following the consent of the parents/ caregivers, it will be important to obtain verbal assent from the participants, after describing the study in their home language. (See Appendix 6)

I will also reassure participants that all results are for purposes of the study only and that it will be held in confidence. All data collected will be kept for a period of ten years in the safe at the Department of Physiotherapy on completion of the study. (See Appendix 1, 2 and 3)

Project Management

The project will commence in July 2012 and is expected to be completed by December 2015

Activity	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature Review	2012						2015					
Preparing Protocol	2012				2012							
Protocol Assessment					2012	2012						
Ethics Application						2012			Obtained 2012			
Permission to conduct research						Obtained 2013				Start 2012		
Collecting Data Study one		End 2014					Start 2013					
Data analysis Study one				End 2014						Start 2013		
Collecting Data Study two - NGT								Start 2014	End 2014			
Data analysis Study two - NGT										Start 2014	End 2014	
Data collection Study two - RCT	Start 2014											End 2014
Data analysis Study two - RCT		End 2015	Start 2014									
Writing up - thesis			Start 2015					End 2015				
Writing up - papers (x 3)	Start 2016						End 2016					

Funding

The predicted budget for the project is as follows:

Item	Estimated costs	Frequency	Actual costs (will be completed as project proceeds)
Movement – ABC kit	R 20 000	Once off	
Laptop for data collection	R 15 000	Once off	
Research assistant/ s (Rate R85 p/h)	R 55 000	Per annum	
Travelling	R 10 000	Per annum	
Stationary	R 10 000	Per annum	
Photocopying (PedsQL & M-ABC sheets)	R4 000	Once off	
Attending conferences – local	R 20 000	Per annum	
Attending conferences – international	R 40 000	Per annum	
Telephone calls	R 2 000	Per annum	
Refreshments for participants	R 5 000	Per annum	
Totals	R 181 000		

Funding will be applied for at the Medical Research Council, The National Research Fund – Thuthuka Grant. The research will be privately funded, through research funds of the researcher until additional funding can be obtained.

APPENDIX 2: Approval of title

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2076

Reference: Ms Salamina Segole
E-mail: salamina.segole@wits.ac.za
02 August 2012
Person No: 0717667A
PAG

Miss NA Benjamin
187 Battersea Avenue
Reservoir Hills
4091
Durban, South Africa

Dear Miss Benjamin

Doctor of Philosophy: Approval of Title

We have pleasure in advising that your proposal entitled "*An investigation of peripheral neuropathy in children who are infected with the human immunodeficiency virus*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX 3: Original ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Natalie A Benjamin

CLEARANCE CERTIFICATE **M120767**

PROJECT An Investigation of Peripheral Neuropathy in Children who are Infected with HIV

INVESTIGATORS Ms Natalie A Benjamin.

DEPARTMENT Department of Physiotherapy

DATE CONSIDERED 27/07/2012

DECISION OF THE COMMITTEE* Approved unconditionally, must be cleared also by UKZN research ethics Committee

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

DATE 28/09/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr J Potterton

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX 4: Amended ethical clearance certificate

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical)
Secretariat: Research Office, Room SH10005, 10th floor, Senate House • Telephone: +27 11 717-1234 • Fax: +27 11 339-5708
Private Bag 3, Wits 2050, South Africa

20 May 2013

Ms Natalie Benjamin
Department of Physiotherapy
Medical School
University

Sent by email to: Natalie.benjamin@wits.ac.za

Dear Ms Benjamin

RE: **Protocol M120767: 'An Investigation of Peripheral Neuropathy in Children Who are Infected with HIV**
Protocol amendment

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has reviewed and approved your request to 'move the study from King Edward VIII Hospital in KZN to Rahima Moosa Mother and Child Hospital in Gauteng' as detailed in your letter dated 09 May 2013.

Thank you for keeping us informed and updated.

Yours sincerely,

Anisa Keshav
Administrator
Human Research Ethics Committee (Medical)

APPENDIX 5: Letter requesting permission to conduct research

Physiotherapy

Faculty of Health Sciences · Private Bag 3, Wits, 2050, South Africa

Tel: +27 11 717 3702 · Fax : 27 11 717 3719 · E-mail: maryanne.cannon@wits.ac.za

13 June 2012

To whom it may concern:

RE: Permission to conduct research at Rahima Moosa Hospital

I, the undersigned, am currently registered at the University of the Witwatersrand for a PhD degree in Physiotherapy. I am conducting research, investigating the presence and extent of peripheral neuropathy in children who are infected with HIV.

I would appreciate it, if I may include children attending the Paediatric Outpatient Clinic at Rahima Moosa Hospital. The procedures are non-invasive to the children and will be a part of the routine visit to the Clinic. I will be conducting Gross Motor assessments as well as a full neurological assessment. In the second part of the study, I will be introducing an intervention program aimed at improving gross motor function. The research will assist therapists in identifying an area of intervention and therapy that needs development.

The parent/ caregiver will receive a copy of the attached letter and verbal assent will be obtained from the participants. Participation in the study remains voluntary and all information collected will be held in confidence.

Your assistance in this regard will be greatly appreciated. Please do not hesitate to contact me should you require further information in this regard.

Kind regards,

Ms Natalie Benjamin

Office: 011 717 3731 e-mail: nbenjamin@mweb.co.za

Cell: 083 501 1969

APPENDIX 6 Letter granting permission



GAUTENG PROVINCE

HEALTH

REPUBLIC OF SOUTH AFRICA

Dr Edward Hank
Clinical Manager
Rahima Moosa Mother and Child Hospital
Tel: (011) 470 9031
Fax: (011) 477 4117
E-mail: Edward.Hank@gauteng.gov.za

9 May 2013

Dear Ms Benjamin

Re Approval : Study looking at the Peripheral Neuropathy in Childhood HIV

On behalf of the Rahima Moosa Mother and Child Hospital and as its Clinical Manager I hereby provide approval for the proposed project. I note that you are registered at the University of the Witwatersrand for a PhD degree in Physiotherapy and that you hope to investigate the presence and extent of peripheral neuropathy in children who are infected with HIV. I have been informed by Professor Coovadia that the participants will be drawn from his unit - Empilweni Clinic on the fourth floor of the Hospital and the Research unit in B Block.

I have noted too the ethical clearance that has already been obtained from the Human Research Ethics Committee at the University of the Witwatersrand (Ref: M 120 767).

Yours faithfully

Dr Edward Hank – BSc Hons B Pharm, MBBCh

APPENDIX 7: Demographic data sheet

Data code: _____

Demographic and anthropometric data sheet

Name of parent/ guardian: _____

Consent form signed: Yes/ No

Name of participant: _____

Surname: _____

Date of birth: _____ Age: ___yrs. ____ mths

Gender: M/F

Physical home address: _____

_____

APPENDIX 8: Clinical data sheet

Data code: _____

Date of first diagnosis: _____

Currently on HAART: Yes/No

Date HAART commenced: _____

Medication issued: Dosage::

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Most recent CD4 results: _____ Date: _____

Most recent Viral load results:_____ Date:_____

Current clinical staging: _____Date: _____

*See staging chart

Currently attending school: Yes / No

If yes, Grade: _____

If no, why

_____

_____

Height: _____ (m)

Weight: _____ (kg)

BPNS Score: _____ Pin-prick sensitivity:*see chart

PedsQL™ baseline: _____ PedsQL™ post: _____

M-ABC Baseline Score _____

M-ABC: 6 months: _____

M-ABC 12 months: _____

APPENDIX 9: Data collection sheet

Data Collection Sheet														
Data Code	Date	HAART -Y/N	CD-4 Count	Viral Load	T-cell count	Current WHO clinical staging	Height	Weight	BPNS Score	PedsQL™	M-ABC Baseline Score	M-ABC 6 months	M-ABC 12 months	PedsQL™ Post intervention

APPENDIX 10: Information document study 1

INFORMATION DOCUMENT – Study One

Study title: An investigation of Peripheral Neuropathy in children who are infected with HIV

Hello,

My name is Natalie Benjamin and I am a student at the University of Witwatersrand. I am doing research on peripheral neuropathy and gross motor function in children. Research is just the process to learn the answer to a question. In this study I want to learn if your child is affected by pain or numbness in his/ her legs and how this affects their ability to move.

I am asking for your permission to include your child in a research study.

During the research I will be looking at your child's legs and testing if there are any problems with the nerves that will cause pain or numbness. Your child will be asked to complete a questionnaire so that I can understand how the pain/ numbness affects their ability to move and play. This will form part of your routine check-up and will take about 45 minutes. I will also be accessing your child's medical files for information on CD4 counts, viral loads, medication taken, height and weight.

Risks

There are no risks involved unless your child has any medical condition that would exclude him/her from participating in the study.

Benefits

The study will help us to determine how many children are affected by pain and numbness in their legs

Participation is voluntary and your child may withdraw at any time should he/she wish to do so. Your child may discontinue participation at any time without penalty loss of benefits to which s/he is entitled.

Confidentiality: Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the University of Witwatersrand Human Research Ethics Committee.
If results are published, may lead to cohort identification.

Thank you very much.
Natalie

Contact details of researcher:
Natalie Benjamin, Physiotherapist
Department of Physiotherapy
011 717 3731
083 501 1969

Contact details of REC administrator and chair – for reporting of complaints / problems.

APPENDIX 11: Consent statement

Consent statement

I, the undersigned, _____, acknowledge that I read
(Full name and Surname of parent/ guardian)
the information sheet and hereby give permission that my son/ daughter,

_____, may participate in the study as described
(Full name and Surname)

above.

YES NO

Signatures:

Parent or Guardian: _____

Researcher: _____

Witness: _____

APPENDIX 12: Verbal assent

Verbal assent form

Hi, my name is Natalie. I am busy with a project for the university. Please can I look at your legs, ask you some questions and look at how you move?

Before we begin, I will look at how tall you are, how much your body weighs. I will then ask you to lie down so that I can examine your legs. I will also be talking to you and asking about how you feel and how the pain/ numbness affects your ability to walk, run and play. If you feel that you do not want to, or cannot carry on, you can stop.

This letter says that I explained what you will be doing and that you either agree or may refuse to help me.

Thank you for your help.

YES NO

Signatures:

Participants' signature_____

Researcher's signature _____

Witness _____

APPENDIX 13: PEDsQL details and Neurological screen form

Paediatric Quality of Life Inventory (PedsQL™)

This is a quality of life questionnaire that has been developed by Dr James Varni, 1998 (Kallianpur et al.) The PedsQL™ builds on and expands a programmatic instrument development effort by Varni and his associates during the past 15 years in paediatric populations. The PedsQL™ 1.0, originally derived from a paediatric cancer database, was designed as a generic quality of life inventory to be utilized noncategorically, i.e., across multiple paediatric populations. Given that instrument development is an iterative process, the PedsQL™ 2.0 and 3.0 were further advancements in the measurement model, including additional constructs and items, a more sensitive scaling range, and a broader age range for patient self-report and parent proxy-report. The PedsQL™ has resulted from our rapid cycle improvement strategy, and has been field tested with children and adolescents in paediatrician's offices, hospital specialty clinics, and community settings. The PedsQL™ Generic Core Scales are currently in use in several school districts nationwide, as well as by State Departments of Health as a way of monitoring the health of large populations of healthy and ill children. Clinical trials and treatment interventions utilizing the PedsQL™ are in the planning stages internationally. The PedsQL™ has been translated into numerous international languages.

Objective:
To assess health related quality of life in children in various disease areas. Applicable for healthy school and community populations, as well as with paediatric populations with acute and chronic health conditions.

Varni et al (2007 and 2008) conducted field trials to assess reliability, validity, responsiveness and practicality of the PedsQL™. Internal consistency and reliability was found to be excellent with alpha values greater than 0.70 for the self- and proxy-report and alpha values reaching 0.90 for the full 23-item scale. Validity of the PedsQL™ was done using comparisons to other measures of disease burden. The PedsQL™ was found to be responsive to clinical change as well.

PedsQL™ Administration Guidelines

The following guidelines are intended for use by individuals trained in the administration of standardized questionnaires. The PedsQL™ administrator is crucial in developing rapport with the respondents, emphasizing the importance of the questionnaire, addressing concerns, and ensuring that the PedsQL™ is completed accurately and confidentially.

General Protocol

Create a procedure for assigning identification numbers that will allow for parent/child

1. Comparisons as well as comparisons of baseline/follow-up data.
2. If feasible, the PedsQL™ should be completed before the respondents complete any other health data forms and before they see their physician or healthcare provider.
3. The parent/child should first complete the PedsQL™ Generic Core Scales and then complete any additional PedsQL™ Module.
4. Parents, Children (8-12) and Teens (13-18) may self-administer the PedsQL™ after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ □ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ □ should be read aloud to the child or teen. For the Young Child (5-7), the PedsQL™ should be administered by reading the instructions and each item to the young child word for word. At the beginning of each subscale repeat the recall interval instructions (one month or 7 days) to remind the young child to respond only for that specific recall interval. Use the separate page with the three faces response choices to help the young child understand how to answer. When reading items aloud to a child, intonation should be kept neutral to avoid suggesting an answer.
5. If a child has difficulty understanding the age-appropriate PedsQL™ □, the preceding age group version may be administered to the child (e.g., administering the Young Child (5-7) Self-Report version with the three faces response choices to an 8 year old). However, if a child presents with severe cognitive impairments (as determined by the administrator), the PedsQL™ □ may not be appropriate for that child. In such cases, only the Parent-Proxy Report should be administered to the child's parent.
6. The parent and child must complete the questionnaires independently of one another. Discourage the parent, child, or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel free to discuss their answers following completion of the questionnaires, but that it is important

to get both the parent's and the child's individual perspectives. If you are administering the questionnaire to the child, the child should be facing away from the parent.

7. If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item according to what they think the question means. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child and/or the parent has the option of not answering a question if they truly do not understand the question.
8. If a parent/child asks you to interpret the responses, tell her/him that you are not trained to interpret or provide a score for the answers given. If the PedsQL™ is being used for a clinical study, let the parent/child know that their answers will be combined with other participants' answers and analyzed as a group rather than as individual respondents.
9. Document all reasons for refusals and non-completions of the PedsQL™.

Administering the PedsQL™

The following scripts have been developed as a guide to introduce the PedsQL™ to the child and his/her parent(s). Modify the language to a style that is most appropriate for you and the respondent.

For the child:

The PedsQL™ asks you questions about how you feel and what you think about your health. It is not a test, and there are no right or wrong answers. It takes about 5 minutes to complete. If you have any questions, please let me know.

For the parent:

The PedsQL™ is a questionnaire that assesses health-related quality of life in children and adolescents. It contains questions about your child's physical, emotional, social, and school functioning in the past one month (or for the Acute version, in the past 7 days).

The PedsQL™ is brief and typically takes less than 5 minutes to complete. It is not a test, and there are no right or wrong answers. Please be sure to read the instructions carefully and choose the response that is the closest to how you truly feel. Please do not compare your answers with

your child's responses. We are interested in your and your child's individual perspectives. However, feel free to discuss the questionnaire with your child after you have both completed it and returned it to me. If you have any questions, please let me know.

1. Provide the respondent with a pen or pencil and a solid writing surface. If a table is not available, the participant should be provided with an item such as a clipboard. Remain nearby should questions or concerns arise.
2. When the parent/child returns the PedsQL™ ™, look it over and check to see that all answers have been completed. Verify that no item has more than one response. If any responses are incomplete, illegible, or there are multiple responses for an item, please ask the parent or child to indicate their response.
3. Ask the participants if they had any difficulties completing the questionnaire or if they have any other comments regarding the questionnaire. Document any important feedback.
4. Thank the parent and child for taking the time to complete the questionnaire. If the study design involves following up with these respondents, let them know that they may be asked to complete the PedsQL™ again at another time. Indicate when they can expect to be contacted again if known

The Brief Peripheral Neuropathy Screening Tool

NEUROLOGICAL SCREEN

Symptom description:

1. Have you ever had odd/strange/painful feelings or discomfort in your feet?

Yes ☐ **No** ☐

2. Do you currently have odd/strange/painful feelings or discomfort in your feet?

Yes ☐ **No** ☐

If "No", go to Question 4, in the "Testing of signs" section on page

3. If you currently have odd/strange/painful feelings or discomfort in your feet, how well does each of the following words describe this feeling or discomfort? Please rate the severity of these symptoms using the scale (mild, moderate of severe pain):

Symptom	**Symptom presence** (tick one)			**If "YES", what is the intensity** (tick one)
	NO	**UNSURE**	**YES**	
a) Hot / burning *isiZulu: kuyashisa / kuyavutha* *Setswana: go molelo / go a fisa / go a asha* *Sesotho: ho a tjesa / ho ho tjang*				□ Mild □ Moderate □ Severe
b) Cramping *isiZulu: inkwantshu / amacrampu* *Setswana: go bogatsu* *Sesotho: ho bahatsu*				□ Mild □ Moderate □ Severe
c) Painful / sore / aching *isiZulu: kubuhlungu* *Setswana: go botlhoko* *Sesotho: ho botlhoko*				□ Mild □ Moderate □ Severe
d) Itching *isiZulu: kuyaluma* *Setswana: go a baba* *Sesotho: ho a baba*				□ Mild □ Moderate □ Severe

Question 3 continued…

Symptom	**Symptom presence** (tick one)			**If "YES", what is the intensity** (tick one)
	NO	**UNSURE**	**YES**	
e) Numb / lack of feeling *isiZulu: kundikindiki* *Setswana: go a bogatsu* *Sesotho: bohatsu*				□ Mild □ Moderate □ Severe
f) Cold / freezing *isiZulu: kuyabanda/ kuyiqwa* *Setswana: go maruru / go tsididi* *Sesotho: ho a bata*				□ Mild □ Moderate □ Severe
g) Pins & needles / stabbing / pricking *isiZulu: kuyahlaba* *Setswana: mo go tlhabang* *Sesotho: hoo hlabang*				□ Mild □ Moderate □ Severe

Testing of signs:

4. Vibration sense

INSTRUCTIONS FOR EVALUATING PERCEPTION OF VIBRATION

Strike the end of a 128 Hz tuning fork hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the participant's wrist to be sure that they can recognise the vibration or "buzzing" quality of the tuning fork. Instruct the participant to tell you when the "buzzing" stops. Again, strike the ends of the tuning fork hard enough so that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint. Start your stopwatch from the time you strike the tuning fork, and stop it when the participant says that they can no longer feel the "buzzing". Repeat for the other great toe.

Great toe DIP joint perception of vibration (time in seconds)		
Could feel vibration for 10 second or more? (0 = "less than 10 seconds", 1 = "10 seconds or more")		

5. Ankle reflexes

INSTRUCTIONS FOR EVALUATING DEEP TENDON REFLEXES

With the participant seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the participant's ankle to 90 degrees. Using a reflex hammer, the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner's hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck. Use reinforcement, if necessary, by having the participant perform the Jendrassick manoeuvre.

Ankle reflexes

0 = absent

1 = Present

2 = unable/did not assess

	R	L
Ankle reflexes		

6. Pin-prick sensitivity

EVALUATING PIN PRICK SENSITIVITY IN LOWER LIMBS

With the participant seated confirm whether they can distinguish sharp versus dull on in an unaffected area (e.g., forearm) while they watch you perform the procedure. With the participant not looking, confirm with three random stimuli that they can correctly identify sharp versus dull stimuli in the unaffected area. Then, check their ability to recognize the sharp stimulus in the lower limbs. Check the medial and lateral side of each limb at the level of the toes (dorsal surface of the great toe and 5th toe), ankle (medial and lateral malleolus), and the knee (just below the knee on each side). If the participant is able to detect "sharp" at a proximal point but states "dull" more distally, check with additional stimuli between the two points to establish the level at which sensation changes (on both sides of the leg) and record the level in the table below. If the participant responds "dull" at a site proximal to a site where they previously identified a sharp stimulus distally, repeat test 2-3 times at sites marginally (1-2cm) away to determine whether pinprick sensation is generally intact in that area or not; mark the local area of anaesthesia.

	R	L
Is there any deficient? (0 = deficit present, 1 = no deficit)		

If a deficient is present, indicate the level at which the deficit occurs by ticking the appropriate box or boxes

	R	L
Foot only		
Foot and ankle only		
Foot to knee		

INSTRUCTIONS FOR RECORDING SUBJECTIVE ELICITED SYMPTOMS

Ask the subject to rate the severity of each symptom listed in question 1 on a scale of 01 –mild to 10 – most severe for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb). If a symptom has been present in the past, but not since the last visit, enter ’00- Currently Absent’. If the symptom has never been present, enter ’11 – Always Been Normal’

Always been normal	Currently absent	Mild ----------Severe									
11	00	01	02	03	04	05	06	07	08	09	10

1. Symptoms R L
   a. Pain, aching or burning in feet, legs
   b. “Pins and needles” or odd/ strange/ funny feeling in feet or legs
   c. Numbness (lack of feeling) in feet, legs

INSTRUCTIONS FOR GRADING SUBJECTIVE ELICITED SYMPTOMS

Location of symptoms

Use Score of:

0 = None

1 = Feet only

2 = Extends to ankles

3 = Extends above ankle but not to knee

4 = Extends to knees

5 = Extends above knees

R L

a. Pain, aching or burning in feet, legs
b. “Pins and needles” or odd/ strange/ funny feeling in feet, legs
c. Numbness (lack of feeling) in feet, legs

INSTRUCTIONS FOR EVALUATING PERCEPTION OF VIBRATION

Compress the ends of a 128Hz tuning fork just hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subjects' wrist or hand to be sure that they can recognise the vibration or 'buzzing' quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough so that the sides touch, immediately place the vibrating tuning fork gently on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops. Repeat for the other great toe.

2. Vibration perception

R L

a. Great toe DIP joint perception of vibration in seconds

R L

b. Vibration perception score

Anything less than 10 seconds is documented as abnormal

INSTRUCTIONS FOR EVALUATING DEEP TENDON REFLEXES

With the subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subjects' ankle to 90 degrees. Using a reflex hammer the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner's hand as plantarflexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck. Use reinforcement by having the subject clench his/her fist before classifying the reflex as absent.

Ankle Reflexes

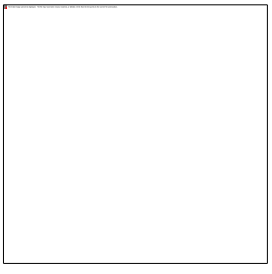
0 = Absent

1 = Hypoactive

2 = Normal deep tendon reflexes

R L

3. Ankle reflexes



APPENDIX 14: Literature review matrix

Title	Author Date	Research Question /Aim	Research Objectives	Methodology	Analysis and Results	Conclusions	Implications for practice	NOTES:
HIV Peripheral Neuropathy and Foot Care Management: A Review of Assessment and Relevant Guidelines	By Joyce K. Anastasi, PhD, DrNP, Bernadette Capili, PhD, NP-C, and Michelle Chang, MS ***AJN*** ▼ December 2013 ▼ Vol. 113, No. 12	Overview				Foot care management can prevent further complications in polyneuropathy	Foot care management includes improving circulation via exercise.	Pedro: 0/11
Whole body vibration therapy for painful diabetic peripheral neuropathy: A pilot study	21 December 2012 Nathan J. Kessler, BA a, Junggi Hong, PhD, ATC	Is whole body vibration efficient in treating diabetic peripheral neuropathy?	To apply the treatment from previous case studies to a larger participant group, further testing the efficacy of whole body vibration as a treatment for diabetic peripheral neuropathy.	Pre-test, post test Pilot study	Normality test (ShapiroeWilk) HolmeSidak ANOVA Significant decrease in acute and chronic VAS. Significant increase in duration of pain reduction over 4 weeks.	It supports previous research indicating whole body vibration's efficacy as a potential treatment for diabetic peripheral neuropathy.	It potentially can assist with pain and it is safe and there are no known complications.	Very small sample size, poor attrition rate, 1 month after treatment 7 out of 8 participants symptoms had returned to – levels. Pedro: 0/11

Weight-Bearing Versus Nonweight-Bearing Exercise for Persons With Diabetes and Peripheral Neuropathy: A Randomized Controlled Trial	Michael J. Mueller, PT, PhDa, Lori J. Tuttle, PT, PhDb, Joseph W. LeMaster, MD, MPHc, Michael J Strube, PhDd, Janet B. McGill, MD, MAe, Mary K. Hastings, PT, DPT, ATCf, and David R. Sinacore, PT, PhDg 2013 May	The purpose of this prospective randomized controlled trial was to determine the effect of a WB exercise program compared with an NWB exercise program on the primary outcome measures of the 6-minute walk distance (6MWD) and daily step counts (steps/d).	WB exercise would show greater improvements in primary outcomes compared with the NWB exercise group.	Randomised controlled trial Inclusion: step count 2000 to 9000 steps per day; Type 2 DM, PN; ex <3x/week <20mins Exclusion: weight>136kg; foot deformity Sample size 29	Statistical analysis on an intention-to-treat basis was performed - alpha was set to .05. A 2 group (WB, NWB) × 2 time (preand posttesting) repeated-measures analysis of variance was used 95% confidence interval Results: The WB group showed greater gains than the NWB group over time (significant interactions) in the primary outcomes of the 6MWD and average daily step count (P<.05) The mean between-group difference over time was 29m (95% CI, 6–51) for the 6MWD and	People in the WB exercise group showed greater gains in daily step count and 6MWD compared with those in the NWB exercise group.	WB ex seems to be more effective for pts with PN in DM than NWB ex. But the intensity and duration needs to be significant.	Small sample size thus statisticall y not very powerful. Pedro: 11/11

					1178 steps (95% CI, 150–2205) for the average daily step count.			
Physical Therapy Modalities and Rehabilitation Techniques in the Management of Neuropathic Pain	**2014** **Akyuz G, Kenis O**			Literature Review		Physical therapy modalities such as superficial and deep heat agents, analgesic currents, and laser are not sufficient in the management of neuropathic pain when applied alone. Even though neurostimulation techniques are being used more frequently, their effectiveness in	Rehabilitation programs must be emphasized and combined with pharmacotherapy in daily practice.	**Pedro: 0/11**

						the treatment of neuropathic pain are still disputed.		
Exercise Interventions, Gait, and Balance in Older Subjects with Distal Symmetric Polyneuropathy	Quigley PA, Bulat T, Schulz B, Friedman Y,Hart-Hughes S,Richardson JK,BarnettS: 2014	The specific hypothesis was that compared with an education-only control group (EC), a once-a-week program for 10 wks in TC or FBT would improve clinical assessments, gait, and balance.	Older patientswith a distal symmetric polyneuropathy are at markedly increase risk for falls and fall-related injuries. Despite this, few studies have investigated the effect of exercise regimens on gait and balance in this high-risk group.	Parallel, three-group, randomized controlled trial.	The Tai Chi subjects demonstrated a decreased (faster) Timed Up and Go and increased stride length and time spent in single limb support at the end of intervention as compared with baseline. The functional balance training group demonstrated a significant increase in ankle plantar flexor power and near significant decreases in step width and step width variability	Older patients with distal symmetric polyneuropathy may benefit from Tai Chi and/or functional balance training, with the former improving functional mobility and gait and the latter possibly improving trunk stabilization and forward progression. Whether these laudable changes can be maintained or	Functional balance training can help improve gait inn pts with PN.	**Good study design but the study had a high attrition value and thus is not very powerful. Pedro: (cant find article)**

					No changes in the education-only control group were observed.	translate into decreased risk for falls and fall-related injuries is unknown.		
Exercise-Induced Modulation of Pain in Adults With and Without Painful Diabetic Neuropathy	**Matthew T. Knauf and Kelli F. Koltyn** **June 2014**		**Purpose of this study was to examine exercise-induced pain modulation in diabetic** adults with painful diabetic neuropathy (PDN) compared to diabetic adults without PDN.	Pre-test post-test	**Results indicated that ratings** of perceived exertion and muscle pain during exercise were significantly higher ($P < .05$) for diabetic adults with PDN versus diabetic adults without PDN. Diabetic adults with PDN did not experience changes in thermal pain ratings following exercise, whereas diabetic adults without PDN reported significantly lower pain ratings following exercise.	It is concluded that diabetic adults with PDN experienced high levels of muscle pain during exercise and a lack of exercise-induced hypoalgesia following exercise, in comparison to diabetic adults without PDN, who experienced lower	Exercise may be painful for pts with PN	**Weak study design Pedro: 4/11**

						levels of muscle pain during exercise and a hypoalgesic response following exercise.		
Dynamic stability training improves standing balance control in neuropathic patients with type 2 diabetes	**Hoda Salsabili, MS;1* Farid Bahrpeyma, PhD;1 Bijan Forogh, MD;2 Sanaz Rajabali, MS3** **2011**		**To determine if balance training will treat context specific** instabilities of postural control of patients with DN.	quasi-experimental time series study	**KolmogorovSmirnov** test **ANOVA paired *t*test**	In conclusion, training that compensates for disordered balance indicated by subclinical constraints with respect to the guidance effect of external visual feedback improves standing postural control in patients with type 2 DN	Balance training can improve postural control	**Only diabetics Pedro: 5/11**

Do diabetic neuropathy patients benefit from balance training?	**Mohammad Akbari, PhD;1 Hassan Jafari, PhD, PT;1* Afsaneh Moshashaee, MSc;1 Bijan Forugh, MD2** **2012**		**The purpose of this study was** to investigate the effects of balance exercises on sway indices in diabetic patients with neuropathy.	Controlled trial but does not discuss methodology in detail	**Student and paired *t*-tests** **The overall stability index and** anterior-posterior stability index were significantly decreased after treatment in the experimental group during different conditions. Balance indices in the experimental group were significantly higher than the control group before treatment. There was no significant difference in indices between the two groups after treatment.	balance training can improve stability indices in diabetic patients with neuropathy.	Balance ex may be beneficial	**Small sample size and lots of info is missing from the article Pedro: 5/11**

Effects of an Exercise Program on Balance and Trunk Proprioception in Older Adults with Diabetic Neuropathies	**Chang Ho Song, Ph.D.,1 Jerrold S. Petrofsky, Ph.D., J.D.,2 Seung Won Lee, Ph.D.,1** Kyoung Jin Lee, M.S.,1 and Jong Eun Yim, M.S.2 **2011**	**To** assessed the effects of an exercise program on balance and trunk proprioception in older adults with diabetic neuropathies.		Thirty-eight patients with diabetes having peripheral neuropathies were enrolled, randomized, and subdivided in two groups: an experimental group of 19 participants with diabetes (72.95.6 years old) and a control group of 19 participants with diabetes (73.25.4 years old). Both groups received health education on diabetes for 50 min/week for 8 weeks. The experimental group practiced an additional balance exercise program for 60 min, two times a week. The exercise training was performed two times per week for 8 weeks. Results were evaluated by both static and dynamic balance and trunk proprioception.	**Postural sway significantly decreased (P<0.05), the one-leg stance test significantly increased (P<0.05),** and dynamic balance from the Berg Balance Scale, Functional Reach Test, Timed Up and Go test, and 10-m walking time improved significantly after balance exercise (P<0.05). Trunk repositioning errors also decreased with training (P<0.05).	The balance exercise program improved balance and trunk proprioception . These results suggested that a balance exercise is suitable for individuals with diabetic neuropathy.		**Pedro: 7/11**

Effects of a combined strengthening, stretching and functional training program versus usual-care on gait biomechanics and foot function for diabetic neuropathy: a randomized controlled trial	**Cristina Dallemole Sartor, Ricky Watari, Anice Campos Pássaro, Andreja Paley Picon, Renata Haydée Hasue and** Isabel CN Sacco* **2011**	**aim is to investigate the effect of exercise** therapy intervention on foot rollover during gait, ROM, and muscle strength and function of the foot and ankle complex, as well as balance confidence when performing walking tasks.	**Our hypotheses are:** (I) The specific training proposed could improve muscle function and foot and ankle ROM. (II) It could be reflected in the foot rollover during gait, improving plantar pressure distribution and lower limb kinematics.	A randomised, controlled trial, with blind assessment, was designed to study the effect of a physiotherapy intervention on foot rollover during gait, range of motion, muscle strength and function of the foot and ankle, and balance confidence. The main outcome is plantar pressure during foot rollover, and the secondary outcomes are kinetic and kinematic parameters of gait, neuropathy signs and symptoms, foot and ankle range of	**No results stipulated**	No conclusion		**Strange study, seems as though it was never actually conducted as there are no results** **The next study discusses the results Pedro:10/11**

				motion and function, muscle strength, and balance confidence. The intervention is carried out for 12 weeks, twice a week, for 40-60 min each session. The follow-up period is 24 weeks from the baseline condition.				
Effects of strengthening, stretching and functional training on foot function in patients with diabetic neuropathy: results of a randomized controlled trial	**Cristina D Sartor1, Renata H Hasue1, Lícia P Cacciari1, Marco K Butugan1, Ricky Watari1, Anice C Pássaro1,** Claudia Giacomozzi 2 and Isabel CN Sacco1 **2014**	**To investigate the effects of strengthening, stretching, and functional training on foot rollover process during** gait.		A two-arm parallel-group randomized controlled trial with a blinded assessor was designed. Fifty-five patients diagnosed with diabetic polyneuropathy, 45 to 65 years-old were recruited. Exercises for foot-ankle and gait training were administered twice a week, for 12 weeks, to 26 patients assigned to the intervention group, while 29	**Even though the intervention group primary outcome (PP) showed a not statistically significant change** under the six foot areas, intention-to-treat comparisons yielded softening of heel strike (delayed heel TPP, p=.03), better eccentric control of forefoot contact (decrease in ankle extensor moment, p<.01; increase in function of ankle	Intervention discreetly changed foot rollover towards a more physiological process, supported by improved plantar pressure distribution and better functional condition of the foot ankle complex.	Intervention works but doesn't last. Ex therefore just manages the symptoms but if not done then the problem returns	**The main limitation of this clinical trial is the lack of** follow-up for the CG. Therefore, follow-up results could not be compared between CG and IG. Pedro: 9/11

				patients assigned to control group received recommended standard medical care: pharmacological treatment for diabetes and foot care instructions. Both groups were assessed after 12 weeks, and the intervention group at follow-up (24 weeks). Primary outcomes involved foot rollover changes during gait, including peak pressure (PP). Secondary outcomes involved time-to-peak pressure (TPP) and pressure–time integral (PTI) in six foot-areas, mean center of pressure (COP) velocity, ankle kinematics and kinetics in the sagittal plane, intrinsic and extrinsic muscle function, and functional tests of foot and ankle.	dorsiflexion, $p<.05$), earlier lateral forefoot contact with respect to medial forefoot (TPP anticipation, $p<.01$), and increased participation of hallux (increased PP and PTI, $p=.03$) and toes (increase in PTI, medium effect size). A slower COP mean velocity ($p=.05$), and an increase in overall foot and ankle function ($p<.05$) were also observed. In most cases, the values returned to baseline after the follow-up ($p<.05$).			

Physiotherapy intervention in two people with HIV or AIDS-related peripheral neuropathy	**JUDITH GALE** **2003**	**Peripheral neuropathy is one of the adverse effects of patients living with AIDS and patients live longer these days therefore what can we do to improve quality of life.**		Case report	**Subject 1: After 12 months of treatment every second week, Decreased pain and numbness, improved ambulation, reduction in pain meds** **Subject 2: After weekly treatment for 18months, reduction in pain and pain meds and return to work full time**	the combination of joint mobilization, microcurrent, soft tissue mobilization and selfmanagement appears to be an effective intervention when no other methods have provided signif icant relief. In the f irst subject, signs and symptoms included pain, allodynia, gait abnormality and contractures.	Used a combination of joint mobilization, soft tissue mobilization, microcurrent, stretching and instruction in a home programme. Touch seems to have a huge impact on these patients.	**This intervention needs to be tested with quantitative research Pedro: 0/11**

						By decreasing these signs and symptoms, the functional limitations — in this case inability to walk one block or sleep through the night — were minimized. As a result, quality of life improved allowing the patient to travel and become more independent. In the second case, numbness, pain, stiffness and gait abnormalities were addressed. Decreasing		

						these signs and symptoms allowed increased functional ambulation. Because of the increased functional abilities, the patient was able to return to work, decreasing disability and promoting independence.		
Managing HIV Peripheral Neuropathy	***Alejandra Gonzalez-Duarte, MD, Katia Cikurel, MD,*** *and David M. Simpson, MD* **2007**	**Sx's:** slowly progressive numbness and paresthesias, with burning sensations in the feet usually in a symmetrical pattern.	**Current management:** The current treatment for HIV-associated DSP is symptomatic, with pain modifying medications, including anti-inflammatory	Etiology: The etiology of HIV-associated DSP is unknown, although neurotoxic effects of cytokines, toxicity of HIV proteins, and mitochondrial damage have been implicated.			physical approaches, including biofeedback, relaxation therapy, and cognitive and behavioral modalities are suggested as management	**Overview: good information on etiology Pedro: 0/11**

			agents, opioids, antidepressants, antiepileptics, topical anesthetics, and capsaicin. Sustained virologic control may improve DSP.					
HIV-Associated Peripheral Neuropathy Epidemiology, Pathophysiology and Treatment	***Enrique A. Wulff, Annabel K. Wang* and *David M. Simpson*** **2000**	**There are different forms of HIV peripheral neuropathy:** • **Inflammatory demyelinating** polyneuropathy • Distal symmetric polyneuropathy • Mononeuritis multiplex • Progressive polyradiculopathy • Autonomic neuropathy	**They report that there is a** very low rate of peripheral neuropathy in the paediatric population infected with HIV.[9,1	They have found: • Loss of myelinated fibres with disproportionately greater loss of large myelinated fibres. • Demyelination and axonal degeneration. • Mild epineural and endoneural perivascular inflammatory cells, such	**The major clinical symptoms of DSP are distal** numbness, paresthesias and dysesthesias (‘burning feet’), usually occurring symmetrically in the lower extremities. Distal and symmetrical numbness of the upper extremities may occur later in the course	The pathogenesis of these toxic neuropathies is thought to be due to their interference with mitochondrial DNA synthesis.	Treatment: • The first step in the treatment of DSP, after metabolic causes are excluded, is the consideration of withdrawal or dose reduction of neurotoxic antiretroviral agents	**An overview. Concentrated on distal symmetrical polyneuropath Pedro: 0/11**

				as T lymphocytes and activated macrophages. • The lack of CD4 receptor expression in the nerve surface suggests that direct infection with HIV is unlikely.	of DSP. The most common signs of DSP on neurological examination are absent or depressed ankle reflexes.[26,27] While joint position remains relatively normal, vibratory thresholds are increased in the feet. Pain and temperature sensation is reduced in a stocking and glove distribution. Motor examination generally reveals minimal weakness, usually restricted to intrinsic foot muscles.		• The current treatment of DSP is primarily symptomatic. • The guidelines of the World Health Organization 'analgesic ladder'[43] serve as a helpful approach to painfulDSP	

Diagnosis and Management of HIV-Associated Neuropathy	**Alejandra Gonzalez-Duarte, MD,** Jessica Robinson-Papp, MD, David M. Simpson, MD* 2008	**The clinical features of HIV-DSP and ARV-DSP are identical,** with pain and paresthesias being the principal symptoms.	**It is** thought that HIV disease progression leads to dysregulation of macrophages and overproduction of proinflammatory cytokines and chemokines, which in turn leads to DSP.	Symptoms: Distal painful dysesthesias, allodynia, severe burning pain, pins and needles sensations, and numbness are the main symptoms. Symptoms usually begin in the feet, often on the soles, and progress up the legs	**Diagnsosis:** Skin biopsy is a validated technique for the detection of small-fiber neuropathy. A punch biopsy is performed at a distal (calf) and proximal (thigh) site in the lower extremity, and intraepidermal nerve fiber density is measured [18]. This technique is valuable for the diagnosis of DSP, for monitoring its progression over time, and for predicting the likelihood of the condition developing in asymptomatic patients. **The vibratory threshold has the best discriminatory**		Summary As advances in the treatment of HIV lead to improved longevity, managing the neurologic sequelae of HIV infection becomes an increasingly important part of comprehensive HIV care. DSP is the most common neurologic complication of HIV. Although neuroregenerative therapies are not yet available, early recognition of this condition can lead to a treatment strategy to identify modifiable risk factors, to control symptoms, and to improve patients' quality of life.	**Lots on pharmacology treatment. Pedro: 0/11**

					ability for symptomatic HIV-DSP in comparison to the usual findings of impairment of threshold for heat, pain, and cooling in diabetic neuropathy.			
Therapeutic exercise in physiotherapy practice is beneficial: a summary of systematic reviews 2002–2005	**Nicholas F Taylor, Karen J Dodd, Nora Shields and Andrea Bruder** **2007**	**Is therapeutic exercise of benefit in reducing** impairment, improving activity, and increasing societal participation for people who would be expected to consult a physiotherapist?		Systematic review	**The search yielded** 38 systematic reviews of reasonable or good quality. The results provided high level evidence that therapeutic exercise was beneficial for patients across broad areas of physiotherapy practice, including people with conditions such as multiple sclerosis,	Therapeutic exercise was beneficial for patients across broad areas of physiotherapy practice. Further high quality research is required to determine the effectiveness of therapeutic exercise in emerging areas of practice.	Higher intensity ex is more beneficial. I.e 4-5 times a week for at least 20mins. Few adverse effects were associated with high intensity ex and very few exacerbation of symptoms was reported.	**Didn't mention anything about peripheral neuropathy, Pedro: 0/11**

					osteoarthritis of the knee, chronic low back pain, coronary heart disease, chronic heart failure, and chronic obstructive pulmonary disease. Therapeutic exercise was more likely to be effective if it was relatively intense and there were indications that more targeted and individualised exercise programs might be more beneficial than standardised programs. There were few adverse			

					events reported. However, in many areas of practice there was no evidence that one type of exercise was more beneficial than another.			
HIV Neuropathy Risk Factors and Symptom Characterization in Stavudine-Exposed South Africans	Antonia L. Wadley, BSc Hons, Catherine L. Cherry, MBBS, PhD, Patricia Price, PhD, and Peter R. Kamerman, PhD April 2011		To determine the prevalence, risk factors, and clinical characteristics of symptomatic HIV-SN in a Black South African cohort of patients exposed to stavudine.	Cross sectional study: HIV-positive Black South Africans (n ¼ 395) who had received stavudine for at least six months were recruited at the Virology Clinic of the Charlotte Maxeke Academic Johannesburg Hospital, South Africa, and screened for neuropathy using the AIDS Clinical Trials Group neuropathy screening tool.	The prevalence of symptomatic HIV-SN was 57% (226 of 395). Increasing age and height were independently associated with the development of SN among patients who had used stavudine. Pain was the primary symptom reported by participants with HIV-SN (76%, 172 of 226), followed by numbness	HIV-SN was common in this population and frequently associated with moderate to severe pain in the feet. HIV-SN was significantly associated with increasing age and height, factors that could be measured at no added cost prior		risk of symptom atic HIV-SN increases with increasing age and height, across all ages and heights, has important clinical implicatio ns Pedro: 1/11

				HIV-SN was defined as present if the patient had both symptoms and signs of peripheral neuropathy. If present, the distribution and intensity of symptoms were recorded. In addition, anthropomorphic, demographic, and clinical information were recorded and analyzed as risk factors.	(48%, 108 of 226), and pins and needles (46%, 105 of 226). About three-quarters of participants rated their symptoms as being of moderate to severe intensity. Symptoms were always present in the feet and only 23% experienced symptoms proximal to the feet. Normally distributed continuous data are presented as mean (SD), and nonparametric data as median (range). Univariate analyses of risk factors associated with neuropathy were undertaken	to stavudine prescription, allowing higher risk patients to be offered priority		

					using Chi-squared tests (dichotomous variables), unpaired t-tests (parametric continuous variables), and Mann-Whitney tests (nonparametric continuous variables).			
Exercise for people with peripheral neuropathy	White CM, Pritchard J, Turner-Stokes L. 2011		**The primary objective was to examine the effect of exercise therapy on functional ability in the treatment of people with peripheral**	Systematic Review Two authors independently selected eligible studies, rated the methodological quality and extracted data.	Only one trial fully met the inclusion criteria. An additional two trials assessed outcomes less than eight weeks after randomisation and were also included. Methodological quality was poor for several criteria in each study. Data used in the three studies could not be	There is inadequate evidence to evaluate the effect of exercise on functional ability in people with peripheral neuropathy. The results	Ex has not been proven to improve people's functional ability in patients with PN but resisted exercise my help to strengthen muscles.	Only 1 RCT was found. Pedro: 1/11

			neuropathy. In addition, secondary outcomes of muscle strength, endurance, broader measures of health and well being, as well as unfavourable outcomes were examined.		pooled due to heterogeneity of diagnostic groups and outcome measures. The results of the included trials failed to show any effect of strengthening and endurance exercise programmes on functional ability in people with peripheral neuropathy. However, there is some evidence that strengthening exercise programmes were moderately effective in increasing the strength of tested muscles.	suggest that progressive resisted exercise may improve muscle strength in affected muscles.		

Exercise Intervention Studies in Patients with Peripheral Neuropathy: A Systematic Review.	Streckmann, Fiona; Zopf, Eva; Lehmann, Helmar; May, Kathrin; Rizza, Julia; Zimmer, Philipp; Gollhofer, Albert; Bloch, Wilhelm; Baumann, Freerk 2014 September		**Our objective in this systematic** review was to analyze exercise interventions for neuropathic patients in order to evaluate the possible benefits of exercise.	Three independent reviewers used PubMed, MEDPILOT (MEDLINE), Cochrane, and relevant reference lists to obtain the data. Relevant studies were graded according to the Oxford Levels of Evidence.	Eighteen studies (ten randomized controlled trials and eight controlled clinical trials) met all inclusion criteria. Three (diabetic) studies were ranked very high quality [1b (A)], nine high quality (four diabetes, one cancer, four others) [2b (B)], while six (four diabetes, two others) showed low quality (4/C). Current data suggests that exercise is a feasible, safe, and promising supportive measure for neuropathic patients.	Overall, balance training appears to be the most effective exercise intervention. Studies focusing exclusively on strength, or a combination of endurance and strength, appear to have a lower impact. For metabolically-induced neuropathies, endurance training also plays an important role. Further research with high methodologic al quality needs to be conducted in order to	Balance ex are more effective than strengthening ex	Good systematic review Pedro: 1/11

					This is best documented for patients with diabetic peripheral neuropathy (DPN), suggesting that endurance training has the potential to prevent the onset of and reduce the progression of DPN. In general, balance exercises showed the highest effect on the motor as well as sensory symptoms in all types of PNP.	establish evidence-based clinical recommendations for neuropathic patients.		
Evidence-based guideline: Treatment of painful diabetic neuropathy	V. Bril, MD, FRCP(C) J. England, MD, FAAN G.M. Franklin, MD, MPH, FAAN		**To develop a scientifically sound and clinically relevant evidence-based guideline for**	We performed a systematic review of the literature from 1960 to August 2008 and classified the studies according to the American Academy of Neurology classification of evidence	Pregabalin is established as effective and should be offered for	Based on a Class I study, electrical stimulation is probably effective in lessening the pain of	1. Percutaneous electrical nerve stimulation should be considered for the treatment of PDN (Level B).	Only for diabetic peripheral neuropathy. Pedro: 1/11

	M. Backonja, MD J. Cohen, MD, FAAN D. Del Toro, MD E. Feldman, MD, PhD, FAAN D.J. Iverson, MD, FAAN B. Perkins, MD, FRCP(C), MPH J.W. Russell, MD, MS, FRPC D. Zochodne, MD April 2011		the treatment of painful diabetic neuropathy (PDN).	scheme for a therapeutic article, and recommendations were linked to the strength of the evidence. The basic question asked was: "What is the efficacy of a given treatment (pharmacologic: anticonvulsants, antidepressants, opioids, others; and nonpharmacologic: electrical stimulation, magnetic field treatment, low-intensity laser treatment, Reiki massage, others) to reduce pain and improve physical function and quality of life (QOL) in patients with PDN?"	relief of PDN (Level A). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin are probably effective and should be considered for treatment of PDN (Level B). Other treatments have less robust evidence or the evidence is negative. Effective treatments for PDN are available, but many have	PDN and improving QOL. Based on single Class I studies, electromagnetic field treatment, lowintensity laser treatment, and Reiki therapy are probably not effective for the treatment of PDN. There is not enough evidence to support or exclude a benefit of amitriptyline plus electrotherapy in treating PDN	2. Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for the treatment of PDN (Level B). 3. Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment of PDN (Level U).	

					side effects that limit their usefulness, and few studies have sufficient information on treatment effects on function and QOL.			
ELECTROTHERAPY FOR THE TREATMENT OF PAINFUL DIABETIC PERIPHERAL NEUROPATHY: A REVIEW*	Karin Pieber, MD, Malvina Herceg, MD and Tatjana Paternostro-Sluga, MD, PhD 2010		**To review different types of electrotherapy for the treatment of painful diabetic peripheral neuropathy.**	**A structured search of the electronic database MEDLINE was performed from the time of its initiation to July 2009. Articles in English and German were selected.**	**The efficacy of different types of electrotherapy for painful diabetic peripheral neuropathy has been evaluated in 15 studies; the effects of transcutaneous electrical nerve stimulation are consistent. The beneficial effects of prolonged use have been reported in three large studies and one small**	**Further randomized, double-blind, placebo-controlled studies comprising larger sample sizes, a longer duration of treatment, and longer follow-up assessments are required.**	ET seems to reduce pain in these patients but the evidence is not good quality and therefore a statement cannot be made to say it is effective.	Only on diabetics Pedro: 1/11

					study. The effects of frequency-modulated electromagnetic neural stimulation were assessed in one large study, and a significant reduction in pain was reported. Treatment with pulsed and static electromagnetic fields has been investigated in two small and three large studies, and analgesic benefits have been reported. In one large study focusing on pulsed electromagnetic fields, no beneficial effect on pain was registered.			

					Only small studies were found concerning other types of electrotherapy, such as pulsed-dose electrical stimulation, high-frequency external muscle stimulation or high-tone external muscle stimulation.			
Pilot Trial of a Patient-Specific Cutaneous Electrostimulation Device (MC5-A Calmare) for Chemotherapy-Induced Peripheral Neuropathy	Thomas J. Smith, MD, Patrick J. Coyne, RN, MSN, Gwendolyn L. Parker, RN, MSN, Patricia Dodson, BSN, MA, and Viswanathan Ramakrishnan, PhD	An evolving hypothesis for reducing CIPN pain involves direct nerve stimulation to reduce the pain impulse.	**To evaluate the impact on CIPN associated with the MC5-A** Calmare therapy device.	The MC5-A Calmare therapy device is designed to generate a patient-specific cutaneous electrostimulation to reduce the abnormal pain intensity. Sixteen patients from one center received one-hour interventions daily over 10 working days.	Of 18 patients, 16 were evaluable. The mean age of the patients was 58.6 yearsdfour men and 14 womendand the duration of CIPN was three months to eight years. The most common drugs were taxanes, platinums, and	Patient-specific cutaneous electrostimulation with the MC5-A Calmare device appears to dramatically reduce pain in refractory CIPN patients	Electrostimulation reduced pain but it returned after 2 months	Small unblinded study with short term follow up. Population: Cancer patients with peripheral neuropathy Pedro: /11

	December 2010				bortezomib (Velcade, Millenium Pharmaceuticals, Cambridge MA). At the end of the study (Day 10), a 20% reduction in numeric pain scores was achieved in 15 of 16 patients. The pain score fell 59% from 5.81 1.11 before treatment to 2.38 1.82 at the end of 10 days (P < 0.0001 by paired t-test). A daily treatment benefit was seen with a strong statistically significant difference between the preand post-daily pain scores (P < 0.001). Four patients had their CIPN reduced to	with no toxicity. Further studies are underway to define the benefit, mechanisms of action, and optimal schedule		(could not find article)

					zero. A repeated-measures analysis using the scores from all 10 days confirmed these results. No toxicity was seen. Some responses have been durable without maintenance.			

Balance Interventions for Diabetic Peripheral Neuropathy: A Systematic Review	Ites, Katherine I. PT, DPT1; Anderson, Elizabeth J. PT, DPT2; Cahill, Megan L. PT, DPT3; Kearney, Jenny A. PT, DPT4; Post, Emily C. PT, DPT4; Gilchrist, Laura S. PT, PhD4 September 2011		**The purpose of this study was to assess the effectiveness of interventions used by physical therapists to minimize balance dysfunction in people with DPN.**	When conducting this systematic review, we searched the electronic databases CINAHL, EMBASE, Cochrane Review, and Medline using specific search terms for the period from inception of each database to June 2009. Two independent reviewers analyzed the abstracts obtained to determine whether the article focused on balance interventions that are within the scope of physical therapy practice. All study designs were eligible for review with the exception of case reports and systematic reviews. The Delphi criteria was used to assess methodological quality. This literature search and methods assessment resulted in 2213 titles, 82 abstracts, and 6 articles, including 1 randomized controlled trial eligible for inclusion.	The 6 articles contained 4 physical therapy interventions including monochromatic infrared energy therapy, vibrating insoles, lower extremity strengthening exercises, and use of a cane. Upon thorough analysis of outcome measures, statistical significance, and clinical relevance, the intervention of lower extremity strengthening exercises was given a fair recommendation for clinical use in treating balance dysfunction in patients with DPN.	This systematic review revealed that there is a significant need for further research to investigate the effectiveness of physical therapy interventions to improve balance in patients with DPN. Currently, there is very little evidence to support such interventions. Of the evidence that is available, many studies are poorly designed and do not utilize reliable and valid outcome measures.	the intervention of lower extremity strengthening exercise can be given a fair recommendation for clinical use in addressing balance dysfunction in patients with DPN.	Patient population was diabetics only. Pedro: 1/11

Pharmacological Treatment of Painful HIV-Associated Sensory Neuropathy: A Systematic Review and Meta-Analysis of Randomised Controlled Trials	Tudor J. C. Phillips1*, Catherine L. Cherry2,3,4, Sarah Cox5, Sarah J. Marshall6, Andrew S. C. Rice1 December 2010		**To evaluate the clinical effectiveness of analgesics in treating painful HIV-SN.**	Design: Systematic review and meta-analysis. Data sources: Medline, Cochrane central register of controlled trials, www.clinicaltrials.gov, www.controlled-trials.com and the reference lists of retrieved articles. Selection criteria: Prospective, double-blinded, randomised controlled trials (RCTs) investigating the pharmacological treatment of painful HIV-SN with sufficient quality assessed using a modified Jadad scoring method. Review methods: Four authors assessed the eligibility of articles for	Of 44 studies identified, 19 were RCTs. Of these, 14 fulfilled the inclusion criteria. Interventions demonstrating greater efficacy than placebo were smoked cannabis NNT 3.38 95%CI(1.38 to 4.10), topical capsaicin 8%, and recombinant human nerve growth factor (rhNGF). No superiority over placebo was reported in RCTs that examined amitriptyline (100mg/ day), gabapentin (2.4g/day), pregabalin (1200mg/day), prosaptide (16mg/day), peptide-T (6mg/day), acetyl-L-carnitine (1g/	Evidence of efficacy exists only for capsaicin 8%, smoked cannabis and rhNGF. However,rhNGF is clinically unavailable and smoked cannabis cannot be recommended as routine therapy. Evaluation of novel management strategies for painful HIV-SN is urgently needed.	It seems that first line medications are no better than placebo in the management of pain in HIV-SN.	Pharmacology Pedro: 1/11

				inclusion. Agreement of inclusion was reached by consensus and arbitration. Two authors conducted data extraction and analysis. Dichotomous outcome measures ($30% and $50% pain reduction) were sought from RCTs reporting interventions with statistically significant efficacies greater than placebo. These data were used to calculate RR and NNT values.	day), mexilitine (600mg/day), lamotrigine (600mg/day) and topical capsaicin (0.075% q.d.s.).			

APPENDIX 15: Delphi round one questionnaire

Delphi Survey – Round one

This survey comprises of ___ questions which is divided into two sections and takes ___ minutes to complete. Section 1 is a demographic section, section 2 highlight the complications of HIV and ARV's on the nervous system in children.

The complications presented are based on the findings from my study which investigated the presence of peripheral neuropathy and gross motor dysfunction in children infected with HIV, on ARV's between the ages of four and ten years. Following the findings you will be required to suggest possible intervention strategies to prevent or reduce the impact of the highlighted complications.

At the end of each section you can suggest any prevention, intervention or treatment strategy that you feel should be included in the management of children infected with HIV.

Once received, the information from each participant will be collated and sent as a second Delphi round for consensus. A third Delphi round will only be considered if consensus is not achieved in the second round. Consensus will be determined by the central tendencies and convergence of responses around a particular prevention, intervention or treatment reached. The time allocation per round is two weeks. A general one week reminder will be sent to everyone on the panel. A gap (maximum two weeks) for collations will be administered between the surveys.

The information received will be invaluable as it will assist us in improving the lives of children infected with HIV. The information will add to the evidence for the physiotherapy management of children infected with HIV and will strengthen our role within this context.

I would like to thank you in advance for your time and willingness to participate.

Questions marked with and * are required

1. **Are you willing to participate in the Delphi Survey***

This serves as consent that you are willing to participate in the study. Please note that you can withdraw at any time and anonymity will be maintained throughout the survey.

Mark only one option

- ☐ Yes, I would like to participate in this survey
- ☐ No, I do not want to participate in this survey

Section 1: Demographics

2. What gender are you?*
    - ☐ Female
    - ☐ Male

3. How old are you?*
    - ☐ <30 years old
    - ☐ 30 -40 years old
    - ☐ 40 – 50 years old
    - ☐ > 50 years old

4. Which province do you currently reside in?*

If you not a South African citizen, please state your country of origin

_____

5. What year did you qualify?*_____

6. Do you hold any postgraduate qualification(s) in paediatric physiotherapy?*

E.g. Masters of PhD

- ☐ Yes
- ☐ No

7. If yes, please state your highest qualification.

_____

_____

8. Have you had any postgraduate training in paediatric physiotherapy?*

E.g. courses

- ☐ Yes

□ No

9. If yes, please list the courses attended

_____
_____
_____
_____
_____
_____

10. Please state how many years of clinical experience you have in paediatrics

_____

Section 2 – Complications associated with HIV and ARV's in children

Participants (139) were assessed for the presence of peripheral neuropathy using the Brief Peripheral Neuropathy Screen as well as for Gross motor function using the Movement-ABC II.

11. Thirty six participants (25.9%) presented with bilateral signs of peripheral neuropathy. Please list ***specific intervention*** strategies to address the above. E.g. exercise

_____
_____
_____
_____
_____
_____

12. Please list specific ***prevention*** strategies to address the above. E.g. Vitamin B12 supplements

_____
_____
_____
_____
_____

_____

13. Twenty-four participants (17.2%) presented with pain in the lower limbs as a result of the neuropathy.

Please list ***specific intervention*** strategies to address the above. E.g. exercise

_____

_____

_____

_____

_____

_____

14. Please list specific ***prevention*** strategies to address the above. E.g. Vitamin B12 supplements

_____

_____

_____

_____

_____

_____

15. Seven participants (5.0%) presented with itching in the lower limb as a result of the neuropathy.

Please list ***specific intervention*** strategies to address the above. E.g. exercise

_____

_____

_____

_____

_____

_____

16. Please list specific ***prevention*** strategies to address the above. E.g. Vitamin B12 supplements

_____

_____

_____
_____
_____
_____

17. Four participants (2.8%) presented with numbness in the lower limb as a result of the neuropathy.

Please list ***specific intervention*** strategies to address the above. E.g. exercise

_____
_____
_____
_____
_____
_____

18. Please list specific ***prevention*** strategies to address the above. E.g. Vitamin B12 supplements

_____
_____
_____
_____
_____
_____

19. Six participants (4.3%) presented with pins and needles in the lower limb as a result of the neuropathy.

Please list ***specific intervention*** strategies to address the above. E.g. exercise

_____
_____
_____
_____
_____
_____

20. Please list specific ***prevention*** strategies to address the above. E.g. Vitamin B12 supplements

_____
_____
_____
_____
_____
_____

21. __ participants (_____) presented with poor manual dexterity

Please list ***specific intervention*** strategies to address the above. E.g. writing exercise, improving proximal stability

_____
_____
_____
_____
_____
_____

22. __ participants (_____) presented with poor ability to do aiming and catching

Please list ***specific intervention*** strategies to address the above. E.g. improving proximal stability

_____
_____
_____
_____
_____
_____

23. __ participants (_____) presented with poor balance ability

Please list ***specific intervention*** strategies to address the above. E.g. gluteal strengthening exercises

_____
_____

_____

_____

_____

_____

http://goo.gl/forms/z9mEAzeU8z

APPENDIX 16: Delphi round two questionnaire

Delphi Survey – Round Two

Thank you for your participation in round two of the Delphi study. In this round the information collated from round one will be presented. You are required to select on a scale of 1 to 5, how likely (1= very unlikely, 2=unlikely, 3=neutral, 4= likely, 5=very likely) you are to use the management strategies presented for the complication specified as well as for the preventative management techniques mentioned. At the end of each question you will be asked for your reason(s) for your 'likely' and 'unlikely' selections

The information received will be invaluable as it will assist us in improving the lives of children infected with HIV. The information will add to the evidence for the physiotherapy management of children infected with HIV and will strengthen our role within this context.

I would like to thank you in advance for your time and willingness to participate.

Questions marked with and * are required

Section 1 – Management of Peripheral Neuropathy (PN)

1.1 The general management of PN – intervention

a. Balance exercises
b. Fitness/ endurance exercises
c. Proprioception exercise
d. Strengthening exercises
e. Stretching exercises
f. Weight-bearing exercises
g. Education of the child
h. Education of the caregiver
i. Sensory stimulation
j. Pain management – medication
k. Pain management – heat
l. Pain management – stopping neurotoxic meds
m. Functional electrical stimulation
n. Orthotics
o. Kinesio-taping
p. Treadmill training

1.2 The general management of PN – prevention

a. Early intervention and screening
b. Referral to occupational therapy
c. Referral to a dietitian
d. Education of the child
e. Education of the caregiver
f. Nutrition/ dietary advice
g. Non-steroidal anti-inflammatories

1.3 The management of PN related pain – intervention

a. Balance exercises
b. Fitness/ endurance exercises
c. Proprioception exercise
d. Strengthening exercises
e. Stretching exercises
f. Weight-bearing exercises
g. Education of the child
h. Education of the caregiver
i. Sensory desensitisation
j. TENS
k. Neural mobilisation
l. Pain management – medication
m. Pain management – heat
n. Pain management – topical analgesics
o. Massage
p. Aquatic therapy

1.4 The management of PN related pain – prevention

a. Balance exercises
b. Fitness/ endurance exercises
c. Proprioception exercise
d. Strengthening exercises
e. Stretching exercises
f. Weight-bearing exercises
g. Education of the child
h. Education of the caregiver
i. Pain management – medication
j. Discontinue ARV's
k. Nutrition/ dietary advice

1.5 The management of PN related itching – intervention

a. Balance exercises
b. Proprioception exercise
c. Circulation exercises

d. Stretching exercises
e. Weight-bearing exercises
f. Education of the child
g. Education of the caregiver
h. Sensory desensitisation
i. TENS
j. Management – medication
k. Management – keeping skin cool
l. Management – topical analgesics
m. Massage
n. Referral to an occupational therapist

1.6 The management of PN related itching – prevention

a. Balance exercises
b. Proprioception exercise
c. Stretching exercises
d. Weight-bearing exercises
e. Education of the child
f. Education of the caregiver
g. Early intervention
h. Nutrition/ dietary advice

1.7 The management of PN related numbness – intervention

a. Balance exercises
b. Fitness/ endurance exercises
c. Proprioception exercise
d. Strengthening exercises
e. Stretching exercises
f. Sensory awareness
g. Weight-bearing exercises
h. Education of the child
i. Education of the caregiver
j. Early screening and intervention
k. Management – discontinue neurotoxic drugs
l. TENS
m. Neural mobilisation
n. Massage
o. Kinesio-taping

1.8 The management of PN related numbness – prevention

a. Balance exercises
b. Proprioception exercise
c. Stretching exercises
d. Weight-bearing exercises

e. Education of the child
f. Education of the caregiver
g. Early intervention
h. Nutrition/ dietary advice

1.9 The management of PN related pins and needles – intervention

a. Balance exercises
b. Proprioception exercise
c. Circulation exercises
d. Stretching exercises
e. Weight-bearing exercises
f. Education of the child
g. Education of the caregiver
h. Early intervention
i. Nutrition/ dietary advice
j. TENS
k. Massage

1.10 The management of PN related pins and needles – prevention

a. Balance exercises
b. Proprioception exercise
c. Stretching exercises
d. Weight-bearing exercises
e. Education of the child
f. Education of the caregiver
g. Early intervention
h. Nutrition/ dietary advice

Section 2 – Motor development intervention strategies

2.1 Intervention strategies for poor manual dexterity

a. Activation and strengthening of core muscles
b. Strengthening of the shoulder girdle muscles
c. Weight bearing through the upper limbs
d. Mobile weight bearing of the upper limbs
e. Strengthening exercises of the hand
f. Fine motor/ dexterity exercises
g. Posture re-training and improving postural control
h. Task/ functional activity training
i. Education of the child
j. Education of caregivers
k. Education of teachers
l. Pilates
m. Refer to an occupational therapist

2.2 Intervention strategies for poor manual dexterity

a. Activation and strengthening of core muscles
b. Strengthening of the shoulder girdle muscles
c. Weight bearing through the upper limbs
d. Mobile weight bearing of the upper limbs
e. Strengthening exercises of the hand
f. Fine motor/ dexterity exercises
g. Posture re-training and improving postural control
h. Task/ functional activity training
i. Education of the child
j. Education of caregivers
k. Education of teachers
l. Pilates

2.3 Intervention strategies for poor balance ability

a. Activation and strengthening of core muscles
b. Strengthening of the pelvic girdle muscles
c. Weight bearing through the lower limbs
d. Mobile weight bearing of the lower limbs
e. Strengthening exercises of the lower limbs
f. Balance exercises on a stable and unstable surface
g. Posture re-training and improving postural control
h. Increase proprioceptive input through the feet
i. Education of the child
j. Education of caregivers
k. Education of teachers
l. Pilates
m. Hippotherapy
n. Kinesio-tape

2. 4 Intervention strategies to improve quality of life

a. Education of the child
b. Education of caregivers
c. Education of teachers
d. Exercise
e. Refer to a Social Worker
f. Refer to a Psychologist
g. Refer to a Dietitian
h. Refer to an Occupational Therapist
i. Advice on activities of daily living

APPENDIX 17: Information document study 3

INFORMATION DOCUMENT – Study Three

Study title: An investigation of sensory neuropathy in children who are infected with the Human Immunodeficiency Virus

Hello,

My name is Natalie Benjamin and I am a student at the University of Witwatersrand. I am doing research on peripheral neuropathy and gross motor function in children. Research is just the process to learn the answer to a question. In this study I want to learn if exercise will help your child to move better and if it will ease some of the discomfort.

I am asking for your permission to include your child in a research study.

During the research I will be teaching you and your child some exercises and how to take care of their feet. You will be asked to carry on doing the exercises at home every day to see if it will help your child.

After three months and again after six months, I will test his/ her ability to move, to see if it has changed.

Risks

There are no risks involved unless your child has any medical condition that would exclude him/her from participating in the study.

Benefits

The study will help us to determine if exercise and advice will help your child to develop and move better

Participation is voluntary and your child may withdraw at any time should he/she wish to do so. Your child may discontinue participation at any time without penalty loss of benefits to which s/he is entitled.

Confidentiality: Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Research Ethics Committee.
If results are published, may lead to cohort identification.

Thank you very much.
Natalie

Contact details of researcher:
Natalie Benjamin, Physiotherapist
Department of Physiotherapy
031 260 7181
083 501 1969

Contact details of REC administrator and chair – for reporting of complaints / problems.

APPENDIX 18: Information booklet for patients

Information Booklet

Table of contents:

- Welcome to Programme……..pg 2
- Why Exercise is important for me?.....pg 2-3
- Home exercise programme……pg 3
- Contact details…… pg 4

UNIVERSITY OF THE WITWATERSRAND
JOHANNESBURG

Welcome to the programme!

Dear Parent/ guardian and children,

I would personally like to welcome you to the study! Thank you for agreeing to participate and thus further the research. This information booklet is a way to explain your role in the above study as well as a guide to the exercise programme.

You have been selected to participate in the study because you have shown signs of peripheral neuropathy. The effects of exercise on peripheral neuropathy have not yet been scientifically proven and through this study we aim to determine just that! Your child will participate in a 30 minute exercise programme at home three times a week over the next four months.

First appointment:
An individual appointment with the physiotherapist will be booked to reassess your child. Participants and caregivers will be taught the home exercise programme by a qualified physiotherapist who will ensure correct and safe execution of the exercises.

This booklet contains an exercise sheet to remind you what to do when you get home. Participants are required to complete these exercises three times a week for the four month duration of the study. Monday, Wednesday and Friday are preferred exercising days to allow for sufficient rest periods.

Second appointment/ Eight week follow up date:_____.

Third appointment/ Twelve week follow up date:_____.

*****Expect a sms from us once a week to remind you of your exercises.

Why Exercise is Important for me?

Exercise should be an important part of your daily routine as it improves:

- General health
- Cardiovascular fitness
- Weight control
- Sleep quality
- The immune system
- Bone density
- Optimal daily function to enhance independence in ADL's
- Optimal psychological and social well-being

What is aerobic exercise?
'Aerobic' means using oxygen during exercise. These are usually exercises which causes you to breathe harder and your heart to beat faster. This is because your muscles need more oxygen to deal with the increased demand on the body. Examples include running, cycling, swimming and dancing.

What is strengthening exercise?
These are exercises which causes your muscles to adapt to an increased load on them. An increased load can be applied to the muscle by using weights, therabands or body weight training.

Home Exercise Programme

2. Warm-up:

- Marching on the spot – two repetitions of 2 minutes each;
- Spinning arms in small circles – two repetitions of 1 minute each.

3. Stretching:

- Touching toes – two repetitions of 30 seconds each;
- Pull arm across body – two repetitions of 30 seconds each side;
- Pull hand up in front of body using other hand – one repetition of 30 seconds;
- Reaching up – two repetitions of 30 seconds each;
- Ankle exercise, writing the alphabet with your big toe – two repetitions of "A" through to "Z".

4. Aerobic Exercises:

- Jumping jacks – two repetitions of 20 each;
- Skipping – one repetition of 30 seconds;
- Running with high knees for 20m – two repetitions ;
- Walking with heels to the bottom for 20m – two repetitions;
- Sideways skipping for side 20m – one repetition for each side.

5. Strengthening Exercises:

- Sit ups – two repetitions of 20 each;
- Push ups – two repetitions of 20 each;
- Squats – two repetitions of 20 each;
- Air cycling – two repetitions of 20 each.

6. Balance Exercises:

- Standing on one leg for 30 seconds with eyes open – one repetition on each leg
- Standing on one leg for 30 seconds with eyes closed – one repetition for each leg;

- Hopping on one leg with eyes open – one repetition of 10 seconds on each leg.

9. Cool Down:

Walking for 5 minutes at a slow and comfortable pace.

DON'T:

- Give child stars for other reasons like good behaviour; the star chart is primarily for completion of daily exercise programme
- Give child more than one star a week

DO:

- Encourage your child to keep doing their exercises
- Include siblings and peers into exercise programme to encourage optimal participation

You have the right to

- Refuse to participate in the study
- Terminate participation in the study at any given time
- Have the purpose of the study explained
- Confidentiality of personal information
- Receive an intervention programme of high quality
- Be informed on outcome of the study

Contact us!

Natalie Benjamin, Physiotherapist

Department of Physiotherapy

University of the Witwatersrand

011 717 3731

083 501 1969

APPENDIX 19: Exercise diary

PiNC Study: Exercise Diary

Week 1

Day	Date
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	

_____

STAR

Week 2

Day	Date
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	

_____

STAR

Week 3

Day	
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	

_____

STAR

---

*Please give a star for every week of exercise completed.

APPENDIX 20: Turnitin Report

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