PREVALENCE OF PERIPHERAL NEUROPATHY AND EFFECTS OF PHYSIOTHERAPEUTIC EXERCISES ON PERIPHERAL NEUROPATHY IN PEOPLE LIVING WITH HIV ON ANTIRETROVIRAL THERAPY IN RWANDA

David Kabagema Tumusiime

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Doctor of Philosophy

Johannesburg, 2014

DECLARATION

I, David K. Tumusiime, declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

29th day of August, 2014

DEDICATION

To my beloved wife; Florence, for the love and kindness, encouragement and "standing in my feet" whenever I was away,

To my children; Solomon and Shiloh; "you missed me at the time of most need",

To my mother; Edinance; and father; late Kabagema "the foundation you laid makes me what I am today".

PUBLICATIONS AND PRESENTATIONS IN SUPPORT OF THIS THESIS

DK Tumusiime

PUBLICATIONS

Tumusiime DK, Stewart A, Venter F & Musenge E, 2014. Prevalence of Peripheral Neuropathy and associated demographic and health status characteristics, among People living with HIV on Antiretroviral Therapy in Rwanda: BMC, public health, under review

Tumusiime DK, Stewart A, Venter F & Musenge E, 2014. The validity and reliability of modified lower extremity functional scale among adult people living with HIV on Antiretroviral Therapy, in an African environment: SAHARA Journal, under review.

Tumusiime DK, Musabeyezu E, Mutimura E, Hoover DR, Shi Q, Rudakemwa E, Ndacyayisenga E, Dusingize JC, Sinayobye JD, Stewart A, Venter WDF & Anastos K, 2014. Over-reported peripheral neuropathy symptoms in a cohort of HIV infected and uninfected Rwandan women: the need for validated locally appropriate questionnaires: African Health Science, 14(2): 460 – 467.

CONGRESS AND CONFERENCE PRESENTATIONS

Tumusiime DK, Stewart A, Venter F, 2010, Reliability of Lower Extremity Functional Scale (LEFS) among African adult individuals living with HIV and on Antiretroviral Therapy (ART), *Platform presentation*, World Confederation of Physiotherapy Congress – Africa region; Accra Ghana 21st - 23rd July 2010

Tumusiime DK, Stewart A, Venter F, 2010, Prevalence of neuropathic pain and associated quality of life, among people living with HIV on Antiretroviral Therapy in Kigali Rwanda, *Platform presentation*, Eastern African Physiotherapy Scientific Conference; Kigali Rwanda 19th October, 2010.

Tumusiime DK, Stewart A, Venter F, 2011, Prevalence of Peripheral Neuropathy and associated functional limitations of lower extremity, among people living with HIV on Antiretroviral Therapy, Platform presentation, World Confederation of Physiotherapy Congress Amsterdam Netherlands 21st - 23rd June 2011

Tumusiime DK, Stewart A, Venter F, 2012, The effect of physiotherapeutic exercises on peripheral neuropathy, related lower extremity functional limitations and quality of life, among People living with HIV on Antiretroviral Therapy, Platform presentation, HIV and rehabilitation Symposium; School of Therapeutic Sciences, University of the Witwatersrand 6th - 7th August, 2012.

ABSTRACT

Background

HIV-associated peripheral neuropathy (PN), and related functional limitations that affect the quality of life (QoL), may now be one of the most formidable challenges in the health care of people living with HIV (PLHIV). The most common PN is distal sensory polyneuropathy (DSP). It is likely that there is a high prevalence of PN among PLHIV in Rwanda. The available data on the prevalence of PN are poor and there are none on how PN is associated with functional abilities and the QoL of PLHIV, which can guide management. In addition, current management of PN is mostly related to symptomatic management and is mainly pharmacological which may not rehabilitate the neuromuscular function that has been affected by PN. This thesis planned to re-validate and adapt the lower extremity functional scale (LEFS) and the brief peripheral neuropathy screen (BPNS), establish the prevalence of PN, and determine the effects of physiotherapeutic exercises on PN, lower extremity functional limitations and QoL, among Rwandan PLHIV receiving antiretroviral therapy (ART).

Methods

Study 1 translated LEFS from English to Kinyarwanda, modified it accordingly, and tested its reliability among 50 adult PLHIV on ART. The study also piloted and adapted the BPNS.

Study 2 conducted cross sectional PN assessments among 507 PLHIV aged between 18 and 60 years, on ART, randomly selected from eight Rwandan clinics.

Study 3 tested the effects of physiotherapeutic exercises (PTExs) on PN, lower extremity functional limitation and QoL, in a 12 weeks randomised controlled trial (RCT).

One hundred and twenty PLHIV with PN on ART were randomised equally to PTExs or no intervention.

Results

Study 1: The LEFS reliability with *rho* ≥ 0.7 for most of the lower extremity functional activities was obtained.

Study 2: The overall prevalence of PN was high at 59% [95% CI (54%, 63%)], with 78% among urban and 40% in rural participants. Participants with PN had lower mean functional ability scores than those without PN ($p<0.001$). PLHIV with PN had QoL domain scores significantly lower than those without PN, ($p<0.001$); for physical, psychological and social relationships, ($p<0.05$); for environmental and general QoL and health satisfaction.

Study 3: Improvements in PN symptoms (neuropathic pain [$p< 0.001$], PN symptom severity [$p<0.001$], and location of PNS [$p<0.001$]), were observed at 12 weeks in the intervention group compared to the control. Non-significant differences were noted between the intervention and control groups for PN signs; sense of vibration [$p=0.26$], and ankle tendon reflex [$p=0.73$]), after the 12 weeks period. All the lower extremity functional activities assessed were improved in the intervention group compared to the control group ($p<0.001$). Almost all facets of QoL domains improved in the intervention group, compared to the control group ($p<0.01$), with the exception of non-significant differences in the facet of “having enough money to meet your needs” ($p=0.23$).

Conclusions

LEFS, originally validated in the USA, was re-validated in Rwanda. This is the first validation of the LEFS in PLHIV on ART, from English into Kinyarwanda and the appropriate adaptation to a specific cultural context. It demonstrates the importance of

validating tools derived from developed world contexts to an African environmental setting. The prevalence of PN among PLHIV on ART in Rwanda is high and was higher in urban than in rural areas. Peripheral neuropathy was significantly associated with low performance of functional activities of the lower extremities, and thus resulted in poorer QoL. Physiotherapeutic exercises improved PN symptoms, lower extremity functional abilities, and almost all QoL domains. Physiotherapeutic exercises should be integrated into the routine management of PN and may serve as a prioritised approach in HIV and rehabilitation.

ACKNOWLEDGEMENTS

- To my supervisor Professor Aimee Stewart; your supervisory skills, knowledge, guidance, unforgettable parental encouragements and support, all made my success,
- To co-supervisor Professor Francois Venter; for the critical guidance during the journey to produce this thesis,
- To the Government of Rwanda for the scholarship of my studies,
- To my institution particularly the former Kigali Health Institute, for all the support rendered to me,
- To the participants in the research, for your voluntarily participation in the research,
- To the research assistants; particularly Mr. Sagahutu JB, for your time and skills used to give the exercise intervention,
- To Suzan; you were there to make the studies continue when shortcomings showed up,
- To my PhD colleagues, in particular Jeanne Kagwiza, for your encouragement and parental advise,
- To ADDRF; for the scientific and financial support to my PhD
- To the WE-ACTx management, in particular Dr Eugene Mutimura; for the biostatistics course and other related support given to me during my PhD studies.
- To Dr Musenge E, for the data analysis guidance,
- To all my families, relatives and friends, who stood by my side all along the journey of my studies.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABC	Abacavir
ACTG	AIDS Clinical Trial Group
ADL	Activities of Daily Living
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARVs	Antiretrovirals
AZT	Azidotymidin
BPNS	Brief Peripheral Neuropathy Screen
CD4	Cluster differentiation 4
ddC	Zalcitabine
ddI	Didanosine
d4T	Stavudine
DN4	Douleur Neuropathique 4 questions
DSP	Distal Sensory Polyneuropathy
EFV	Efavirenz
FTC	Emtricitabine
HIV	Human Immunodeficiency Virus
HIV AND AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
LEFLs	Lower Extremity Functional Limitations
LEFS	Lower Extremity Functional Scale
LEFS-M	Lower Extremity Functional Scale Modified

NNRTIs	Non- Nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
PLHIV	People Living with HIV
PN	Peripheral Neuropathy
PTExs	Physiotherapeutic Exercises
QoL	Quality of Life
RCT	Randomized Controlled Trial
RDHS	Rwanda Demographic and Health Survey
RHC	Routine Health Care
rho	Spearman's rank correlation coefficient
TDF	Tenofovir
TRAC	Treatment, and Research AIDS Centre
UNAIDS	The Joint United Nations Programme on Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
WHO	World Health Organization
WHOQOL-BREF:	World Health Organisation quality of life questionnaire, for Human Immunodeficiency Virus - short form
3TC	Lamivudine

CHAPTER 1

1.0 INTRODUCTION

This chapter highlights the background of the study, problem statement, research questions, aim and specific objectives, the justification/significance and lastly the summary and outline of the thesis.

1.1 Background

Although the rate of new human immunodeficiency virus (HIV) infection declined by 33% between 2001 and 2012, the infection is still a burden and a concern for global health, development and economies (Joint United Nations Programme on HIV and AIDS [UNAIDS], 2013). The global prevalence of people living with HIV (PLHIV) was estimated to be 35.3 million in 2012. The prevalence has increased as the number of PLHIV on antiretroviral therapy (ART) increased by 1.6 million in 2012 over 2011, in low and middle income countries (UNAIDS, 2013). ART has prevented PLHIV from getting the acquired immunodeficiency syndrome (AIDS) and saved an estimated 6.6 million people from AIDS-related deaths globally, between 1995 and 2012. Out of the 6.6 million, 5.5 million people are from low and middle income countries (UNAIDS, 2013).

Sub Saharan Africa is the most affected region with 23.5 million PLHIV, equivalent to 69% of the global HIV prevalence at the end of 2011 (UNAIDS, 2012). Thus, the problem of HIV and AIDS is still a threatening pandemic in sub Saharan Africa. It caused 70% of the mortality and morbidity in the region in 2011 (UNAIDS, 2012).

HIV and AIDS has affected the economic development and growth of various nations around the globe (Ogbuji and Oke, 2010; Imam et al., 2011). Data from more than 15 sub Saharan African countries indicate that regions with a high prevalence of HIV, declined in educational attainment (Fortson, 2010), have effects of mortality and infertility, that impact on their economies (Kalemli-ozcan, 2005).

Rwandan national estimates are that adult HIV and AIDS prevalence is at 3% in the general population (Rwanda Demographic Health Survey, [RDHS], (2010). The country has one of the highest national ART coverage levels in sub Saharan Africa, reaching an estimated 90% and above of those eligible, in December 2010 (UNAIDS, 2012).

HIV and AIDS causes various health problems including neurological ones, which are the first manifestations of symptomatic HIV infection in approximately 20-40% of persons (Miura and Kishida, 2013). The neurological abnormalities is evident in about 60% of people with progressed HIV disease, during the period of their illness (McArthur et al., 2005). Literature shows that peripheral neuropathy (PN) is the most frequent neurological complication in PLHIV (Wulff et al., 2000; Verma, 2001; Sacktor, 2002; Simpson et al., 2002; Luciano et al., 2003; McGurie, 2003; McArthur et al., 2005; Conradie et al., 2014). Furthermore, with the introduction of ART, there is a dramatically reduced mortality rate of PLHIV in the countries where these treatments are available (Iwuji et al., 2011). But because of the likely increased life expectancy and the long-term use of ART, some chronic complications which include ART-associated PN have become a challenge (Morgello et al., 2004; Ferrari et al., 2006; Arendt and Nolting, 2012).

Peripheral neuropathy is defined as a damage to the peripheral nerves (Torpy et al., 2010). There are various types of HIV-associated PN which include; the “inflammatory demyelinating polyneuropathy, progressive polyradiculopathy, mononeuropathy multiplex, autonomic neuropathy, distal sensory polyneuropathy (DSP) and diffuse infiltrative lymphocytosis syndrome” (Wulff et al., 2000; Ferrari et al., 2006; Hahn et al., 2010), and the most common type is DSP (Simpson et al., 2006; Ellis et al., 2010; Robert et al., 2012).

The prevalence of PN in PLHIV was documented to be about 30 – 67% of PLHIV with advanced HIV disease (Simpson et al., 2006; Ellis et al., 2010). In pre-ART patients, the first manifestations of symptomatic DSP is about 55% and 53% in post ART patients (Sarah and Nath, 2012).

Distal sensory polyneuropathy therefore is said to occur in PLHIV due to two main causes; as a complication from HIV infection (HIV-DSP) or ART-associated toxic neuropathy (ATN) (Gonzalez-Duarte et al., 2008). Overall, both HIV and ART-associated PN commonly manifest as DSP (Morgello et al., 2004; Kim et al., 2007; Nicholas et al., 2007; Gonzalez-Duarte et al., 2008), and because of that reason, “peripheral neuropathy” and “PN” is used to mean DSP for both HIV and ART-associated PN, in this thesis except otherwise indicated.

However, there are still debates on the aetiology of PN and it is said to be unclear, but the “neurotoxic effects of cytokines, toxicity of HIV proteins, and mitochondrial damage” are mentioned associated, as reported by Gonzalez-Duarte et al. (2008). Many risk

factors are reported to be associated with PN; such as old age, progressed HIV disease, and use of ART or other neurotoxic medications (Simpson et al., 2006). Antiretroviral drugs, namely; the nucleoside reverse transcriptase inhibitor (NRTI) drugs mainly stavudine (d4T); didanosine (ddI), and zalcitabine (ddC) were known causes of PN as one of common adverse effects (Morgello et al., 2004; Kim et al., 2007; Nicholas et al., 2007; Gonzalez-Duarte et al., 2008). Thus, all of those drugs have been reduced or replaced with other alternatives from the ART regimens. Nevertheless, it is not yet clear whether the prevalence of PN reduced with the elimination or reduction of those ART drugs commonly used to cause the neuropathy. In addition, PN may occur because of overlapping toxicity of various drug combinations, including medication used to treat HIV-related complications. Symptoms of ART-PN may start immediately after beginning on one of the PN-causing drugs, but generally the PN occurs after taking the drug for a long time, for instance after months or years (Skopelitis et al., 2006).

The first appearances of PN are reported as “slowly progressive numbness and paraesthesia, with burning sensations in the feet usually in a symmetrical pattern” (Nicholas et al., 2007; Gonzalez-Duarte et al., 2008). The signs of PN include reduced or no ankle jerks, reduced sense of vibration in the feet, reduced sense of pain and temperature in a “stocking” distribution, and sometimes intrinsic foot muscle weakness (Schifitto et al., 2002).

The PN symptoms and signs, are reported as the most common causes of morbidity among PLHIV (McArthur et al., 2005; Dubey et al., 2013). Peripheral neuropathy affects functional ability and hence results in considerably compromised QoL of PLHIV (Smyth

et al., 2007; Ellis et al., 2010; Robinson-Papp et al., 2010; Dubey et al., 2013). With PN negatively impacting on the QoL of PLHIV, it may compromise their adherence to ART (Gonzalez-Duarte et al., 2008).

According to Gonzalez-Duarte et al. (2008), the present management for PN is symptomatic, particularly in regard to neuropathic pain in order to preserve neurological function and prevent disability. Pain modifying medications are reportedly used and these include; the "anti-inflammatory agents, opioids, antidepressants, anti-epileptics, topical anaesthetics, and capsaicin" (Gonzalez-Duarte et al., 2008), but these medications may also have their own adverse effects. Again, studies demonstrate that sustained virologic control using ART is likely to improve PN. Generally, ART benefits PLHIV but some ARV types still lead to PN which is a painful condition (Gonzalez-Duarte et al., 2008). Stavudine as one the main drugs that cause PN, has been reduced in the ART regimens. Studies have indicated that reducing d4T dosage from 40mg to 30mg or 20mg, resulted in a reduced PN but there was a non-significant difference in PN between the cohort on d4T40mg and 30mg or 20mg, dosage (Pahuja et al., 2012). Hence, the study by Pahuja et al., (2012) concluded that PN still persists especially among PLHIV who have already developed it. Moreover, d4T is still used in some resource-limited settings because it is easily available and cheaper than the drugs that can replace it (Renaud-Théry et al., 2007; UNAIDS, 2010; Pahuja et al., 2012). Thus, PN may still be prevalent with its associated functional limitations and reduced QoL, among PLHIV. Nevertheless, there is minimal data on function and QoL in PLHIV with PN, to guide rehabilitation approaches in Rwanda, and probably in other developing settings, particularly in the sub Saharan Africa.

In Rwanda specifically, there are a few studies on PN among PLHIV and these have largely been conducted in a few selected health facilities. One of the studies showed that 65% to 70% of PLHIV who are on ART reported having PN related symptoms, which needed treatment. Such symptoms included paraesthesia, pain and numbness (Uwimana and Struthers, 2007). Later on, another study by Biraguma & Rhoda (2012) reported the prevalence of PN as 40% in one of the rural district hospital. However, these prevalences may be inaccurate because both studies were carried out with small sample sizes, each at one site only, and the tools assessed only subjective symptoms. Thus, there is likely increased prevalence of PN in the in the general population of PLHIV on ART in Rwanda, but there are poor data on the prevalence and its related functional limitations. This makes it difficult to develop management strategies for PN in PLHIV.

Therapeutic exercises have been used to manage pain related to PN and other related neuromuscular disorders in people with diabetes (Adeniyi et al., 2010). Again, exercises were successful in modifying body composition and metabolic profiles, and improving cardio-respiratory ability in PLHIV on ART in Africa (Mutimura et al., 2008) and studies have shown that exercises are safe and affordable among PLHIV (O'Brien et al, 2010). However, to the author's knowledge, the effectiveness of exercise in the management of PN and the related functional disorders in PLHIV on ART have not been well described.

1.2 Problem statement

Peripheral neuropathy management has been hindered by insufficient data regarding the prevalence of PN and how it is associated with functional limitations and QoL, among PLHIV in Rwanda, and in other developing countries. To obtain such data, there needs to be a clear definition of PN and diagnostic/assessment outcome measures that are locally adapted and which consider the cultural and environmental differences between developed and developing settings, where such tools have been validated. Kim et al (2007) commented that without common definitions and diagnostic procedures, it is difficult to define the true prevalence of PN. Therefore, as a need to appropriately improve the management of the effects of PN on the QoL of PLHIV in Rwanda, the data regarding the prevalence of PN and how it is associated with functional limitations and QoL, using locally adapted outcome measures, are essential.

In addition, both pharmacological and non-pharmacological modalities are recommended in the management of PN (Nicholas et al., 2007). But it is not clear and there is insufficient literature on how non- pharmacological modalities, such as physical exercise in particular are applied and effective in the management of HIV-associated PN and its related functional limitations. Exercise has been considered as important management of PN related to diabetes (Adeniyi et al., 2010) and exercises have been indicated to be safe and affordable in PLHIV, but it is not known how effective exercises are, in managing PN and the related functional disorders in PLHIV on ART, particularly in Rwanda. Thus, it becomes important to test the effectiveness of non-pharmacological management; such as physiotherapeutic exercises using RCT

methodology, to understand the effects of exercises on PN and its related functional limitations among PLHIV on ART. Health care professionals need treatment options for PLHIV with established PN, irrespective of the aetiology of the PN.

Research questions

1. What is the prevalence of peripheral neuropathy among PLHIV on ART HIV in Rwanda?

2. Does PN related to HIV and ART have an effect on the functional ability and quality of life, among PLHIV on ART HIV in Rwanda?

3. How effective is physiotherapeutic exercise in the management of peripheral neuropathy and its associated lower extremity functional limitations and QoL, among PLHIV on ART?

Aims and specific objectives

1.4.1 Aims

1. To establish the prevalence of peripheral neuropathy among PLHIV on ART in Rwanda,

2. To identify the effects of peripheral neuropathy on the functional ability and quality of life among PLHIV on ART in Rwanda,

3. To establish the effects of physiotherapeutic exercises on peripheral neuropathy, its associated functional limitations and quality of life, among PLHIV on ART in Rwanda.

1.4.2 **Specific objectives**

1. To pilot and adapt valid and reliable outcome measures for the assessment of peripheral neuropathy, it's associated functional limitations and quality of life, among PLHIV on ART in Rwanda,

2. To establish the prevalence of peripheral neuropathy in relation to the demographic and health status characteristics, of PLHIV on ART in Rwanda,

3. To identify the effect of peripheral neuropathy on functional ability of PLHIV on ART in Rwanda,

4. To identify the effect of peripheral neuropathy on quality of life among PLHIV on ART in Rwanda,

5. To test the effects of physiotherapeutic exercise on peripheral neuropathy, its associated functional limitations of the lower extremities and quality of life, among PLHIV on ART in Rwanda,

6. To identify factors associated with and influencing the effects of exercises on peripheral neuropathy, related lower extremity functional limitations and QoL, among PLHIV on ART

1.5 Significance of the study

The re-validating and adapting of the outcome measures may contribute to appropriate clinical assessment and evaluation of patients with PN and related lower extremity functional limitations and QoL, in Rwanda, and probably other developing countries. This will guide an appropriate diagnosis of PN and its related disorders, thus establishing data on the prevalence of PN and associated lower extremity functional limitations and QoL. The data on prevalence may contribute to the understanding of the

magnitude of the PN problem in PLHIV, which will likely be a basis on which to design appropriate health care strategies for PLHIV on ART, in Rwanda and probably in other resource-limited settings.

Establishing the effects of physiotherapeutic exercises on PN may help to understand if the exercises can be integrated into the routine management of PLHIV on ART with PN and the associated lower extremity functional limitations, as a non-pharmacological approach to rehabilitate chronic disabling conditions related to PN. Furthermore, the results of the studies may serve as basis for further studies; such as an in-depth study to understand the mechanism of the effects of therapeutic exercises on PN in PLHIV on ART.

1.6 The outline of the thesis

The thesis consists of eight chapters and three studies;

- **Chapter 1**; the introduction of the thesis that highlights the general background, problem statement, research questions, aims and objectives, and finally the contribution to be made by all three studies
- **Chapter 2**; the background literature review for all three studies,
- **Chapter 3**; Study one *(Aim 1; specific objective 1*)
- **Chapter 4**; Study two; *(Aim 1; specific objectives; 2, 3 & 4)*
- **Chapter 5**; Methodology of study three
- **Chapter 6**; Results of study three; *(aim 3; specific objectives; 5 & 6);* an intervention study with

- **Chapter 7**; Discussion of the results of study three,
- **Chapter 8;** Summary, conclusions and recommendations from all the three studies of the thesis.

CHAPTER 2

2.0 LITERATURE REVIEW

2.1 Introduction

The HIV and AIDS pandemic has changed from being a terminal illness to a chronic manageable condition with the introduction of ART. The chronic conditions and disorders associated with the virus and side effects of ART, include neurological disorders of which PN is the most prevalent one (Wolfort and Dellon, 2012; Chen et al., 2013; Dubey et al., 2013; Gabbai et al., 2013; Ramírez-Crescencio et al., 2013). Peripheral neuropathy is the main focus of this thesis and is discussed in detail and includes; its prevalence, types, possible risk factors with attention to the PN due to HIV and ART that affects the lower extremities of PLHIV. The effects of PN on the functional ability of the lower extremities and QoL of PLHIV on ART are highlighted. The current management of PN and its related chronic conditions are discussed with an emphasis on rehabilitation approaches and the use of exercise for the improvement of QoL among PLHIV on ART.

The information was gathered by searching data bases such as; PubMed, Science Direct, Academic Search Premier, Cochran systematic reviews, PEDro, HINARI, WILEY online library and searching using Google Scholar. Keywords such as HIV and antiretroviral therapy; effects of HIV AND neuromuscular disorders; effects of HIV AND treatment; side effects AND ART OR HAART; HIV and peripheral neuropathy; ART and peripheral neuropathy; HIV-associated peripheral neuropathy; ART and associated peripheral neuropathy; types of ART associated peripheral neuropathy; ART and distal

sensory polyneuropathy, prevalence and HIV-associated peripheral neuropathy; epidemiology of peripheral neuropathy; peripheral neuropathy and pathophysiology; pharmacological management of HIV-associated peripheral neuropathy; non–pharmacological management of HIV-associated peripheral neuropathy; effects of peripheral neuropathy on physical AND functional ability; quality of life and HIV; exercises and HIV AND peripheral neuropathy; quality of life and HIV; peripheral neuropathy AND HIV and quality of life; were all used in the search. A manual search was also done with related references used by other studies.

2.2 An overview on HIV

This section gives an overview on HIV and its prevalence globally, with a focus on sub Saharan Africa where the impact is more severe than elsewhere in the world. The treatment of HIV and its access in countries in sub Saharan Africa, including Rwanda, are highlighted.

2.2.1 Incidence and prevalence of HIV

The UNAIDS report of 2012 indicates that by the end of 2011, there were approximately 34.0 million PLHIV globally. A year later, the prevalence of HIV increased to 35.3 million globally (UNAIDS, 2013). The statistics show that globally, the prevalence increased by 17% from 2001 to 2010 (UNAIDS, 2011). The UNAIDS global report of 2013 shows that there has been a decrease of approximately 33% in new infections since 2001 (UNAIDS, 2013). Though the rate of new HIV infection has decreased globally the overall number of PLHIV continues to increase mainly because of the ART programme

success. UNAIDS (2011) shows that the HIV and AIDS pandemic is found globally but its distribution is different with some countries having a higher distribution than others. More than 80% of the affected populations globally are found in developing countries.

Sub Saharan African is still the region mostly affected by HIV (UNAIDS, 2013). About 68% of all PLHIV lived in sub Saharan Africa in 2010, which has only 12% of the global population. Sub Saharan Africa was affected with 70% of new HIV infections in 2011. Women in sub Saharan Africa are more (60%) affected than men. The women in this region are more vulnerable than men for various reasons; such as being poor, violence against women such as rape, lower education levels which gives them less economic security, and less decision making for their protection ("WHO | Gender inequalities and HIV", n.d. & Wabiri and Taffa, 2013). The age range of 15 to 35 years is the most affected with HIV and AIDS in sub-Saharan Africa. Around 80% of the infected group are aged 20 – 29 years (Onokerhoraye et al., 2012).

2.2.2. Incidence and prevalence of HIV in Rwanda

The HIV prevalence in Rwanda has declined over the past few years. The country's national estimates for HIV prevalence decreased from 12.8% in 1998 to 5.2% in 2004 (Kayirangwa et al., 2006), 3% in both 2005 and in 2010, according to the Rwanda national health demographic survey that is usually carried out every five years (2010). The prevalence is higher in urban areas (7.1%) than in rural areas (2.3%). The HIV prevalence is distributed differently between genders; 3.7 % for women and 2.2 % for men. Again, the widows and the divorced or separated people have the highest HIV prevalence of 16.6% (RDHS, 2010). The HIV prevalence also is differently distributed

by age groups; with highest among women aged 35 – 39 and men age 40 – 44 years. Kigali City also has the highest HIV prevalence of 7.3% among the adults age 15 – 49 years.

2.2.3 The HIV AND AIDS impact

Globally, the HIV and AIDS epidemic had killed almost 30 million people by the end of 2011 (UNAIDS, 2012). About 1.2 million people died in sub Saharan Africa in 2011, which is equivalent to 70% of all AIDS-related global deaths (UNAIDS, 2012). UNAIDS (2011) reported that approximately 16.6 million children were orphaned in 2010 due to HIV and AIDS. The UNAIDS (2012) report shows that since 1998 about one million people have died annually due to HIV and AIDS in sub-Saharan Africa.

However, since 2002 the deaths related to HIV and AIDS decreased steadily, as a result of the availability of free ART in the region (UNAIDS, 2013). Nevertheless, the impact of HIV still prevails. The HIV and AIDS pandemic has become a major challenge to health, development and humanity (UNAIDS, 2013), with more people currently living with HIV, largely because of increased access to HIV treatment (UNAIDS, 2013). A study by Hosegood (2009) indicates that the demographic impacts of HIV and AIDS in sub Saharan Africa are numerous such as breaking up of family and household structures, reduced fertility and reproduction, marriage breakdown, union instability in couples, as well as widow and orphan headed families. HIV in sub Saharan Africa continues to cause negative effects and the major challenges are the long term socio-demographic, economic and health effects that lead compromised QoL of PLHIV (Hosegood, 2009).

Like any other developing country in sub Saharan Africa, Rwanda faces the impact of HIV which include the loss of active labourers (Bitran et al., 2003). This is probably due to the fact that HIV prevalence is higher in working than non-working men (RDHS, 2010). The education sector has also been affected with HIV and AIDS through loss of teachers. Kinghorn and colleagues (2003) projected a loss of 2500 teachers in Rwanda during the 21st century. An increase in the number of orphans of (0 – 16) years was projected to increase from 64,000 in 2003, to 208,000 in 2015. Economically, the increase in dependants at the family, community and national levels reduces manpower and increases health expenses (Kinghorn et al., 2003). HIV in Rwanda also is reported to be higher in educated women than those without education (RDHS, 2010), which also impacts on employed people thus reducing work productivity ("The Effect of HIV and AIDS on Society," n.d.). But the reasons to why higher educated women are more affected with HIV than those with less educated are not well documented. The health sector has been affected, more especially with challenges of managing the HIV related health conditions.

2.2.3 HIV and treatment

ART has dramatically changed the experience of PLHIV (O'Brien et al., 2010), and the nature of HIV illness (Ryder et al., 2012). HIV-related health conditions appear now as chronic ones with features of changing incidents of normal health and sickness instead of illness that used to end in steady advancement to death (Ryder et al., 2012). By December 2012, an estimated 9.7% million PLHIV were on ART in low and middle-income countries, with an increase of 1.6 million in 2011 (UNAIDS, 2013). As ART

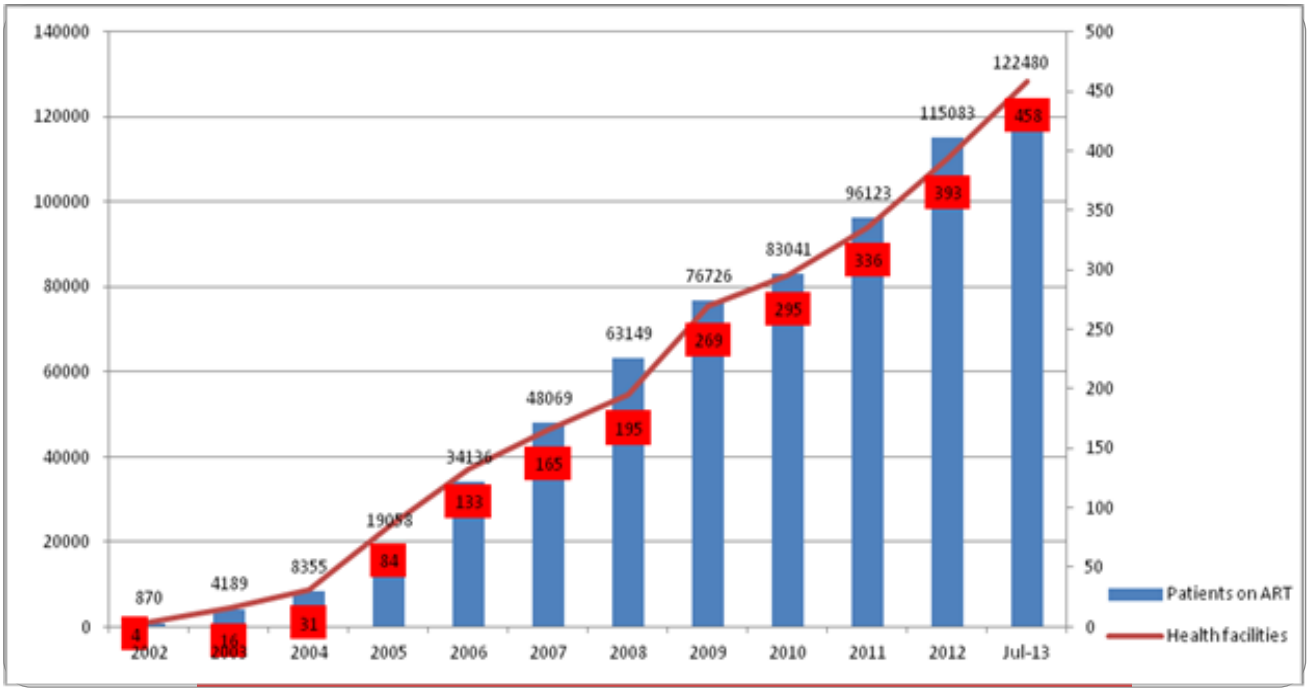
becomes increasingly important and accessible, reduction of the long-term morbidity and mortality in PLHIV has become more of a focus. Accessibility and adherence to available ART improves the standard of care of PLHIV (Scanlon and Vreeman, 2013). Nevertheless, access to ART still differs in different resource-limited settings. The universal access is defined as 80%, or greater coverage. In some countries the access to treatment is above the 80%. Such countries include; Botswana, Namibia and Rwanda, with Rwanda having more than 90% of people eligible for ART, on it (RDHS, 2012), while Swaziland and Zambia are reported to have reached between 70% and 80% of ART coverage levels of the eligible people (UNAIDS, 2011). It is reported that the introduction of HIV treatment in sub Saharan countries has dramatically reduced AIDS-related mortality (UNAIDS, 2011). In general, ART has been shown to decrease the infection and has likely contributed to the reduced HIV new infection rate, which has been reduced by more than 50% in most sub Saharan African countries (UNAIDS, 2012).

2.2.4. HIV treatment in Rwanda

In Rwanda, the government and donors provide support to the population through provision of HIV and AIDS health services, aiming to scale-up HIV and AIDS service provision and access to ART for all eligible PLHIV. This is purposely to give appropriate healthcare and treatment to those living with the infection and prevent particularly new infection.

As mentioned earlier, more than 90% of PLHIV who are eligible for ART, are on it in Rwanda. The country had attained one of the highest national ART coverage level in

sub Saharan Africa by December 2010 (UNAIDS, 2010). ART access has increased progressively since 2002 in Rwanda as indicated in Figure 1 below;



Y-axis = Number of patients, X-axis = Period in years

Figure 1 : Progressive increase and accessibility ARVs to PLHIV in Rwanda (RBC, 2013)

2.2.5 HIV treatment guidelines in Rwanda

Like any other countries with limited resources, Rwanda uses most of the ART drugs recommended by the WHO. The WHO indicates that the most commonly used ART drugs in poor resource countries are those that it recommends. The drugs mainly comprise of; “NRTIs; AZT, 3TC, and d4T and NNRTIs; NVP and EFV” (WHO, 2006; Hill et al., 2007). However, d4T has been replaced with TDF recommended by the new WHO guidelines (WHO, n.d.). But, the d4T is one of the most potent causes of PN (Scarsella et al., 2002; Subbaraman et al., 2007 & Agu and Oparah, 2013), and was used in Rwanda before its replacement with TDF recently (RBC, 2011). Although d4T

has been reduced or replaced in the ART regimen, it was a first line antiretroviral in the Rwandan programme prior to 2011. In addition to d4T having the adverse effect of PN, the drug has other several adverse effects including lipoatrophy, lactic acidosis and hepatic steatosis (Gallant, 2012). With the cessation of the use of d4T in the first line ART regimen since 2011 for new eligible people, Rwanda currently uses the regimen combination comprised of: TDF+FTC/3TC+NVP/EFV or ABC+3TC+NVP/EFV; AZT and PIs are reserved for second line therapy and Etravirine + Darunavir + Raltegravir for third line ART regimen (Rusine et al., 2013). The ART guidelines shifted mainly from D4T+3TC+NVP in 2011 to TDF+3TC+EFV, as the first recommended in the first line regimen (RBC, 2011).

2.3 Effects of HIV and ART

2.3.1 General effects

Previously, HIV and AIDS was a disease with progressive, weakening and fatal illness without applicable management and ended into sudden failing in health resulting to death (Gaidhane et al., 2008). But from the last two decades, HIV treatment has tremendously altered the survival rate of PLHIV ("Recent developments in the HIV neuropathies," n.d.; Tehranzadeh et al., 2004a; Anderson et al., 2006; Louwagie et al., 2007). PLHIV are now able to strive for fulfilling and meaningful lives (Hsiung et al., 2005). HIV/ AIDS is no longer an end point to death or the starting up of losses of employment or family life (Phaladze et al., 2005). Consequently, ART returned life expectancy to near normality. However, although the mortality and morbidity rates have been reduced with the introduction of ART, morbidity still prevails. This is because of

several significant adverse effects from HIV infection and its associated treatments (Tehranzadeh et al., 2004; Vidrine et al., 2003; Worthington and Krentz, 2005), that more people live with for such a long time. Living longer with HIV and AIDS and its numerous complications associated with both the virus as well as the drugs used to treat it, including the neurological ones were found to be the major causes of morbidity (McArthur et al., 2005).

Peripheral neuropathy is reported to be the most prevalent among the neurological complications of HIV infection and ART (Lichtenstein et al., 2005; McArthur et al., 2005; Dorsey & Morton, 2006; Ferrari et al., 2006; Cherry et al., 2009; Hammersla and Kapustin, 2012; Cettomai et al., 2013; Chen et al., 2013; Dubey et al., 2013; Gabbai et al., 2013 & Theroux et al., 2013). A study conducted in Tanzania, demonstrated that the most reported adverse drug reactions among patients using ARVs were; anaemia, liver toxicity, skin rashes and PN (Minzi et al., 2009). The study indicated that PN was reported more frequently among participants taking d4T40mg than d4T30mg, twice daily, as was previously shown by a systematic review by Hill et al. (2007). Though the d4T dose was reduced, Pahuja et al. (2012) still reported that patients on d4T30mg twice daily had a high risk of developing PN which can lead to disability. The same authors indicated that the PN cannot be reversed in most cases unless the offending drug is replaced. Thus, the revised 2006 WHO guidelines recommend replacing d4T with TDF from first-line ART regimens (WHO, 2006). But (Walensky et al., 2010) showed that the implementation of the guidelines might not be possible in some poor resource-limited settings, suggesting that d4T is likely still used in those countries.

Since, PN has been indicated as the most prevalent neurological complication of HIV in the era of ART (McArthur et al., 2005 & Cettomai et al., 2013), this literature review focusses on and discusses PN in details in the following sections.

2.3.2 Peripheral neuropathy and its definition

Peripheral neuropathy is briefly defined as damage to the peripheral nerves, through injury, inflammation, or degeneration of the peripheral nerve fibres (Magrinelli et al., 2013). Anatomically, the peripheral nerves denote the nerves outside the brain and spinal cord and comprise of motor, sensory and autonomic nerve fibres ("Central Nervous System Anatomy," 2013). "Neuropathies are segmented into motor, motor and sensory, and pure sensory categories, depending on the fibre classes affected" (Magrinelli et al., 2013). Sensory neuropathies are said to be as result of sensory nerves being affected (Robinson et al., 2011; Kamerman et al., 2012). Mostly, the sensory neuropathies affect the lower extremities, and the feet and legs more, than the hands and arms (Cherry, Wesselingh, Lal & McArthur, 2005).

2.3.3 HIV-associated PN

Different types of PN include; "inflammatory demyelinating polyneuropathy, progressive polyradiculopathy, mononeuropathy multiplex, autonomic neuropathy, DSP and diffuse infiltrative lymphocytosis syndrome" (Wulff et al., 2000; Keswani et al., 2002). The most common HIV-associated PN is reported to be the DSP type. The HIV-associated DSP is said to occur usually in the last phases of HIV disease (Evan, et al., 2012). Symptoms and signs of HIV-associated sensory neuropathies, particularly DSP and ART-ATN, are almost the same. These two (DSP and ATN) neuropathies are not easily distinguished

(McArthur et al., 2005) and are the most common types of HIV-associated neuropathy and commonly appear in combination in PLHIV on ART. As stated earlier in Chapter one ‘peripheral neuropathy’ or ‘PN’ is used to mean DSP and ATN in this review of the literature and in the rest of the thesis, except where differently mentioned.

The symptoms of ART-associated PN, which are fundamentally indistinguishable to the syndrome of PN related to HIV infection, consequently puzzle the diagnosis and management of PN (Simpson & Cikurel, 2006). Differentiating the neuropathy related to HIV from PN related to ART can done by “investigating the sequential association of symptoms with initiation of ART, clinical or electrophysiological improvement after dose reduction or drug discontinuation, plus the ‘coasting effect’ from which the symptoms progress for two to four weeks after stopping the medication, followed by clinical improvement”, as reported by Simpson & Cikurel, (2006). Additionally, the ART-PN is likely more painful than the HIV-induced PN, has a sudden beginning, and advance very fast (Nicholas et al., 2007a).

2.3.4 Prevalence and incidence of HIV-associated PN

Certain contradictions exist, some studies indicate that the problem of PN has been reduced since the introduction of ART (Maschke et al., 2000) but others demonstrate that the ART-associated PN continues to be prevalent (Morgello et al., 2004; McArthur et al., 2005; Smyth et al., 2007; Milogo et al., 2008; Evans et al., 2011). The ART-associated PN was mostly related to the d-drugs; ddI, ddc and d4T (Lichtenstein et al., 2005), but it is not yet clear if the discontinuation of neurotoxic drugs such as d4T has reduced the prevalence of PN (Pahuja et al., 2012). In developing countries, the

prevalence of PN has been reported as 20%-50%, (Oshinaike et al., 2012), in some studies while others report 30% - 67% (Wulff et al., 2000).

The prevalence of PN in African countries was shown in the 90's to range from 15 % - 56% (Parry et al., 1997). Recent studies demonstrate the prevalence as; 21% in Cameroon (Luma et al., 2012), 45% in Guinea-Bissau, (Choi et al., 2011) and a range of 24.4% - 57% in South Africa (Maritz et al., 2010; Wadley et al., 2011; Conradie et al., 2014), 21.3% - 44% in Malawi (Tapsfield et al., 2011; van Oosterhout et al., 2012 & Kampira et al., 2013) and 21.9% - 36% in Kenya, (Mehta et al., 2010; McGrath et al., 2012).

In Rwanda, there is insufficient data on the prevalence of HIV-associated PN at a national level. To my knowledge, there are only two studies that were conducted by Uwimana and Struther (2007) and by Biraguma and Rhoda (2012). Both of these studies were conducted in single health centre, and with small sample sizes. However, the studies indicated that the prevalence of PN ranged from 65 to 70% (Uwimana & Struther, 2007) and 40% (Biraguma & Rhoda, 2012). This leaves a gap in the data on the prevalence of PN at national level and from both rural and urban settings in Rwanda. The gap may hinder management strategies for PN and associated co-morbidities.

The following Table 1 indicates a summary of some studies done from different settings and reported PN prevalence.

Table 1 : A summary of prevalence of HIV-associated PN in adults; by different studies

Study areas, participants and the sample	Definition, methods of assessment tool	Prevalence	Reference
A cross sectional study among 187 outpatient PLHIV attending one rural district hospital of Rwanda	PN symptoms were screened with Subjective Peripheral Neuropathy Screen. Was not clear of how diagnosis of PN was confirmed.	40.5%	Biraguma & Rhoda, 2012
A cross sectional study among 295 adult PLHIV patients at Douala general hospital in Cameroon	Used BPNS to screen HIV – SN, where by the neuropathy was defined as presence of neuropathy symptoms and at least an abnormal perception of vibration sense or reduced ankle tendon reflex	21% had HIV – SN	Luma et al., 2012
Participants in an ART – naïve who initiated ART were annually screened for symptoms and signs of PN: USA	Brief Peripheral Neuropathy Screen (BPNS) was used to screen at least mild loss of vibration in the both great toes and hypoactive ankle reflex bilaterally.	32.1% after three years on ART	Evans et al., 2011
Cross sectional data of 1539 PLHIV in USA	Neurological clinical signs and PN diagnosed with at least one sign with BPNS	57% with signs and 61% with signs and symptoms	Ellis RJ et al., 2010
A cross sectional PN screening of 102 Patients receiving ART in Mombasa, Kenya	PN was determined with a combination of at least one symptom grade > 0 and one bilateral sign, assessed with BPNS	36%	Mehta et al., 2010
In a large randomised controlled trial of 775 PLHIV, from 12 sites in USA	Peripheral neuropathy was examined wit revised signs and symptoms checklist	44%	Nicholas et al., 2010
A 2 week cross sectional comparative study using a convenient sample of 100 adults with HIV in Melbourne, Australia	One or more PN symptoms together with at least one sign; either reduced vibration sense or	42%	Smyth et al., 2007

	reduced ankle jerk, screened with BPNS		
A cross sectional data was analysed from PLHIV on ART (d4T, 3TC and NVP), in a home-based AIDS care program in rural Uganda	Assessment tool not clearly mentioned	36 % had PN	Forna et al., 2007
101 adults with advanced HIV were evaluated for DSP over 48 weeks	Screening done with BPNS	52 % with DSP	Simpson et al., 2006
2515 HIV Outpatients were tested for symmetrical peripheral neuropathy, in 7 cities of USA.	Clinical evaluation in a cohort sample; Tools used not mentioned	13.1%	Lichtenstein et al., 2005
49 HIV positive adult patients in Brazil were clinically evaluated over a period of 17 months	Isolated or combined impaired sensory, absent deep tendon reflex were assessed	69.4%	Zanetti et al., 2004
Clinical examinations were performed among randomly selected PLHIV at different stages of the disease, in Zimbabwe	Nerve conduction with electrophysiological procedures	44% to 56%	Parry et al., 1997

2.3.5 The pathophysiology, causes, and risk factors of HIV-associated PN

The pathogenesis of PN is reported to be multifactorial, and is still unknown (Nicolas et al., 2007b). The pathophysiology is mentioned to have “three specific mechanisms; dying back or axonal degeneration of long axons in distal regions, loss of unmyelinated fibres, and an adjustable degree of macrophage infiltration in peripheral nerves and dorsal root ganglia” (Pardo, McArthur and Griffin, 2001; Laast et al., 2011).

According to Simpson & Cikurel (2006a), the ART drugs particularly the NRTIs are reported to restrict the DNA synthesis and cause mitochondrial defects which are connected to the demonstration of the PN symptoms. The driving force for the occurrence of PN is said to be the mitochondrial toxicity and its powerful pathogenic responsibility in various organ system toxicities (Simpson et al., 2006b), in PLHIV on ART. But this has been reported as a hypothetical theory which is still a subject of discussion, according to the same authors. However, Kallianpur and Hulgan, (2009) in their study on the pharmacogenetics of NRTI-associated PN, confirmed that there is evidence of ART-associated PN partly as a result of the drug induced mitochondrial dysfunction. Additionally, a review by Kamerman et al. (2012) reported that the sequence of those events of the mitochondrial dysfunction that results in hypernociception, is still not clear. Nonetheless, the neurotoxicity of some of the NRTIs affecting the mitochondria function has been implicated (Kamerman et al., 2012). Conclusively, the ART-associated PN is increasingly demonstrated as a result of the toxic effect of drugs that possibly cause mitochondrial injury and dysfunction (McArthur et al., 2005; Kamerman et al., 2012). On the other hand, PN can be caused directly from

the HIV-infection to the neurons, and opportunistic infections of neurons due to generalized immunosuppression (McArthur et al., 2005; Keswani et al., 2006; Kamerman et al., 2012; Moss et al., 2012 & Mangus et al., 2014)

Generally, PN frequently is reported as the most common complaint among PLHIV receiving ART in resource limited settings (van Oosterhout et al., 2005; Boulle and Ford, 2007; Forna et al., 2007). Various studies indicate these risk factors for PN as; old age and neurotoxic ARV drugs (Smyth et al., 2007; Shurie and Deribew, 2010; Wadley et al., 2011). Other factors reported as predisposing include; diabetes mellitus, malnutrition, isoniazid exposure, ethnicity and increased height (Kamerman et al., 2012). In addition, Robinson-Papp et al. (2012) showed that substance or drug abuse and long periods of HIV infection are influencing factors for PN.

Peripheral neuropathy is said to be the most prevalent adverse effect leading to the regimen changes among PLHIV in sub Saharan Africa, (Mehta et al., 2010). The same authors showed that though d4T has been known to be the most common risk factor for developing PN in PLHIV on ART, there are likely other factors that contribute to the presence of PN among PLHIV. These factors are said to include; nutritional deficiency, toxic effects of anti- tuberculosis medication, alcoholism, diabetes, and HIV-infection itself (Mehta et al., 2011). The pre-ART studies indicate that advanced immunosuppression, shown by reduced CD4+ cell counts and increased HIV viral load increased the risk and severity of neuropathy in PLHIV (Lichtenstein et al., 2005). ART reduces viral load and increases CD4+ cell counts (Iwuji et al., 2013). Controversially however, ART has been found to lead to an increased prevalence of neurologic

conditions particularly ART-associated PN in long-term survivors of HIV disease (Evans et al., 2011). There is a pool of evidence that PN has not declined in frequency, even in the ART era, particularly in recipients of d-drug ARV regimens (Smyth et al., 2007); Oshinaike et al., 2012). PLHIV have an improved life expectancy because they are on ART, and in some cases have long periods of PN, and this has increased the prevalence of PN (Evans et al., 2011).

Peripheral neuropathy has become the main neurological adverse effect of ART, and people at any stage of HIV can be affected. Peripheral neuropathy was demonstrated to appear throughout the range of HIV disease and its occurrence has been augmented because of extended survival rates and the development of ART (Dorsey & Morton, 2006). Contrarily, Schiftto et al. (2005) indicated that ART reduces disease advancement, improves immunity, and extends the proportion of therapeutic to toxic effects of individual ARVs, causing a lower possibility of evolving PN, but PN has not decreased since ART was introduced (Simpson et al., 2006). Such conflicting findings probably suggest the presence of other influencing factors that enhance or prevent the development of PN. People are probably living longer, and have more time to develop PN, whether associated to viral, ART or other factors.

Dalakas (2001) indicated that ddC is one of the medications that increase the risk of PN in PLHIV. However, recent studies have also indicated that PN has remained unchanged even in the reduction of all d-drugs from the ART regimens (Oshinaike et al., 2012). This generates research questions such as whether PN is mainly associated

with HIV itself and or with most of the ARV types in the ART regimens, rather than d-drugs alone.

The prevalence of PN rises as CD4 cell count drops (Lichtenstein et al., 2005). A similar relationship was confirmed in the study by Evan et al. (2012) in which patients with PN at ART initiation presented more progressive HIV disease than those without PN. Such associations suggest that a patient with low CD4 counts may not suffer from PN related to HIV alone, but also from neurotoxicity or other associated conditions. Hence, the risk of developing PN increases at starting stages of ART, and more specifically when therapy is initiated in patients with low CD4 counts (Lichtenstein et al., 2005).

2.3.6 Symptoms, signs and progression of PN

Peripheral neuropathy manifests symptomatically with pain and paraesthesia in a “stock and glove distribution” and dysaesthesia in the feet, as demonstrated by Hung et al. (2008). The studies by Dalakas (2001); Simpson and Cikurel (2006), highlight that PLHIV experiencing PN can present with various complaints; such as the earliest symptoms of PN that include; “pain, numbness, and tingling in the hands and feet in the classic ‘stocking and glove’ distribution”. In their study on controlling neuropathic pain in HIV, Verma et al. (2005) showed that neuropathic pain comprised of about 25% to 50% of all visits at their pain clinic. The study further explained that some people express changed “sensation when picking up objects, as if their fingers are made of ‘plastic’, or feeling as if their hands and feet are ‘falling asleep’. Furthermore, the patients may also complain of their feet “throbbing or cramping at night or of stumbling”

when they try to walk. Additionally, the symptoms are said to be largely symmetric, even though are likely to be more severe on one side. In cases of severe neuropathy, it is described that touching the affected extremity can feel like “an open wound is being touched”. Additionally, the study by Simpson & Cikurel (2006) found that several patients have no any symptoms or PN mild at start. One of the studies conducted at one of the ART clinics in Rwanda, by Uwimana & Struthers (2007) found that the numbness and paraesthesia in the hands and feet were the most common symptoms among PLHIV. Other reported clinical features of PN were increased vibratory thresholds, reduced pinprick, and sense of temperature in the stock and glove distribution.

The PN symptoms are shown to advance constantly, or can be worse very fast within a time frame of days or weeks (Schifitto et al., 2002; Evans et al., 2012). Altered sensations and pain progress in a pattern starting with the toes and soles of the feet; then, the symptoms may spread to the ankles, as nerve injury continues, in most PLHIV (Evans et al., 2011). Progressed PN symptoms are mostly characterised by painful sensation, which can easily be elicited with any touch to the affected part of the limb. Such touch may include socks, bed sheets, or shoes, and this usually results into embarrassment. In the most advanced stages of PN, the upper extremities may also be affected with involvement of the fingers, hands, and wrists. When PLHIV with PN are asked to explain their symptoms, it is said that the most common descriptor used is pain, then numbness, tingling, burning, and stinging (Nicholas et al., 2002). Muscle strength and joint position sensation are reported usually to be normal. Symptomatic

weakness occurs late during the disease and is largely restricted to the distal intrinsic foot muscles (Schifitto et al., 2002).

2.4 Effects of PN on lower extremity functional ability

HIV and its treatment are known to have complications and effects on body systems and particularly on the neuro-musculoskeletal system (McGuire, 2003; Luciano et al., 2003 & McArthur, 2005). The chronic conditions as side effects and complications of HIV and ART have resulted in functional limitations or difficulties with mobility, impaired self-care and pain which are commonly reported in various studies (Rusch et al., 2004; O'Brien and Nixon 2010).

The study by Van As et al. (2009) indicated a significant association between pain related to PN of the lower extremities in PLHIV, and functional activity limitations. The sensory loss and pain; which are commonly major symptoms and signs of PN, were the most common (71%) of the impairments identified by Van As et al. (2009), among PLHIV. The same authors described the impairments of sensation and pain as strong predictors of the mobility problems affecting PLHIV. Similarly, the neuropathic pain as one of the symptoms of PN was found to be strongly associated with limitations of daily activities and thus a major influencing factor for disability among PLHIV (Ellis et al., 2010). The functional limitations as a result of PN among PLHIV are various and therefore may point to the need to concentrate on individualized efforts in dealing with the problem (Sandoval et al., 2013).

2.4.1 Relationship between PN, lower extremity functional limitations and QoL

HIV and its associated health conditions are now increasingly viewed as chronic, long term conditions with functional limitations rather than as a terminal illness (Worthington et al., 2005; Mkanta and Uphold, 2006). These functional limitations likely result in disability if not dealt with. However the understanding of the limitations is still a challenge. O'Brien, et al. (2008) stated that disability is conceptualised by PLHIV, as being multi-dimensional and occasionally with features of irregular phases of normal health and sickness. Consequently, HIV infection and its treatment have potentially resulted in a variety of functional limitations which may be the patient's primary problem (Zonta et al., 2003), which likely influence poorer QoL. A study conducted in Brazil among PLHIV to evaluate functional disabilities confirmed that the majority of patients (91%) presented with some degree of functional limitations that predicted poorer QoL (Zonta et al., 2003)

Improvements in functional ability and wellbeing are essential outcomes of the management of HIV and should be measured regularly (Hsiung et al., 2005; Jelsma, 2009). The demand on the management will place greater emphasis on maximizing patients' individuality, diminishing the functional limitations and improving the patient's functional ability thus contributing to their improved QoL (Anderson, 2006). Health care professionals are challenged in assisting PLHIV to adapt to the living longer with HIV and AIDS and its complications (Phaladze, et al., 2005). This is because living longer with HIV and AIDS has associated disabling conditions. The involvement and empowering of the community to develop management strategies, using affordable

approaches, is essential. The preventive measures for such disabling conditions like PN that is common with the chronicity of HIV should be the goal in the rehabilitation of PLHIV. Thus, the potential to enhance QoL is increased through providing interventions that will meet the essential functional needs to ensure reasonable QoL of PLHIV (SOWELL et al., 1997; Crystal et al., 2000).

2.5 Quality of life of PLHIV with PN

2.5.1 An overview on QoL

Various studies have defined and described QoL in terms of being both objective and subjective. The objective QoL has been shown to include; “income, living situations and physical functioning while subjective QoL includes individual’s perception of important life domains and satisfaction with those domains” (Njoki et al., 2007). Furthermore, a study by (Casado et al., 2004) described an operational definition of QoL as a complex and multidimensional concept which is difficult to define and measure. Casado (2004) continued to describe the QoL as a term which is universally used to give an overall sense of wellbeing and that includes aspects such as happiness and satisfaction with life as a whole. The QoL in clinical settings may be defined as a condition with specific symptoms; “body discomfort, social and role functioning, overall perception of health, cognitive status, and general well-being”. While in research, the QoL tools give new understandings into the nature of disease by measuring how disease weakens or influences the subjective well-being of a person throughout entire range of daily activities (Hakuzimana, 2005). There are other influences including demographics, personality, economic status, environment, and social relationships that impact on QoL

(Hakuzimana, 2005). Thus, the negative results of the disease and its treatment represent a single category of influences, but there other many influences or factors of QoL.

2.5.2 Quality of life and HIV AND AIDS

PLHIV are found to have lower scores on QoL which deteriorates along with a cumulative number of symptoms (Herrmann et al., 2013). Extensive studies on QoL among PLHIV have been done, and some have attempted to both assess QoL and determine predictors for good or poor QoL (Mweemba et al., 2009). PLHIV are not only concerned with a treatment's ability to extend life but also with the QoL they are able to lead (Basavaraj et al., 2010). Quality of life for PLHIV is increasingly becoming important, as therapy should not only be concerned with suppressing the virus, reducing symptoms and extension of survival but also be concerned with improving QoL (Oguntibeju, 2012). PLHIV experience numerous symptoms due to the disease, side effects of medication and co-morbidities and have severe symptoms. Thus, the QoL of PLHIV is associated with disease stage and disease symptoms, hence with proper management of HIV and AIDS symptoms, improves the QoL (Gakhar et al., 2013).

The concept of QoL in PLHIV has received increased attention in the literature, and it is recognized that HIV illness impacts on all aspects of patients' lives (Worthington and Krentz, 2005). As stated by (Yen et al., 2004), QoL levels of PLHIV are different according to the method used to measure it. The same authors found that male outpatients who presented fewer HIV symptoms had medium QoL levels using the

WHOQOL-BREF. Higher QoL scores are found among asymptomatic PLHIV compared with symptomatic ones and with an AIDS diagnosis (Imam et al., 2011).

There are various results on the relationship of ART and QoL in different studies regarding improvements made (Oguntibeju, 2012; Wen et al., 2013; Gakhar et al., 2013). The long-term use of ART has positive effects on controlling the disease, prolonging survival, reducing incidence and mortality rates (Oguntibeju, 2012), moderating the symptoms due to HIV-infection, and slowing the development of AIDS, and hence improving the QoL. Therefore, considerable improvements in the QoL of symptomatic HIV subjects have been noted on QoL measures following ART (Margalho et al., 2011). However, some consequences of ART on the QoL were reported by some studies such as direct toxicity (Oguntibeju, 2012) that is highlighted to likely cause PN. This is likely to result in more morbidity consequences of the PN if appropriate management approaches are not put in place.

2.5.2.1 Factors affecting QoL of life among PLHIV

Differing results has been reported, particularly when determining predictors of poor QoL. Variables, such as; female gender, older age, close family members or friends, stigma and marital status are among the sociodemographic and psychosocial, variables that have been associated with lower QoL in PLHIV (Subramanian et al., 2009), while higher income and employment have been associated with better QoL (Viswanathan et al., 2005). Also, studies have found that employed PLHIV, have significantly higher overall QoL than unemployed PLHIV (Rueda et al., 2012).

In regard to gender as a socio-demographic factor, low performance for women in some aspects of QoL is documented (Vigneshwaran et al., 2013) and married women are said to be more vulnerable than men to interruptions in their QoL (Thomas et al., 2009). Married women are likely to have more sexual disruptions over time than men and also sexual relationship discontinuation in women is documented more frequent than in men (Thomas et al., 2009).

Younger age is reported to be related to better QoL, as opposed to old age (Skevington, 2012). It is reported that adult people of 35 and above years are likely to suffer from more depression and other psychological symptoms that compromise their QoL, than the young (Basavaraj et al., 2010). When comparing educated and less educated groups, the findings show that those with low levels of education have significantly poorer QoL than those with higher levels of education (da Silva et al., 2013). Nevertheless, few studies have documented the QoL of PLHIV who have PN. The few that are available on QoL and PN, according to the domains of QoL, are discussed below.

2.5.2.2 Physical health domain of QoL

The physical health domain of QoL is described to assess the effects of disease on the daily living activities, dependence medications, deficiency of energy and creativity, mobility limitations and work capacity (Skevington et al., 2004; Wig et al., 2006). Physical health gives an individual the ability to perform and adapt to the environment.

The domain is estimated by an individual's perceptions of "energy and fatigue, pain and discomfort, sleep and rest". There is a confirmed association found between the physical health domain and overall QoL. In cases where physical status with high levels of physical activity, perceptions were that physical health and QoL were more positive (Pucci et al., 2012).

HIV infection affects various domains associated with physical health since frequent illness and increasing fatigue affect the individuals' ability to perform employment related and routine activities (Kohli et al., 2005). Jenkin et al. (2006) demonstrated that fatigue is common in PLHIV and may affect one's functional activity level. As a result, symptoms of fatigue and pain often lead to limitations in leisure time and physical activities (Harmon et al., 2008). PLHIV experience problems with physical function and activity limitations (Van As et al., 2009). However, there are few studies on the QoL of PLHIV with PN; it is likely that their QoL is worse than those without PN. One of the studies conducted in one district hospital in Rwanda demonstrated that PLHIV with PN had lower physical health QoL (Biraguma and Rhoda, 2012).

2.5.2.2.1 Factors affecting the physical health QoL

Certain factors such as occupation and education were shown to affect the physical health domain in some studies on QoL of PLHIV (Wig et al. 2006; Adewuya et al., 2008). Active workers and business persons scored better in physical health domain in relation to others, meaning that people with good occupations likely have better physical health (Basavaraj et al., 2010).

Other factors regarding ART and physical QoL have been established. It is mentioned that adherence to ART reduces viral loads and allows the immune system to improve (Cambiano et al., 2010) yet, non-adherence of ART ranges from 22% to 47% (Naidoo et al., 2013; Pefura-Yone et al., 2013). Some reasons for non-adherence to ART have been identified to include depression and poor QoL associated with ART adverse effects such as neuropathy (Uzochukwu et al., 2009; Bhat et al., 2010; Chen et al., 2013). In comparison, some studies indicate improved overall QoL with the use of ART (Wang et al., 2009), while others observe a decreased physical QoL with the use of ART (Gill et al., 2002; Chen et al., 2013).

2.5.2.3 Psychological health

Wig et al. (2006) describes that the psychological domain incorporates the "patient's own thoughts about body image and appearance, negative feelings, positive feelings, self-esteem and personal beliefs". Psychological health parameters that include the level of depression and anxiety, have been found by (Mitro et al., 2008), to be a source of resilience against stress and becoming ill, thus an individual's positive psychological well-being influences having good QoL. HIV infection does not only affect the physical health of PLHIV, but also morbidity which commonly leads to weakening of the psychological domain of QoL, as indicated by Liu et al. (2006).

Depression is reported as the most commonly observed mental health disorder among 18% to 81% of PLHIV (Arseniou et al., 2014). The disorder is reported as the major

predictor of poor QoL in PLHIV (Hou et al., 2014). The comprehensive study on how depression relates to QoL in PLHIV in Nigeria by Adewuya et al. (2008) demonstrated a strong relationship between the depression diagnosis and poorer QoL. Reductions in depression has been observed with ART management in PLHIV (Wagner et al., 2012). However, despite the positive effects of ART, significant psychological challenges have been noted for both people who respond positively to treatment and those who do not (Sherr et al., 2007). Thus, the HIV infection causes psychological disorders and some are as a result of ART side effects such as PN that may still be challenge for PLIHV (Chen et al. 2013). Again the study by Biraguma and Rhoda (2012) indicated lower psychological health QoL as result of PN due to HIV infection and or ART in Rwanda.

2.5.2.4 Social relationships

According to Wig et al. (2006) the social domain examines the personal relationships, social support and sexual activity. Social support is one of the identified mediators to reduce the impact of stigma among PLHIV with depression and symptomatology (Rao et al., 2012). The QoL is mostly and negatively affected by social relationships compared to other health domains of QoL (Imam et al., 2011). This is likely because social relationships are one of the main areas affected in PLHIV and includes being stigmatised by society, and this impacts on other aspects of QoL (Greeff et al., 2010). It makes PLHIV to often experience social isolation, stigmatization, discrimination and marginalization, as put forward by (Greeff et al., 2010). Stigmatization has been found to be a major barrier to improved QoL for PLHIV (Mahajan et al., 2008; Jin et al., 2010)

2.5.2.5 Environmental health

Environmental factors are among others that have a main role in determining health situations of people. According to Wig et al. (2006) the environmental domain examines the effects of factors such as “financial resources, the work environment, accessibility to health and social care, freedom, security, participation and opportunities for leisure activities on QoL”. In daily life people would like to have the financial resources that they need to meet their daily needs and this gives life satisfaction (Xiao et al., 2009), and is thus a predictor for positive QoL.

As mentioned previously, physical safety and security are important aspects of the environment as they give the individual emotional freedom. It is also considered essential to access good quality health and social care that provide chances for obtaining new information and skills. A safe and secure environment that enable participation opportunities for recreation and leisure, and hence promotes a high level of QoL (Arcury et al., 2012).

According to (Misfeldt et al., 2014), financial support such as giving incentives delivers more benefits in addition to financial, and also structures for social support, role identity and personal meaning, for working individuals. The impact of employment on QoL and psychological functioning among employed PLHIV, results in significantly higher overall QoL than unemployed individuals with HIV (Blalock et al., 2002).

A study on the influence of HIV on the QoL by Skevington (2012) found that the support from the family, and occupation, are important factors that affect the QoL in the environmental domain among PLHIV. The same study demonstrated family as the most significant element of the direct environment of the individual. The family is considered as the main backing, not only for financial support, but also for security and safety, noting that decent and helpful home surroundings may assist PLHIV to feel healthier. It is also shown that expert workers and business persons scored better in environment domain (Wig et al., 2006). The same authors concluded that improving surroundings of PLHIV can give them a better QoL.

2.5.3 Relationships between PN and QoL

Most literature indicates that PLHIV experience different neurological complications associated with clinical manifestations of the epidemic, related opportunistic conditions and side-effects from medication, such as the neurocognitive disorders (Alfahad and Nath, 2013) and PN (Chen et al., 2013; Conradie et al., 2014; Dubey et al., 2013; Scott R. Evans et al., 2011; Forna et al., 2007; Gabbai et al., 2013; Hahn et al., 2010; Luma et al., 2012; Maritz et al., 2010; Mehta et al., 2010; Nicholas et al., 2007a; Simpson et al., 2006; Wadley et al., 2011; Wolfort and Dellon, 2012; Wulff et al., 2000). The neurological complications are reported to be the most challenging among HIV researchers (Alfahad and Nath, 2013), and PN is said to be the most common among the neurological co-morbidities (Luma et al. 2012; Chen et al. 2013; Dubey et al. 2013; Gabbai et al. 2013; Conradie et al. 2014). Peripheral neuropathy is reported to impact on daily activities of PLHIV and their relationship with the external environment, and can

greatly affect their QoL (Padua et al., 2005). Worsening QoL of affected individuals may increase their disability (Hogan and Wilkins, 2011).

However the data available regarding QoL and PN in PLHIV is not sufficient to guide the rehabilitation approach for the PLHIV with PN. Most information on QoL and PN is about diabetes associated PN. Like any other chronic pain the PN related to diabetes has a significant negative effect on QoL of the affected person. One study by (Gore et al., 2005) demonstrated that QoL was strongly lower in patients with diabetes with severe pain related to PN than among patients with diabetes without the severe pain related to PN. It was further noted that people with diabetes and chronic pain, have reductions in sleep, walking and ability to perform domestic duties and hence such painful PN has been shown to have severe adverse effect in physical, psychological functioning and the overall QoL of people with diabetes (Bouhassira et al., 2013; Vinik and Casellini, 2013). Similarly, one of the few studies on PN in PLHIV, indicated that neuropathic pain was strongly associated with the sleep disturbances which impacted on the mobility functioning (Sandoval et al., 2013). Thus, the PN related to HIV is characterised by painful symptoms as demonstrated with PN related to diabetes. The same effects of PN related to diabetes on the QoL are likely to be similar to the ones in HIV-associated PN. Biraguma & Rhoda (2012) indicated that PN was significantly associated with QoL, among PLHIV in one of the district hospital in Rwanda. However, the sample size of this study was small and the study was done in one setting. Hence, it is important to conduct other studies with a bigger sample size and in more settings, to improve surveillance for PN. This may facilitate in developing an appropriate data base to enable better understanding of the effects on PN on the QoL of PLHV, as well

as for the development of early interventions to improve QoL and prevent disabling pain and the associated functional limitations. The study by Griswold et al. (2005) assessed the coping approaches of PLHIV with PN and discovered that the approach strategies can vary depending on age, gender and the ethnic background of PLHIV. It is therefore, important to conduct studies with interventional methodologies among PLHIV on ART who have associated PN.

In conclusion, despite all the progress in HIV care and treatment, there is minimal data related to HIV–associated PN and the related functional limitations and rehabilitation approaches in Rwanda. It is an issue of concern as there is a need to improve and maintain the QoL of PLHIV on ART in the region.

2.6 Management of HIV-associated PN, related functional limitations and QoL

2.6. 1 Introduction

This section highlights the identified and suggested management strategies of PN, the related functional limitations of the lower extremities and the QoL.

2.6.2 Treatment of HIV-associated peripheral neuropathy

Peripheral neuropathy management aims at relieving painful neuropathic symptoms and to educate patients regarding prevention and care of PN-related disorders that affect people's lives (Brix Finnerup et al., 2013). However, the management is still a challenge for the health care professionals of these patients because of lack evidence

based data on the management approaches. There is a need to develop effective management for PN as highlighted by (Phillips et al., 2010)

The management of PN incorporates pharmacological and non - pharmacological approaches (Nicholas et al., 2007; Dworkin et al., 2007; Phillips et al., 2010). There is enormous evidence based on the pharmacological management of painful neuropathy. In this evidence, systematic literature reviews, RCTs, and existing guidelines were evaluated by Dworkin et al. (2007). In the systematic literature review, the same authors found and recommended that the first-line treatments for the PN, which contain some antidepressants such "(tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), and calcium channel α2-δ ligands (i.e., gabapentin and pregabalin), and topical lidocaine". They then indicated that opioid analgesics and tramadol be recommended usually for second-line treatments, but further mentioned that could be used for first-line in chosen clinical conditions (Dworkin et al., 2007). The authors demonstrated that there are other drugs that would be used as third-line treatments but might also be applied in the second-line treatment in some conditions. These included some of the antiepileptic and antidepressant medications, such as "mexiletine, *N*-methyl-d-aspartate receptor antagonists, and topical capsaicin" as indicated by Dworkin et al. (2007). Similarly, gabapentin and pregabalin that were added to the management of PN in patients with diabetes have been effective and lowered the costs of health care (Sicras et al., 2013). The pregabalin is reported as safe and effective in reducing pain associated with diabetic PN (Deli et al., 2013), and also improves mood, sleep disturbances, and QoL (Vinik et al., 2013). However, when pregabalin was tested for the same effect on PN in PLHIV, it was not superior to

placebo. The authors concluded that the pregabalin did not show a significant difference on being effective than placebo for the management neuropathic pain PLHIV (Simpson et al., 2010).

Furthermore, a systematic review and a meta-analysis of RCT's was conducted by Phillips et al. (2010), with the objective of evaluating the clinical effectiveness of analgesics in treating painful PN. The conclusions from the review were that an evidence of efficacy exists only for capsaicin 8%, smoked cannabis and rhNGF. However, the rhNGF could not be available for clinic purpose and the smoked cannabis could not be commended as routine therapy (Phillips et al., 2010). The same authors recommend that assessment of new management approaches for the PN associated with HIV is urgently essential (Phillips et al., 2010). Contraliry, a double – blind RCT carried out by Clifford et al. (2012), did not indicate a significant effect of the capsaicin 8% patch in the treatment of HIV – DSP. But some improvement in the pain were felt as reported by the same study. Earlier, Simpson et al. (2003) and later Titlic et al. (2008) had showed that lamotrigine was effective in treating the HIV-associated neuropathic pain among PLHIV on neurotoxic ART.

It has also been shown that there is no dramatic improvement of PN with ART-related reductions in HIV viral load, as the neuropathy damage is likely irreversible due to the virus, or the ongoing damage with ART. This may mitigate the benefit of viral control (Evans et al., 2011; Oshinaike et al., 2012). The non-improvement of PN with ART management indicates a definite need for the supplemental treatment management and could include non-pharmacological management.

Non-pharmacological management of PN generally, has also been tried. Exercise programme and lifestyle changes were both recommended (Ahmad and Goucke, 2002). The same authors emphasised that such management approaches are important to maintain mobility and independence, particularly of elderly patients with PN, because old age is susceptible to PN. This was mainly to avoid the adverse effects of drug – treatment in this group.

Thus, diet control and exercises are some of the lifestyle interventions used in pre - diabetic neuropathy to prevent pain. Most of the non-pharmacological management for PN has been reported in patients with diabetes (Smith et al., 2007). In some studies, it has been highlighted that management of the neuropathic pain among the people with mild PN symptoms, can be managed through lifestyle changes such as avoiding; wearing limiting shoes, standing for long time and walking long distances (Nicholas et al., 2007a). The same authors further indicated that nutritional supplements, putting feet in warm water, rest, elevation of limbs, rubbing the feet with cream, and exercises, are some of the approaches that have been mentioned to help people with PN (Nicholas et al., 2002 & 2007a). Additionally, Nicholas and the colleagues (2007a) showed that complementary modalities are supportive to help people in prevention and reducing of the ART side effects as well as managing the PN symptoms. The modalities which are commonly used include but not limited to; yoga, meditation, physical modalities such as heat, whirlpool, and massage, traditional Chinese medicine such as; acupuncture and tai chi (Galantino et al., 1999; Phillips et al., 2004; Meyer-Hamme et al., 2012). Again, Dorfman et al. (2013) found that brief hypnosis interventions may give a useful and a

well-torelated management of HIV – PN but further investigations are needed. All such modalities aim at long term improvement and have less adverse effects (Meyer-Hamme et al., 2012).

There are a variety of treatment modalities available for PN, but preferences should be made based on the safety and the adverse effects of the modalities, and should depend on the individual. The lifestyle changes and complimentary approaches were preferred to be added to the health care of people with PN (Nicholas et al., 2007a). The same author stated emphasised that the pharmacological remedies can only be used in the management of the PN if the lifestyle changes and complementary approaches are not able to control the pain associated with PN. Yet, the patient usually request the symptomatic treatment with the pharmacologic agents but there are no precise features of the pain that can estimate what kind of remedies would work better for the relief of the symptoms, as described by Nicholas et al. (2007a). The selection of the drug is said to be centred on how severe the symptoms are, and the likely adverse effects known from the drug (Dworkin et al., 2007; Phillips et al., 2010).

Improvements in QoL of PLHIV has been obtained through the treatment of PN, with relief their neuropathic symptoms and depression levels (Dorfman et al., 2013). Thus, effective treatment of symptoms is essential for improving QoL. According to Lorenz et al. (2001), most persons living with chronic illnesses appraise their QoL, at least in part, according to the symptoms (including treatment side effects) they experience. Nevertheless, few studies have investigated the management of physical and functional

impairments as a result of PN, for the purpose of early rehabilitation so as to prevent patients remaining prone to disability (Myezwa et al., 2009)

It is not yet clear if there standard treatments for PN available, but the ones available, are oriented to relief of the symptoms (Verma et al., 2005). But the rehabilitation of the function that may have been affected by PN is not probably described in the treatment strategies available for the purpose of preventing functional limitations and improving the QoL of the affected PLHIV.

2.6.3 The rehabilitation needs for PN-related functional limitations

There is a dearth of literature on PN-related functional limitations to inform rehabilitation professionals. However, there is literature that highlights the association or a link between PN and functional limitations, specifically of the lower extremities. The study by Ellis et al. (2010) found that PN impairments; specifically for neuropathic pain was strongly related to limitations of activities of daily living, unemployment and reduced QoL. Vinik et al. (2013) showed that PN related to diabetes is found to be associated with both impairments and functional limitations and that PN is closely associated with functional limitations which finally result in reduced QoL if not dealt with appropriately. This shows the need for rehabilitation of the impaired function with PN.

The study by Myezwa et al. (2009) found that it is necessary for rehabilitation professionals to be familiar with the impairments and rehabilitation diagnosis for appropriate treatment plans, identification of patients and outcomes. The authors

emphasised that rehabilitation professionals such as physiotherapists need to identify appropriate patients themselves and primary care physicians should understand the subsequent disabilities seen in AIDS for proper referral to rehabilitation (Myezwa et al., 2009). Regardless of the evidence that there is an important role for rehabilitation providers to play in the health care of PLHIV, there is a potential gap between the documented rehabilitative needs of PLHIV and services provided by rehabilitation professionals (Worthington et al., 2008).

2.7 Effects of exercises on PN, related functional limitations and QoL

2.7.1 An overview of the effects of exercise interventions in HIV-related disorders

Exercise is known to have positive effects in various conditions and in particular in rehabilitation of chronic illness, including those in PLHIV. In this section, different exercise approaches and interventions in the common HIV related conditions are highlighted. As the focus of this study is on PN, the available exercise interventions for PN, related functional limitations and QoL are also demonstrated in the following sub-sections.

The literature includes various studies that have tested the effectiveness and safety of exercises among PLHIV. The effects of some exercise intervention studies among PLHIV were highlighted in a systematic review by O'Brien et al. (2010). The authors conducted the systematic review with the objective of examining the "safety and effectiveness of aerobic exercise interventions on immunologic and virologic, cardiopulmonary, psychological outcomes, strength, and weight and body composition"

in adult PLHIV. The review included RCT's with comparisons of the aerobic exercise interventions against interventions without aerobic exercise or any other exercise or treatment approaches. According to their criteria of study selection, the exercise must have been done at a frequency of at least three sessions per week and for at least a period of four weeks with adults PLHIV of 18 years old and above. Altogether, 14 studies fulfilled the authors' set requirements and were included in the review. From the results of the studies examined, the authors concluded that exercises are safe and that they may be helpful for adult PLHIV (O'Brien et al., 2010). However, the same authors further commented that the findings had limitations with smaller sample sizes and high rates withdrawal identified from the studies evaluated. They suggested that further studies would use participants' follow-up and intention-to -treat analysis (O'Brien et al., 2010).

Supervised aerobic exercise done at sub-maximal age predicted maximal heart rate levels of 70% and resistance exercise programmes in PLHIV has been shown to be safe and is known to improve cardiovascular fitness (O'Brien, et al., 2010). Specifically, one of the studies by Mutimura et al. (2008) demonstrated that the exercises are safe and efficient in improving metabolic profiles and cardiovascular fitness, in ART treated PLHIV in Rwanda. Most exercise intervention studies found no effect of exercises on the immune indices, specifically, changes in CD4 count (Baigis et al., 2002; Driscoll et al., 2004; Dolan et al., 2006; Terry et al., 2006; Mutimura et al., 2008). Contrary, a single study by Perna et al. (1999) showed that adherent exercisers improved their CD4 count by 13% while the non-adherent exercisers diminished CD4 count by 18%. The participants in the control in the same study indicated a decrease trend of CD4 count by 10% (Perna et al., 1999). The authors concluded that aerobic exercises significantly

increased CD4 count among symptomatic PLHIV. The non-adherence might be associated with quicker CD4 decline because of numerous probable mechanisms (Perna et al., 1999).

Similarly, some of the exercise interventions indicate that exercise improves strength outcomes (O'Brien et al., 2010). However, most of the studies in the review did not assess strength outcomes (Baigis et al., 2002; Terry et al., 2006; Mutimura et al., 2008b), probably because the muscle weakness is not considered as the primary effect of the HIV and or ART-associated complications. Muscle strength in most cases is included during rehabilitation.

Generally, the benefits of exercise intervention among adult PLHIV are demonstrated in almost all exercise intervention studies, whereby exercises are safe and affordable. However, the studies differed in the objectives of the interventions, types of exercises or approach used. For the purpose and focus of this thesis, the following sections highlight the effects of exercise interventions on PN, functional ability of lower extremity in particular and the QoL, of PLHIV.

2.7.2 Effects of exercise intervention on PN

The exercise interventions for PLHIV with PN seem not to have been conducted yet. The available literature is mostly on the effect of exercise on PN in other health conditions such as diabetes. The effects of exercises in these other conditions may be beneficial to PLHIV with PN, as well. This is because the exercise have been approved

and shown to be safe and beneficial for the population with HIV (Nixon et al., 2002; Nixon et al., 2005; Mutimura et al., 2008b; O'Brien et al., 2010).

Therapeutic exercise that includes progressive resisted exercise, aerobic exercise, individualised exercise programmes, and generalised home programmes, are commonly used in the management of PN in patients with diabetes (Ward, 2005). Taylor et al. (2007) stated that "therapeutic exercise is defined as the prescription of a physical activity or programme where the client carries out voluntary muscle contraction and or body movement with the aim of relieving symptoms or improving, retaining or slowing deterioration of health". The same authors carried out a systematic review on therapeutic exercise studies published from 2002 to 2005, that conducted exercise interventions among participants with neurological, musculoskeletal, cardiopulmonary, and other conditions. The outcomes of interest in the systematic review were to "identify the effect of therapeutic exercise in terms of impairments, activity limitations or participation restriction" as stated by the authors. The review on the therapeutic exercise in neurological physiotherapy yielded six reviews but only one managed to meet the standard criteria and described the effect of exercise on PN. This is likely an indication that very few studies have been conducted with standard methodologies that test the effect of therapeutic exercise on peripheral neuropathies. But the review concluded that therapeutic exercise was extensively effective throughout the big range of physiotherapy treated conditions (Taylor et al., 2007) and these include neurological ones, specifically peripheral neuropathies.

A systematic review by White et al. (2004) included three trials which examined the effect of exercise in people with PN but the three studies had small sample sizes The authors of the systematic review concluded that there is little evidence from the RCTs to assess the effect of exercise on the ability of function among people with PN. Nevertheless, the same authors pointed out an evidence of muscle strength as result of exercises among people with PN. The implication for future research was that there is a deficiency of quality evidence, which can guide assessment of the effect of exercise on the ability of function among people with PN. The implication supports a strong need to develop further research with high quality sufficiently powered trials (White et al., 2004).

Furthermore, a study was conducted to examine the “feasibility and effectiveness of a supervised, moderately intense aerobic and resistance programme” in people with PN related to diabetes (Kluding et al., 2012). The study used a pre-test post-test design and the assessment was done on 17 people after 10 weeks of participation in an aerobic and strengthening exercise programme. The findings from the study indicated significant improvements of pain, neuropathic symptoms, and increased intra-epidermal nerve fibre branching. The authors pointed out that the study indicated an improvement in neuropathic symptoms and cutaneous nerve fibre branching following supervised exercise in people with PN related to diabetes. Despite the fact that the findings were promising the study was for a short time and lacked a control group. The authors further recommended comparison with a control in futures studies (Kluding et al., 2012).

2.7.3 Aerobic exercise in people with PN

An aerobic exercise regimen is reported to include; physical activity done at frequency of at least three times per week for at least four weeks, according to O'Brien et al. (2010). In their meta-analysis, O'Brien, et al. (2010) demonstrated results of different clinical trials that an effective exercise regimen must ideally be at least six weeks long. Studies on aerobic exercises have been documented by various systematic reviews, and their results indicated that the exercises are safe and beneficial for PLHIV (Nixon et al., 2002; Nixon et al., 2005; O'Brien et al., 2010). Conversely, to my knowledge, there is a paucity of aerobic exercise interventions for PLHIV with PN. Nonetheless, strengthening and balance training exercises incorporated into aerobic exercise programmes have been shown to be beneficial for people with PN related diabetes (White et al., 2004; Tofthagen et al., 2012; Kluding et al., 2012). In their study, Balducci et al. (2006) suggested that aerobic exercise training done for long-term may be beneficial in preventing the onset or change nature of PN related to diabetes. The aerobic exercise with less intensity such as brisk walking, were identified as beneficial and relevant for management strategy, like preventing the start or adapt the nature of PN in diabetes (Balducci et al., 2006). Strength training with isometric exercises done against maximal resistance, with no associated joint movement in people with PN, was recommended by White et al. (2004).

2.7.4 Effects of exercise on functional limitation and QoL among PLHIV with PN

The functional activity limitation and participation restriction, which commonly result in deteriorated QoL, are frequently identified in PLHIV with PN (Wong and Sagar, 2006).

Exercises are consistently documented as one of the greatest common self-therapies (Ciccolo et al., 2004). Studies to identify the effects of exercise on functional limitations and the QoL among PLHIV, with HIV-related co-morbidities, indicate improvements in functional limitations and QoL (O'Brien et al., 2010).

A study by Galantino et al. (2005) tested the effect of group aerobic exercise and tai chi on functional outcomes and QoL in patients with HIV. The study considered thirty eight (38) subjects with advanced HIV and AIDS who were randomised to one of the three groups; tai chi, aerobic exercise, or control. The two exercise treatments were carried out at each research site, twice weekly for 8 weeks. The overall goal of the study was to improve strength, flexibility, balance and endurance without using sophisticated equipment (Galantino et al., 2005). The results of the study demonstrate that the tai chi and aerobic exercises improve physiologic parameters, functional outcomes, and QoL, compared to controls. Specifically, the functional improvements were seen in the balance for functional activity that requires balance, balance in sitting and standing and endurance after the intervention. Improved flexibility was one of the main achievements reported by the participants, in addition to improved stair climbing and all the functional measures tested. Tai chi exercise includes balance activities and is likely to improve balance. There were significantly enhanced psychological coping; specifically bewilderment and tension- anxiety among the participants. The participants also reported qualitatively on improvements in the overall health related perceptions in the subscales that measure QoL. Specifically, participants mentioned feeling better after exercising with improved social interactions with their peers which encouraged them to exercise harder (Galantino et al., 2005).

Home exercise programmes have been demonstrated by (Ruhland and Shields, 1997) to as essential in the rehabilitation of people with chronic PN in diabetes. In their study, they assessed the effects of home exercise programme by looking at differences in the changes of impairments and QoL between an exercise and control group. The relationships between the QoL and measures of impairment were also examined. The authors compared the QoL of people with chronic PN and the general population. In the study, the exercise group comprised of 14 participants and exercised for 6 weeks in a home exercise program, while the control group of 14 participants did not exercise. The participants in the intervention improved their muscle strength and walking time that was associated with the physical function, compared to the controls that did not. Finally, the study concluded that the home exercise programme is an essential constituent of the management of chronic PN. In comparing with the general population, people with chronic PN had lower QoL, but some areas appeared to improve after the programme of the home exercise (Ruhland and Shields, 1997).

However, despite all the exercise interventions described above, to my knowledge none so far have indicated the effectiveness of exercises on PN and related functional limitations among PLHIV. It is therefore worthwhile to note that testing the effectiveness of exercise in PN and related functional limitations for the promotion of QoL in PLHIV is essential.

2.7.5 Adherence to exercise

The adherence to exercise is an important consideration in an intervention study because it can influence the actual results of a study (Petroczi et al., 2010). The perception of well-being, lifestyle and cultural beliefs are major contributors to adherence. According to O'Brien et al. (2008) the withdrawal rates in the studies they reviewed ranged from 0 - 76 % and different reasons included; employment, illness, relocation, loss of interest, transportation difficulties, personal issues, lack of motivation, lack of time, and economic reasons.

Table 2 Summary of effects of exercise interventions on PN, lower extremity functional limitations and QoL

Study design and sample size and participants	Type of exercise intervention	Main results on PN, LEFLs, QoL and conclusions	Authors and date
A RCT among 160 PLHIV in selected health facilities in Zimbabwe	Progressive resisted exercises (PRE) were given to 80 participants twice a week for 12 weeks, were compared to 80 control group that walked un supervised at home	The finding of the study did not show a difference of the effects of PRE on performance oriented mobility in PLHIV with PN when compared to advice to exercise at home but showed a positive effect on the QoL of the group that had supervised exercise. The PRE programme may be extended to PLHIV as a home programme exercise was the author's conclusion	Mkandla, 2013
Pre-test and post-test design among 17 participants with Diabetic peripheral neuropathy (DPN)	10 – week aerobic and strengthening exercise	Significant reduction in pain, neuropathic symptoms, and increased intra-epidermal nerve fibre branching**.** **Authors' conclusions:** That was first study to describe improvements in neuropathic and cutaneous nerve fibre branching following supervised exercise in people with diabetes PN. Findings were promising given the short duration of the intervention and recommended a validation with comparison of a control group in future studies	Kluding et al., 2012
A RCT of 100 PLHIV (50 participants at baseline and 48 participants at study completion for the exercise group). And 50 at baseline and 49 at completion for non-	Supervised aerobic exercise was given for Six month. Aerobic Exercise included: proper warm up, stretching, and 15 minutes of brisk walking, followed by 45-60 minutes of jogging, running, stair climbing, low-back and abdominal stabilization and strengthening	Significant improvements in quality of life (QOL) on the psychological, independence, social relationships, HIV+ HAART-specific domains of QOL, and overall QOL score as measured by the World Health Organization Quality of Life HIV Instrument (WHOQOL-BREF) for exercisers compared with non-	Mutimura et al., 2008

exercising control group, in Rwanda.	exercises, followed by a 15 minute cool down and stretching exercises. Duration and Frequency: 3X per week, 1.5 hour per session, alternating days for 24 weeks (6 months). For non-exercising control group; No intervention was given.	exercisers. No difference between groups on the physical QOL domain score. **Author's Conclusions:** Results imply that exercise training is a safe, inexpensive, practical and effective treatment for evolving metabolic and cardiovascular syndromes associated with HIV and HAART exposure in resource-limited settings such as Su-Saharan Africa	
Cross sectional identification of symptoms management and self-care strategies for PN in 1217 PLHIV in USA	Reported symptoms management and self - care strategies	About 20 self-care behaviours including complementary therapies, use of medications, exercise and rest and/or elevation of extremities were identified.	Nicholas et al., 2007
A RCT with three groups of PLHIV (advanced HIV), and tai chi for 38 participant: USA	Tai chi was compared to aerobic exercise and the control groups. Both exercise regimens were conducted twice weekly, for 8 weeks.	Tai chi and aerobic exercises improve physiologic parameters, functional outcomes, and QoL, compared to the control group.	Galantino et al., 2005)
A RCT of 123 participants at baseline	Supervised exercise among 68 (at baseline) and 35 (study completion) participants exercised on Ski machine. 40 minutes total: 5 minute stretching, 5 minute warm-up on machine, 20 minutes constant aerobic exercise at 75-85% HRmax followed by 5 minutes cool-down and 5 minutes stretching. Duration and Frequency: 3X per week for 15 weeks. Constant aerobic versus non-exercising	Significant improvement in overall health subscale of the MOS-HIV found among exercisers compared to non-exercisers **Author's Conclusions:** Exercise appeared to be safe in HIV-infected individuals	Baigis et al., 2002

	control of 55 participants at baseline and 34 at study completion.		
RCT of home programme exercises, among 28 participants; with chronic PN	14 participants were given home based exercises and were compared with 14 other participants without exercises and also were compared with the general population	Study indicated an increase in the average muscle score in the exercise group compared with the control group after the intervention. Also the exercise group improved the scores on the role limitation. The authors concluded that the home exercise programme appears to be an important component of the treatment of persons with chronic PN	Ruhland and Shields, 1997

2.8 Summary

Chapter two highlights that the HIV pandemic is still a burden around the globe and more especially in sub Saharan Africa. The burden of the pandemic has shifted from a death threatening condition to a chronic lifelong condition often with disabling complications such as PN. The prevalence of PN in different regions of the world has been demonstrated in this chapter, and is still relatively high. In addition, the effects of PN in HIV, specifically on lower extremity function and related QoL have not been clearly demonstrated. The chapter reviewed the existing management strategies for PN and HIV related QoL, which include more pharmacological than non-pharmacological interventions. Finally, the available management strategies of PN and the associated effects on function and QoL, have been demonstrated. Of particularly interest are exercise interventions as a strategy in this era of ART, to minimise or even prevent the disabling chronic PN and related functional limitations.

CHAPTER 3

3.0 STUDY 1

THE OUTCOME MEASURES TO ASSESS PERIPHERAL NEUROPATHY, RELATED LOWER EXTREMITY FUNCTIONAL LIMITATIONS AND QUALITY OF LIFE IN PLHIV ON ART IN RWANDA

3.1 Introduction

This chapter describes the various outcome measures which were used in the data collection of the three studies for the thesis. The outcome measures used were to assess; PN, the related lower extremity functional limitations and the QoL in PLHIV on ART, in Rwanda. Additionally, a checklist for identification of demographic and health status characteristics and included the one for differential diagnosis of the neuropathic pain.

Several outcome measures were available in the literature, such as the Brief Peripheral Neuropathy Screen (BPNS) to assess HIV-associated PN (Cherry et al., 2005), DN4-questionnaire (Bouhassira et al., 2005) for assessing neuropathic pain, and the World Health Organisation (WHO) quality of life HIV instrument-short form (WHOQOL-BREF) (Skevington et al., 2004) to assess the QoL. Furthermore, an outcome measure to assess lower extremity functional activity performance called the Lower Extremity Functional Scale (LEFS) was also available.

However, the LEFS had not been tested to assess the lower extremity functional activity performance limitations related to PN in PLHIV on ART. The scale was originally

developed to assess the functional activity performance limitations in patients with disorders of one or both lower extremities particularly, in old people. The scale also could be applied to screen people with the lower extremity limitation over time and would evaluate treatment intervention effectiveness (Binkley et al., 1999).

The main aim of study 1 was to re-establish the validity, reliability and adapt outcome measures to assess PN and the related functional limitations of the lower extremity among PLHIV in Rwanda, so that the measures could be used in the rest of the studies of the thesis. The exception was the WHOQOL-BREF which had already been adapted through its translation into Kinyarwanda (Hakuzimana, 2005), and had been used in other studies such as by Mutimura et al. (2007), in Rwanda. It was therefore, not re-adapted in this study.

3.2 Specific objectives of study 1

3.2.1 To describe the outcome measures used this study

3.2.2 To adapt the BPNS for assessing PN in PLHIV on ART in Rwanda

3.2.3 To re-establish the validity and reliability of LEFS in Rwanda;

3.2.3.1 To translate the LEFS into Kinyarwanda

3.2.3.2 To pilot and test the translated LEFS for clarity

3.2.3.3 To modify and rectify unclear items found in LEFS for specific Rwandan cultural activities of daily living

3.2.3.4 To re-establish the intra and inter -assessor reliability of the modified LEFS

3.2.1 Description of the outcome measures

The checklist, neuropathic diagnostic tool (DN4), and WHOQOL-BREF, outcome measures are described in this section.

3.2.1.1 Checklist (Appendix 1: section A)

The design of the checklist used in this study was based on related studies conducted among PLHIV on ART (Bouhassira et al., 2005; Hsiung et al., 2005). The content analysis was undertaken by two clinician experts in HIV and AIDS and infectious diseases at the former Treatment, Research and AIDS Centre (TRAC) in Rwanda. The checklist included demographic characteristics such as age, gender, marital status, level of education, and the health status information such as duration since the participant was diagnosed with HIV, the ART regimen the participant is taking, duration on ART, the participant's history of other pathologies (such as diabetes, central neuropathy, alcoholism, kidney disorders, for exclusion purposes when screening HIV-associated PN). The CD4 cell count levels, presence of PN symptoms and if the symptoms commenced before or after starting on ART, were also identified. The checklist was used to collection information from the participants and from their medical records. It was completed by the author with assistance when needed by the medical practitioner working at the respective outpatient ART clinic included in the two following studies.

3.2.1.2: Neuropathic pain diagnostic outcome measure: DN4 (*Douleur Neuropathique 4 questions*) (Appendix 1 section B)

The DN4 is an outcome measure used to differentiate between pain syndromes related to neuropathic pain and somatic component that are non-neuropathic (Bouhassira et al., 2005). DN4 is a validated and researcher/clinician administered outcome measure to score the responses from participants regarding neuropathic pain. It has psychometric properties of; sensitivity (83%), specificity (90%), internal consistence reliability (rho=0.7), inter-rater (rho = 0.68 – 0.79), and intra-rater (rho=0.92 – 0.95), (Bouhassira et al., 2005). The tool was translated into Kinyarwanda and cross checked by experts for the correct use of the terminologies. Thereafter, the scale was piloted to familiarise the assessors about the use of the scale. The DN4 is constituted with altogether 10 items that are in four sections. The first seven items assess the pain quality, that is “burning, painful cold, electric shocks” and how the pain is related with abnormal sensations; “tingling, pins and needles, numbness, itching”. The rest three items are associated with the neurological assessment of the painful area; “touch hypoaesthesia, pinprick hypoaesthesia, tactile allodynia”. It is shown that each positive score is given 1 for every item, and each negative score is given 0 for every item. The sum of all scores of the items is counted out of 10, and the minimal number for the neuropathic pain diagnosis is 4/10 (Bouhassira et al., 2005).

3.2.1.3 Quality of life – questionnaire (Appendix 1 section E).

There are various outcome measures for assessing QoL in PLHIV but the one which was most relevant for these studies was the short form of the WHOQOL-BREF. It is a

short form of the WHOQOL-BREF outcome measure which was developed and validated, based on a well-classified definition of QoL and encompasses physical, psychological, social and environment domains. WHOQOL-BREF is recommended as a useful instrument in patients with HIV infection (Jang et al., 2004; Hsiung et al., 2005) and it has been validated in multi-cultural settings including African countries. The instrument has the psychometric properties tha include; internal consistence of α=0.74-0.85 and test – retest reliability of rho=0.64-0.79, (Jang et al., 2004). This instrument had already been translated and re-validated in Rwanda among PLHIV (Mutimura et al., 2007). The outcome measure facets in each of the following four domains (physical, psychological, social and environmental) have scores measured on a five point Likert interval scale from one to five. One indicates low and five indicates high perception (Jang et al., 2004; Hsiung et al., 2005). The WHOQOL-BREF for the measure of QoL contains items/facets asking about how a "person feels about different aspects of their life in the previous four weeks".

3.2.2.2 Description and adaptation of the BPNS for PLHIV in Rwanda

3.2.2.2.1 Description

The BPNS (*Appendix 1 section C*) is both a self-report and objective PN screening tool, which is a valid and reliable instrument for diagnosis of PN specifically DSP, (Cherry et al., 2005), with psychometric properties of; specificity (88%) and sensitivity (78%), (Evans et al., 2005). The BPNS examines subjective and objective outcomes constant with PN. It has been used in several clinical trial protocols; in particular by the AIDS Clinical Trial Group (ACTG) (Cherry et al., 2005) and evaluated in large-scale studies. It was identified to precisely discover PLHIV who have the highest grade of peripheral

nervous system dysfunction and pathology. The study by Cherry et al. (2005) concluded that the presence of both symptoms and signs on the BPNS provides a useful operational criterion for HIV- associated PN in the era of ART. One of the studies by Mehta, et al. (2010) implemented the validated BPNS in patients receiving ART in Mombasa, Kenya and the study recommended that the tool can easily be integrated into routine care by general practitioners in an outpatient HIV clinic with limited resources. The tool was therefore, a more realistic one to use in a resource limited country like Rwanda due to the high cost and lack of specialized instruments for nerve conduction such as, electromyography or sural nerve testing and electrophysiological changes. However, the tool was still piloted for adaptation to assess PN among PLHIV on ART in Rwanda.

3.2.2.2.2 Adaptation of BPNS in Rwanda

The adaptation of the BPNS was done together with piloting and re-validation of LEFS in study 1 with 50 participants. The procedures of adaptation of the BPNS Included; translating the scale into Kinyarwanda and cross checked by experts for the correct use of the terminologies. Thereafter, the scale was piloted to familiarise the assessors about the use of the scale, and estimate the duration of administration and use of the scale for the assessment of PN

3.2.2.3 Procedure of piloting and adaptation of BPNS

BPNS is a researcher/clinician administered scale. The author (assessor 1) and two other assessors (2 & 3), who were senior physiotherapists, did the assessments. A two

hour training session was conducted by assessor 1 for the other two assessors to familiarise them on using the scale to assess PN symptoms and signs.

A sample of 50 participants was randomly selected from all the PLHIV on ART registered at an outpatient ART clinic at Biryogo health centre, commonly known as “Kwa Nyiranuma” in Kigali city. The sample was 10% of the approximate total sample size ≥ 500 estimated for the prevalence study (Study 2). The health centre attends to more than 50 PLHIV on ART on each day of the five working days of the week. Ten participants were systematically randomly selected from each list of 50 plus PLHIV attending the centre per day. The sample of 50 participants was obtained in one week.

3.2.3 Ethical consideration

An ethical clearance certificate (protocol number M080812) for all the three studies in this thesis was obtained from the Human Research Ethics Committee at the University of the Witwatersrand and the research protocol was approved by the Faculty of Health Sciences at the University. As the research data were collected in Rwanda, national clearance was also obtained from the Institutional Review Board at the former Kigali Health Institute and scientific approval by the National Commission for control of HIV and AIDS, in Rwanda. Also authorisation letters were obtained from all the health facilities where the studies were conducted. A letter containing information describing the details of the study was given to the participants to invite them to participate, before they were recruited into the study. Participants, who agreed to participate and gave permission to use their medical records, signed a consent form. Confidentiality and anonymity were ensured to all participants’ given information and the participation was

voluntary. Participants were informed of their rights to stop the participation from the study at any time.in case one deemed to discontinue.

3.2.4 Data collection

The author and the two assessors administered and assessed the selected participants with the BPNS, for PN, using the procedure described in the original validation of the scale by Cherry et al., (2005). This was done after obtaining the informed consent from each participant before commencing the data collection on each working day of the week; from Monday to Friday.

The participants were requested to score the “presence and severity of symptoms, using a scale of 1 (mild) to 10 (severe) for each leg separately”. The symptoms assessed were; “pain, aching, or burning in feet and/or legs; pins and needles in feet and/or legs; and numbness in feet and/or legs”. The single highest score of the six scores (three for each leg) was transformed to a “subjective PN grade as follows: symptoms absent = grade 0, score of 1–3 = grade 1, score of 4–6 = grade 2, and score of 7–10 = grade 3”. Symptoms had to be bilateral to be graded as ≥ 1. “Objective findings (signs) included in the BPNS are the loss of the sense of vibration and abnormal ankle deep tendon reflexes”. The vibration sense perception was assessed with a 128-Hz tuning fork, “maximally struck and applied at the great toe distal interphalangeal joint of each foot”. The vibration sense was defined as “normal for a vibration felt for > 10 seconds, mild loss for a vibration felt for 6 –10 seconds, moderate loss for a vibration felt for ≥ 5 seconds, and severe loss for no feeling of vibration”. The ankle tendon reflexes were defined as “absent, hypoactive, normal, hyperactive, or clonus”. For testing of the ankle

reflex, the participant was in a sitting position and the assessor used one hand to push up the foot of the participant into dorsiflexion at 90 degrees. Holding the reflex hammer in the other hand, the assessor struck the ankle tendon. The tendon reflex was felt in the assessor's hand as a planter flexion of the participant's foot.

As the above position was found to be too difficult for the patients and thus difficult to get an accurate reading, a modification was made accordingly. In addition, the intra assessor Spearman's rank correlation coefficient for this assessment on reflex responses was weak. Therefore, the position was modified; from sitting to kneeling on a soft cushioned chair or bench or plinth/bed (whichever was available at the site), with the foot hanging over the edge of the chair/bench or plinth/bed. The assessment was repeated in a second pilot study after the above modifications of the starting position.

With this changed position the assessors repeated the assessment of all items in BPNS, using the same instructions as before. Planter flexion was seen and felt through the assessor's hand. The reflex response was recorded as, hypoactive, normal, hyperactive, or clonus, accordingly. The intra correlation coefficient calculated after the second pilot was good and the modified position was adopted to be used in the rest of the studies' assessments. This was the only item modified in the BPNS, and hence the tool was adapted to be used for PLHIV on ART in Rwanda.

The primary outcome of interest in this measure was the presence of PN, which was defined as the combination of at least one subjective neuropathy grade greater than 0 and either reduced or none sense of vibration and, or reduced/none ankle deep tendon

reflex, bilaterally, as has been defined and used in previous studies (Cherry et al., 2005; Mehta et al., 2010).

3.2.5 Re-establishing validity and reliability of Lower extremity functional scale in Rwanda

3.2.5.1 Lower extremity functional scale description

LEFS assesses the subjective functional activity performance of daily living, in the lower extremities. It was developed and validated for various lower extremity conditions centred on the WHO model of impairment, disability and handicap (Hsiung et al., 2005), specifically for the elderly. The sensitivity to change of LEFS is expected to accurately measure even the small effects of impaired activity performance experienced by participants. It has the psychometric properties of; internal consistency (α=0.96), test – retest reliability (rho=0.86), and minimal detectable change of 90%, (Binkley et al., 1999). The scale comprises 20 items which assess the level of difficulty in performing a variety of activities of daily living (ADL). Each item may be scored by the participant as 0 = “unable to perform activity”, 1 = “quite a bit of difficulty”, 2 = “moderate difficulty”, 3 = a little bit of difficulty”, and 4 = “no difficulty”. The scale scores vary from 0 (none) to 80 (normal) (Binkley, et al., 1999) (*Appendix 1 section D).* Function is defined as follows: “extreme difficulty or unable to perform activity (0–19 points), quite a bit of difficulty (20–39 points), and moderate difficulty (40–59 points), a little bit of difficulty (60–79 points), and no difficulty” (80 points) (Schep et al., 2009)

LEFS was validated in the developed world, specifically in the United States of America (USA) where the culture and environment are quite different from the resource limited

world, specifically in Africa, and Rwanda in particular. To my knowledge, there is no validation of this tool that has been done in most, if not all of the African countries. It was therefore, important that such a scale be adapted and re-validated when used in an African context and specifically in Rwanda.

3.2.5.2 Procedure to re-establish validity and reliability of LEFS in Rwanda

The following procedure was used to re-validate and adapt the LEFS in Rwanda.

3.2.5.2.1 Forward and backward translation of English and Kinyarwanda languages

The scale was translated from English to Kinyarwanda, (the local language spoken in Rwanda). Two independent professional language translators from the Language Centre at the University of Rwanda, College of Medicine and Health Science (specifically at former Kigali Health Institute), translated the scale from English to Kinyarwanda. Susequently, two independent professional translators translated the scale back to English, to ensure content validity. The translation was assessed by a consensus workshop of a panel of two physiotherapists and two medical doctors working at the former Treatment, Research and AIDS Centre in Rwanda (TRAC), together with all of the four translators, and the author. Changes and modifications were made for some scientific terms and functional activities in the scale (Table 4). The modifications in the activity performance were based on the activities of daily living that are culturally applicable and used in daily life in Rwanda; an example being a question that asked about having difficulty "*getting in and out of a car*". Most people in Rwanda and in other African countries, travel in public taxi/buses (for those who manage to travel

in vehicles). When participants were asked about having diificulty getting in and out of a car, some mentioned, "*I have never moved with a car*" or "*I seldom move with a car*" So, the item/activity "getting in and out of a car" was modified as having any difficulty of "*getting in and out of the car/public taxi/bus"*

3.2.6 Intra assessor reliability of LEFS prior its modification

Two pilot studies were carried out to collect data for intra and inter assessor reliability.

3.2.6.1 Pilot 1 procedure

In pilot 1, the aim was to pilot the LEFS and establish intra assessor reliability of the scale by the author. The translated and content re-validated LEFS was administered to a sample of 50 PLHIV on ART; (the sample for study 1 has been described in section 3.2.2.2.1 above). The author administered the translated and professionally scrutinised LEFS to the selected participants. Two assessments for each participant were conducted with a one week interval between the two assessments. Participants were assessed in the first week and were given an appointment to come in the following week from Monday to Friday respectively, for the second assessment. The day for each participant's appointment for the second assessment corresponded with the day of the first assessment so as to ensure there was a one week time interval between the two separate assessments. Transport costs for the participants who came for the second assessment were compensated for, by the author.

3.2.6.2. Data collection:

LEFS was self-administered by the participants to assess their lower extremity functional activity performance. All participants who knew how to read and write were given the scale to complete individually. However, the author was nearby to give any clarification or assistance wherever needed. The author administered the scale for the participants who did not know how to read. He read each question/item to an individual participant and the participant gave an individual response. The author assisted interview took place in a well prepared private room. In the latter cases, the author recorded the responses accordingly.

3.2.6.3 Modification of the functional activities in the LEFS

Following the analysis of the intra assessor correlation between the first and second assessment in pilot 1, all activities were classified as; strong [*rho* ≥ 0.8], moderate [*rho* < 0.8 and ≥ 0.5] and weak [*rho* < 0.5] (Black, 2011). In addition, during pilot 1, some activities in LEFS were unclear to the Rwandan participants and needed precise examples, forming the basis for the subsequent modifications. All such activities were modified and made clearer with specific examples, without changing the concepts and context of the original LEFS. The modification was done in consultation with a team of three health professional experts; two physiotherapists and a medical doctor, who were experienced in rehabilitation services, and two participants. The purpose of the team consultation was to establish appropriate activities that are commonly and culturally done by people living in Rwanda and similar to the activities that define LEFS. The activities and their common examples were identified.

3.2.6.4 Intra and inter assessor reliability after modification of LEFS

Again pilot 2 aimed at testing the clarity of the LEFS after modifying unclear, moderate and weak correlated activities in the scale, and also to carry out intra and inter assessor reliability among the author (assessor 1), and the two other assessors.

3.2.6.4.1 Procedure

A sample of 12 participants was randomly selected from PLHIV attending the ART clinic at Rwanda Military Hospital in Kigali. Two assessments with a one week interval in between were carried out to test the intra and inter assessor reliability after the modifications. A two hour training session was conducted for the two assessors to familiarise them on using the scale. The three assessors administered the scale piloted and modified in pilot 1. Each assessor carried out the assessment of each participant independently, and was blinded to the other assessors' assessment outcomes and participants' scores. The order of the assessors was random to reduce the possible learning effect by the participants across the series of the assessments.

3.2.7 Data analysis

The statistical analysis was carried out using STATA (version 11, Stata Corp, College Station, Texas, USA). The variables (activities) in the LEFS were categorical and ordinal in nature. Spearman's rank correlation coefficient was used to measure the strength of statistical dependence between the same functional activities at the two assessments done at two intervals for the same participants. The activity correlation coefficients were

classified according to the levels of strength; as strongly (*rho* ≥ 0.7), moderately (*rho* < 7 ≥ 0.5), and weakly (*rho* < 0.5) correlated activities (Black, 2004). All activities with moderate and weak correlation coefficients (*rho*), according to the classification, in pilot 1 were considered for modification (Table 4).

3.2.8 Results of intra and inter assessor reliability testing

Out of 50 (100%) participants who were assessed in the first week, 42 (84%) returned in the second week for the second assessment, in pilot 1. Test-retest analysis for intra assessor reliability included 42 participants who were able to undergo two assessments with a one week time interval between the two assessments. The Spearman's rank correlation coefficient values between the first and the second assessments for each activity indicated that 90% (18/20) of the activities were were moderately (*rho ≥ 0.5 ≤7*) and only 10% (2/20) were weakly correlated (*rho ≤ 0.5).* Table 3 below describes the results.

Table 3: The intra assessor reliability done by the author in pilot 1 (n=42)

Activities	rho	p-value
Doing daily home activity	0.57	<0.01
Recreational activity	0.63	<0.01
Bath limitation	0.69	<0.01
Walking between rooms	0.54	<0.01
Putting on shoes & socks	*0.44	0.02
Squatting	0.61	<0.01
Lifting small object	0.53	<0.01
Doing light activity at home	0.61	<0.01
Doing heavy activity at home	0.52	0.01
Getting into & out of car	0.53	<0.01
Walking across from one building to another	*0.47	<0.01
Walking a km	0.66	<0.01
Walking up stairs (10 stairs)	0.63	<0.01
Standing for 1hr	0.63	<0.01
Sitting for 1hr	0.65	<0.01
Running on even ground	0.62	<0.01
Running on uneven ground	0.60	<0.01
Making sharp turn while running	0.62	<0.01
Hopping	0.65	<0.01
Roll over in bed	0.68	<0.01

***Weak correlation coefficient**

Table 3 above indicates that most functional activities that define the LEFS were moderately correlated with Spearman's correlation coefficient in each activity as; doing daily home activity (rho=0.57), recreational/leisure activities (rho=0.63), walking between rooms (rho=0.54), squatting (rho=0.61), lifting small objects (rho=0.53), doing light activity at home (0.61), doing heavy activity at home (rho=0.52), getting into & out of car (rho=0.53), walking a km (rho=0.66), and sitting for an hour (rho=0.63), while the

weakly correlated activities were only “putting on shoes & socks” (rho=0.44) and walking across from one building to another (rho=0.47). The last two activities which were weakly correlated are not commonly undertaken, in most of the Rwandan population. Such activities and others with moderate correlations were considered for modification.

The Table 4 below indicates the modifications which were made for these activities, with specific examples applicable to the Rwandan population.

Table 4 Modification of weak and moderate correlated activities with pilot 1 coefficient results

Activities	rho	p-value	Comments and Suggested modifications
Moderately correlated activities and their modifications			
Doing daily usual activity	0.57	<0.02	Specific examples related to activities the person does daily, such as those done at work/employment, going to/coming from work, etc
Recreational/leisure activity	0.63	<0.01	Most people are not involved in traditionally defined recreational/leisure activities; related activities were given as an example, such as attending weddings and visiting friends, going to church, etc
Bath limitation	0.69	<0.01	Examples included taking a shower or bath
Squatting	0.61	<0.01	Giving specific example like squatting on pit latrine
Doing light activity at around home	0.61	<0.01	Examples like, preparing a meal, cleaning a the house, making a bed
Walking a km	0.66	<0.01	Examples such as going to market/shops, church, or other social activities, were given
Walking up stairs (10 stairs)	0.63	0.001	For those who might not experience walking up stairs, additional examples included; walking on relatively steep irregular ground
Standing for 1hr	0.63	0.001	Examples included standing doing some work, e.g. digging, standing in long service lines, shopping
Sitting for 1hr	0.65	0.001	Sitting for 1 hour, like in church, public bus/taxi, or meetings
Walking between rooms	0.54	<0.01	Specific examples, such "walking from bed room to toilet", bathroom etc
Lifting an object like a bag of groceries	0.53	<0.01	Examples like lifting a small container full of water (5 litre container), basket of potatoes, etc
Doing heavy activity at home	0.52	<0.01	Examples of heavy activities like digging, lifting a heavy bag of potatoes, 20 litre container of water, shifting big items, etc
Getting into & out of car	0.53	<0.01	Added on public taxi/bus which is a common mode of transport for the majority of people
Running on an even ground	0.62	0.00	Fast walking on even ground
Running on uneven ground	0.60	0.00	Fast walking on uneven ground
Making sharp turn while running	0.62	0.00	Making sharp turns while walking fast at your pace
Hopping	0.65	0.00	Standing up very fast from squatting as needed
Roll over in bed	0.68	0.00	Turning in bed
Weakly correlated variables and their modifications			
Putting on shoes & socks	0.44	0.02	Some people hardly put on socks or even closed shoes. Question rephrased as "...problems with putting on any kind of shoes, including sandals, etc."
Walking 2 blocks	0.47	0.01	A specific distance of 100m, or walking from his/her home to neighbour's, a distance of not more than 200m away.

Table 4 above indicates that the activities that were moderately (*rho ≥ 0.5 ≤7*) and weakly (rho ≤ 0.5) correlated were modified with specific examples of activities which are culturally and commonly practiced/used in Rwanda.

Table 5 Activities in the original LEFS versus the activities in LEFS-Modified

Original LEFS activities	Modified LEFS Activities
Any of your usual work, housework, or school activities.	Any of your usual work, (e.g. work that earns you income, or any other work you do) housework, or school activities
Your usual hobbies, recreational or sporting activities.	Your usual hobbies, recreational or sporting activities, eg attending weddings, church or visiting friends
Getting into or out of the bath.	Getting into or out of the bath/taking a bath.
Walking between rooms.	Walking between rooms (such as walking from your room to toilet, bath room, kitchen, etc)
Putting on your shoes or socks.	Putting on any kind shoes or socks, including slippers or open shoes, if applied.
Squatting.	Squatting (e.g. squatting on pit latrine/doing any squatting activity)
Lifting an object like a bag of groceries from the floor.	Lifting an object, like a bag of groceries or a small container like 5 litres container full of water, basket of potatoes, etc, from floor
Performing light activities around your home.	Performing light activities around your home(such as preparing a meal, cleaning the house, making a bed, or any other light activity at home)
Performing heavy activities around your home.	Performing heavy activities around your home (digging, lifting a heavy bag of potatoes, 20 litre container of water, shifting big items, etc
Getting into or out of a car.	Getting into or out of a car/public taxi/bus.
Walking 2 blocks.	Walking across from your home to neighbours or walk l 100m
Walking a mile.	Walking a km, such as going to market, church or any other place
Going up or down 10 stairs (about 1 flight of stairs).	Going up or down 10 stairs (about 1 flight of stairs) or walking up steep and irregular ground
Standing for 1 hour.	Examples including standing doing some work, e.g. digging, Standing in long service lines, shopping, etc.
Sitting for 1 hour.	Sitting for 1 hour, like in church, public bus/taxi, or meetings
Running on even ground.	Fast walking on even ground
Running on uneven ground.	Fast walking/running on uneven ground
Making sharp turns while running fast.	Making sharp turns while walking/running very fast
Hopping.	Standing up fast from squatting as needed
Rolling over in bed.	Turning in bed

The modified – LEFS was piloted in pilot 2 to test intra and inter assessor reliability.

The following tables 6 to 7 indicate the results of study part 2.

Table 6 Intra-assessor reliability of functional activity in LEFS – Modified, in both assessment1 and assessment 2

Functional Activities	Assessor 1		Assessor 2		Assessor 3	
	rho	p-value	Rho	p-value	rho	p-value
Any of your usual work, (e.g. work that earns you income, or any other work you do) housework, or school activities	0.9	<0.01	0.75	0.03	0.91	0.02
Your usual hobbies, recreational or sporting activities, e.g. attending weddings, church or visiting friends	0.7	0.02	0.82	<0.01	0.83	0.05
Getting into or out of the bath/taking a bath.	1.00	<0.01	0.99	<0.01	0.73	0.03
Walking between rooms (such as walking from your room to toilet, bath room, kitchen, etc)	1.00	<0.01	0.97	<0.01	0.7	0.05
Putting on any kind shoes or socks, including slippers or open shoes,	0.9	<0.01	0.80	<0.01	1.0	0.01
Squatting (e.g. squatting on pit latrine/doing any squatting activity)	0.7	0.04	0.76	0.02	0.76	0.04
Lifting an object, like a bag of groceries or a small container like a 5 litre container full of water, basket of potatoes, etc, from floor	0.72	0.03	0.81	0.03	0.86	0.03
Performing light activities around your home(such as preparing a meal, cleaning the house, making a bed, or any other light activity at home)	0.8	0.04	0.72	<0.01	0.7	0.05
Performing heavy activities around your home (digging, lifting a heavy bag of potatoes, 20 litres container of water, shifting big items, etc	0.7	0.03	0.77	0.03	0.95	0.02
Getting into or out of a car/taxi.	0.8	0.02	0.75	0.04	0.84	0.03
Walking across from your home to neighbours or walk 100m	0.7	0.05	0.88	0.02	0.75	<0.01
Walking a Km, such as going to market, church or any other place	0.9	<0.01	0.84	0.02	0.85	<0.01
Going up or down 10 stairs (about 1 flight of stairs) or walking up steep and irregular ground	0.78	0.05	0.78	<0.01	0.73	0.04
Standing for 1 hour,	0.9	<0.01	0.83	0.03	0.84	0.03
Sitting for 1 hour, like in church, taxi, or meetings	0.8	0.02	0.70	0.04	0.7	0.03
Fast walking on even ground	0.7	0.04	0.71	0.03	1.0	<0.01
Fast walking/running on uneven ground	0.76	0.02	0.90	<0.01	0.78	0.03
Making sharp turns while walking/running very fast	0.75	<0.01	0.82	<0.01	*0.62	0.05
Standing up fast from squatting as needed	1.00	<0.01	0.90	<0.01	1.00	<0.01
Turning in bed	0.8	<0.01	0.88	0.02	0.8	0.02
Total score	0.79	<0.01	0.85	0.03	0.8	0.02

*Moderately correlated

Table 6 above presents the results of all the three assessors. The results indicate that almost all the weak and moderate correlated variables were improved to *rho* ≥ 0.7, only one "*Making sharp turns while walking/running very fast*" rho=0.62 (p=0.06) remained moderately correlated.

Table 7: Inter- assessor reliability obtained for a pair of assessors, for each functional activity in LEFS – Modified

Functional Activities	Assessor 1 & Assessor 2		Assessor 1 & Assessor 3		Assessor 2 & Assessor 3	
	rho	p-value	rho	p-value	rho	p-value
Any of your usual work, (e.g. work that earns you income, or any other work you do) housework, or school activities	0.8	0.01	0.8	0.01	0.8	0.02
Your usual hobbies, recreational or sporting activities, e.g. attending weddings, church or visiting friends	0.75	0.01	*0.68	0.04	0.9	0.01
Getting into or out of the bath/taking a bath.	1.0	<0.01	1.00	<0.01	1.00	<0.01
Walking between rooms (such as walking from your room to toilet, bath room, kitchen, etc)	1.0	<0.01	1.00	<0.01	1.00	<0.01
Putting on any kind shoes or socks, including slippers or open shoes,	0.7	0.01	0.69	0.03	0.7	0.02
Squatting (e.g. squatting on pit latrine/doing any squatting activity)	0.74	0.02	0.72	0.04	0.8	0.01
Lifting an object, like a bag of groceries or a small container like 5 litre container full of water, basket of potatoes, etc, from floor	0.82	0.01	0.67	0.05	1.00	<0.01
Performing light activities around your home(such as preparing a meal, cleaning the house, making bed, or any other light activity at home)	0.72	0.02	0.71	0.03	1.00	<0.01
Performing heavy activities around your home (digging, lifting a heavy bag of potatoes, 20 litres container of water, shifting big items, etc	0.71	0.03	0.9	0.01	1.0	<0.01
Getting into or out of a car/taxi.	0.8	0.01	0.7	0.01	0.7	0.05
Walking across from your home to neighbours or walk 100m	0.7	0.01	1.00	<0.01	1.00	<0.01
Walking a Km, such as going to market, church or any other place	0.7	0.02	0.83	0.02	1.0	<0.01
Going up or down 10 stairs (about 1 flight of stairs) or walking up steep and irregular ground	0.8	0.01	0.7	0.03	1.0	0.01
Standing for 1 hour,	0.86	0.01	0.9	0.05	0.71	0.03
iioasSitting for 1 hour, like when in church, taxi, or meetings	0.73	0.02	0.81	0.01	1.0	0.01
Fast walking on even ground	0.86	0.01	0.7	0.03	1.0	<0.01
Fast walking/running on uneven ground	0.73	0.03	0.74	0.03	1.0	<0.01
Making sharp turns while walking/running very fast	0.9	<0.01	0.85	0.02	1.0	<0.01
Standing up fast from squatting as needed	0.9	0.01	1.0	0.01	1.0	0.05
Turning in bed	0.81	0.01	0.82	0.02	1.00	<0.01
Total score	0.74	0.01	0.91	0.03	0.95	0.01

*Moderately correlated

The second intra assessor analysis showed that the weak and moderate correlated variables were improved to $r \geq 0.7$, very few remained moderately and none were weakly correlated. The improved correlation coefficients were due to the modification of including precise examples of activities as applied in Rwanda and in most African developing countries.

3.3 Discussion

This study demonstrates the first validation of the LEFS in PLHIV on ART, from English (Binkley et al., 1999) into Kinyarwanda and adapted to an appropriate cultural context. HIV-associated functional limitations have been associated with decreased physical functioning and have numerous impacts on daily activities of living (Cade et al., 2004; Cacchio et al., 2010). The identification of functional activities of the lower extremity is crucial for rehabilitation of patients with chronic illness such as those living with HIV and on ART (Dudgeon et al., 2004).

This study tested the LEFS to assess the functional activities of the lower extremity for rehabilitation purposes in Rwanda. The tested scale can likely be adapted for a similar purpose in Africa and other developing countries. LEFS in the developed world has very high correlation coefficients of about *rho*=0.94. It was developed and validated for the purpose of identification and evaluation of lower extremity functional activity among the elderly (Binkley et al., 1999). Studies suggest that there might be important differences in health related activities between high-income and middle/low-income countries (Karlsson et al., 2010). Scales may not identify the activities among the population in a developing environment (Miranda et al., 2008). The same author pointed out that

“research findings from developed settings are not necessarily appropriate to other contexts; thus, local knowledge is important”. The results of this study confirm this, with most of the activities in the original LEFS only moderately correlated and a few weakly. This was probably attributable to the fact that some of the activities in LEFS were not familiar to most of the population living in Rwanda. In addition, the language and cultural differences might be reasons for such differences seen in the re-validated LEFS. Also the methodological differences such the clinical behaviour of participants, may contribute to the differences, as commented by Perez et al. (2007) in their study which tested the reliability of the Spanish DN4 version from the original French version. The results of this study are similar to the results by Perez, et al. (2007) which indicated that testing of reliability and validity when a tool is used in another language from that in which it was originally validated is crucial. This suggests that it is important that outcome measures used in an environment different from the one in which they were originally developed and validated are re-validated. The validity and reliability of the adapted Kinyarwanda version of the LEFS- Modified tool was good.

3.4. Limitations of the study

Although the DN4 and BPNS were translated into Kinyarwanda and crosschecked by experts for the correct use of the terminologies in the Kinyarwanda language, it was not necessarily re-tested statistically for re-validation in Rwanda. This would be an important consideration for further research.

3.5 Conclusion

The modified, translated LEFS performed well, with very few remaining moderately and no weakly correlated functional activities**.** Modifications to take into account local conditions are critical for evaluations of similar tools that were validated in developed world contexts.

CHAPTER 4

4.0 STUDY 2

PREVALENCE OF PERIPHERAL NEUROPATHY, RELATED LOWER EXTREMITY FUNCTIONAL LIMITATIONS AND QUALITY OF LIFE, IN PEOPLE LIVING WITH HIV ON ART FROM SELECTED ART CLINICS IN RWANDA

4.1 Introduction

This chapter describes the study on the prevalence of PN, the related lower extremity functional limitations and QoL, in PLHIV from selected ART clinics in Rwanda. The existing data on the prevalence of PN in Rwanda is limited, and is likely a barrier to rehabilitation of PLHIV with PN. The aim of this study was therefore, to document the prevalence of PN, its related lower extremity functional limitations and QoL, across urban and rural settings in Rwanda. The specific aims were to;

1. Establish the overall prevalence of PN, its distribution with demographic and health status characteristics,
2. Identify the association of lower extremity functional limitations with PN,
3. Assess the association of QoL with PN,
4. Compare lower extremity functional limitations among PLHIV in urban with rural settings and,
5. Compare QoL among PLHIV in urban with rural settings, in Rwanda.

4.2 Study design, setting, participants and selection

4.2.1 Design and setting

The study was a cross sectional quantitative design. It was carried out at eight simple randomly selected public outpatient ART clinics clustered into provinces; the western,

eastern, northern and southern provinces, and Kigali city, in Rwanda. The lists of all the public ART clinics in each province and Kigali city were availed from the former “Treatment and AIDS research centre” (TRAC) that is currently a unit in the Rwanda Biomedical Centre (RBC), in Rwanda. The list included 186 public ART clinics in Rwanda as per the end of 2011. The list was availed in February 2012 when selection of the settings was carried out. Private ART clinics were not included in this study because of their uniqueness, namely; different medical care protocols and attendance by “a high socioeconomic” class of people and which number is very low (RDHS, 2010), and who might not be true representatives of the general population. Eight (8) clinics (Table 9 below) were selected for this study. Four clinics were simple randomly selected from Kigali city (an urban setting) and the other four from the four provinces; one clinic per province. The provinces of Rwanda are mostly rural and the population there has a homogeneous life style. Kigali city is the only place in Rwanda that has a population with an urban life style; therefore, the selection of four clinics from the provinces and four from Kigali city had a twofold purpose;

1. To ensure representative data from both urban and rural settings in this study.
2. To ensure an appropriate sample for study 3; which was an intervention that was planned to be carried out in Kigali city

Table 8: The number of participants from each selected ART clinics

No.	ART clinics	Province	Average number attending clinic in two weeks (10 days)	Number of participants invited in two weeks (10 days)	Eligible number of participants for the study
1	Biryogo Health Centre	Kigali City	490	98	76
2	Byumba Hospital	Northern	360	72	62
3	Gisenyi Hospital	Western	400	80	73
4	Kabgayi Hospital	Southern	370	74	62
5	Kacyiru Health Centre	Kigali City	420	84	66
6	Kicukiro Health Centre	Kigali City	400	80	62
7	Kimironko Health Centre	Kigali City	390	78	54
8	Nyamata Hospital	Eastern	350	70	52
	Total		**3180**	**636**	**507**

4.2.2 Participants and selection

The study participants were adult men and women aged 18 and above, PLHIV on ART who were attending ART clinics for routine health care and management that included; receiving ARV medication, health care consultations, counselling services and other advice concerning ART in particular, laboratory testing; such as CD4 cell counts. A systematic random sampling of 20% of the PLHIV on ART attending each day at each of the selected clinics was used in this study, to invite volunteers for participation. A list of participants attending at each clinic for a period of two weeks was made available prior to the selection of volunteers at every visit. The total number of the participants on the list made for each visit (denoted by N) was multiplied by 20% to get the number (n) of volunteers for selection on that day; (n=N*20%). The study population was considered as a homogeneous population, thus the systematic random selection was done by taking the every K^{th} number; where K^{th} was a sampling interval on the ordered list made for a day. The K^{th} was calculated by dividing the total number of the participants on the list (N), by the number of sample to be selected for the day (n); (K^{th}

= N/n), (Black, 2011). The procedure was repeated for a period of two weeks (10 working days) which was the maximum period designated for data collection at each ART clinic. A total number of 3180 PLHIV were registered to have attended the eight selected ART clinic services within the two week period of the study. Using the procedure described above, a sample of 636 potential participants was systematically invited from the total registered number (3180). The whole process of data collection at the eight selected ART clinics took 16 weeks (two weeks at each clinic*).*

4.2.3 Inclusion Criteria

I. All people living with HIV on ART from the selected public outpatient ART clinics in Rwanda
II. Aged 18 and above; both females and males
III. No active opportunistic infection such as TB or others

4.2.4 Exclusion Criteria

I. PLHIV with known disorders of the central nervous system
II. PLHIV with a known history of diabetes, Vitamin B12 deficiency, TB, renal failure, hypothyroidism and other pathologies that may be associated with neuropathy

4.3 Outcome measures

Validated and reliable outcome measures were used in this study. The outcome measures used in this study were described in chapter 3.

4.3.1. Identification of demographic and health status characteristics

The checklist was used to assess the bio-demographics such as age, gender, level of education, marital status, and health status information such as duration the participant had been diagnosed with HIV, the type of ARV's the participant was on, duration on ART, other pathologies and behaviour that commonly has PN related disorders (such as diabetes, Vitamin B12 deficiency, TB, renal failure, hypothyroidism and others, to identify the exclusion criteria), the CD4 cell count level, and PN symptoms (PNS) and if the symptoms commenced prior to starting on ART or afterwards. The PN characteristics of neuropathic pain were assessed with DN4 (also described in chapter 3 and in appendix 1 C). The checklist was used to gather the information from the participants and from their medical records. It was completed by the researcher with assistance when needed from the physician working at the respective outpatient ART clinic.

4.3.2 Assessment of peripheral neuropathy

Peripheral neuropathy was assessed with an adapted (described in chapter 3) validated measure, the BPNS tool (McArthur et al, 2005) (*appendix 1).* The BPNS tool assessed subjective and objective measures of PN. The author and two research assistants, who are senior physiotherapists with MSc (physiotherapy) degrees, did the assessments. Training of the research assistants was conducted by the researcher over one day before starting the assessments. Again as mentioned in Chapter 3, the same procedure of administering the BPNS to the participants was used. The participants were requested to score the "presence and severity of symptoms, using a scale of 1 (mild) to

10 (severe) for each leg separately". The symptoms assessed were; "pain, aching, or burning in feet and/or legs; pins and needles in feet and/or legs; and numbness in feet and/or legs". The single highest score of the six scores (three for each leg) was transformed to a "subjective PN grade as follows: symptoms absent = grade 0, score of 1–3 = grade 1, score of 4–6 = grade 2, and score of 7–10 = grade 3". Symptoms had to be bilateral to be graded as ≥ 1. "Objective findings (signs) included in the BPNS are the loss of the sense of vibration and abnormal ankle deep tendon reflexes". The vibration sense perception was assessed with a 128-Hz tuning fork, "maximally struck and applied at the great toe distal interphalangeal joint of each foot". The vibration sense was defined as "normal for a vibration felt for > 10 seconds, mild loss for a vibration felt for 6 –10 seconds, moderate loss for a vibration felt for ≥ 5 seconds, and severe loss for no feeling of vibration". The ankle tendon reflexes were defined as "absent, hypoactive, normal, hyperactive, or clonus". The primary outcome of interest in this measure was the presence of PN, which was defined as the combination of at least one subjective neuropathy grade greater than 0 and either abnormal vibratory sense or ankle deep tendon reflex, bilaterally, as has been defined and used in previous studies (Cherry et al., 2005; Mehta et al., 2010).

4.3.3 Assessment of lower extremity functional limitations

The lower extremity functional limitations were assessed with the LEFS tool piloted and modified LEFS; described in chapter 3). The modified LEFS was self-administered by the participants. All participants who knew how to read and write were given the scale to complete individually. However, the author and the assistants were nearby to give any clarification or assistance wherever needed. The author and the assistants

administered the scale for the participants who did not know how to read by reading each question/item to an individual participant and the participant gave an individual response. The researchers' assisted interviews took place in a well prepared private room. In these cases, the author recorded the responses accordingly. The LEFS comprises of 20 items which assess the level of difficulty in performing a variety of ADLs. Each item was scored by the participant as 0 = "unable to perform activity", 1 = "quite a bit of difficulty", 2 = "moderate difficulty", 3 = "a little bit of difficulty**",** and 4 = "no difficulty".

4.3.4 Assessment of quality of life

The QoL was assessed with the WHOQOL-BREF (described in chapter 3) and in appendix 1 E. The outcome measure was self-administered to the participants and they completed their perceptions and feeling responses for facets assessing QoL, as instructed in the outcome measure.

4.5 Data collection procedure

4.5.1 Recruitment of participants

The participants, who were selected according to the procedure described in section 4.2.2 of this chapter, were asked for their consent to volunteer for the study. Participants' medical records were consulted to get the following data; treatment history such as the type of ARVs the participant was on, the duration on ART and to check if the participant had any other pathology commonly associated with PN (such as the ones mentioned in the exclusion criteria above) apart from HIV and ART. Data from the medical records also included information on all relevant laboratory tests such as CD4 cell count and

blood counts. In addition, the checklist was used to screen for participants' eligibility for the study. The participants who mentioned having pain were further assessed with the DN4 questionnaire to screen for neuropathic pain from other kinds of pains. The checklist was used to compliment clinical data extracted from the patients' record. The screening was followed by the assessment for peripheral neuropathy using the BPNS tool described above in section 4.3.2. All selected participants completed the rest of the questionnaires namely the LEFS and WHOQOL-BREF, to establish lower extremity functional ability and QoL, respectively.

4.6 Data analysis

Descriptive analyses such as tabulations for frequencies and percentages for categorical variables and measures of central tendency (means) and measures of variability (standard deviations) for continuous variables were done. A bivariate analysis using Pearson's Chi – square and Fisher's exact tests were used when analysing the prevalence distribution of PN and its association with categorical demographic and health status variables. The demographic variables included gender, level of education, occupation, marital status and place of residence. Health status variables included; the period since the diagnosis of HIV, current CD4 count, current ARV regimen combination, period since the start on ARVs, presence of PN symptoms, start of PN symptoms; if before or after start on ARVs, and the period since start of PN symptoms. The student's t-test (or Mann Whitney for non-normally distributed data) was used for pairs of continuous variables. Univariate and multivariate logistic regression analysis were used to establish associations, and magnitude (odds ratio) of demographic and health status and influence on occurrence of PN. The same test was used to determine

the association of settings (in terms of urban or rural) of participants, on the lower extremity functional limitations and QoL outcomes. A multivariate regression was carried out to determine the presence of PN as a predictive factor on the domains of QoL, among PLHIV on ART in Rwanda. The analysis was done using STATA (version 11, Stata Corp, College Station, Texas, USA).

4.7 Results

4.7.1 Introduction

This section describes the results of study 2 namely the prevalence of PN, related lower extremity functional limitations and QoL, among PLHIV on ART in Rwanda. The results are presented in sections namely;

- Response rate and the overall prevalence of PN,
- Prevalence of PN and its association with demographic characteristics,
- Prevalence of PN and its association with health status characteristics,
- The demographic and health status characteristics predicting the prevalence of PN.
- The association between PN and lower extremity functional limitations
- The association between PN and QoL
- The association between the participants' settings and lower extremity functional limitations
- The association between the participants' settings and QoL

4.7.2 Response rate

The data collection in this study was done over a period of two weeks at each of the selected ART clinics. A total number of PLHIV attending the ART services at the eight ART selected clinics was registered as three thousand, one hundred and eighty (3180)

within the two week data collection period. Out of this number; 636 who attended the clinics in the two week period were randomly invited to participate in the study. Five hundred and seven (507), equivalent to 80% of the invited volunteers were eligible according to the set selection criteria, fully completed the outcome measures and their data were analysed. Therefore, the response rate in this study is 80%.

4.7.3 Prevalence of peripheral neuropathy

Of the analysed sample of 507, three hundred (300/507) equivalent to 59% [95% CI (54%, 63%)] were diagnosed with PN according to the definition of PN given in Chapter 3. The sections below illustrate the prevalence of PN and its association with different characteristics and measured outcomes of the participants in the sample.

4.7.3.1 Prevalence of PN and its association with demographic characteristics

The prevalence of PN is presented with respect to the demographic characteristics; age, gender, level of education, occupation, marital status, and the place of residence whether urban or rural. The associations between PN and the demographic characteristics are presented in Table 9 below.

Table 9: Prevalence of PN and its association with demographic characteristics

Variable		PN n (%) n=507 Without PN (n=207)	With PN (n=300)	p-value	All
Age (mean±SD)		37(±8.8)	42(±9.2)	*<0.001**	39.8(±9.2)
Gender	Female	156 (43)	210 (57)		366 (73)
	Male	51 (37)	87 (63)	*0.402*	138 (27)
Education	None	39 (35)	73 (65)		112 (22)
	Primary	123 (49)	128(51)		251 (50)
	>=Secondary	45(31)	99 (69)	*0.002**	144 (28)
Occupation	Employed	13 (31)	29 (69)		42 (8)
	Peasant/Farmer	118 (53)	106 (47)		224 (44)
	Self employed	33 (37)	56 (63)	<0.001*	89 (18)
	Unemployed	43 (28)	109 (72)		152 (30)
Marital status	Single	17 (49)	18 (51)		35 (7)
	Married	119 (52)	112 (48)		231 (46)
	Divorced/Separated	18 (22)	63(78)	0.003*	81 (16)
	Window/Widower	53 (33)	107 (67)		160 (31)
Setting/Residence	Urban	58 (22)	200 (78)		258 (51)
	Rural	149 (60)	99 (40)	<0.001*	248 (49)

* Denotes significant association between the PN and the demographic characteristic

The prevalence of PN and its association with the demographic characteristics is shown in Table 9 above, with the mean age of the participants being 39.7 (SD ±9.2). Half of the participants; 251 (50%) had a primary level of education. Participants with PN were slightly older than those without PN; [42(SD±9.2) vs 37 (±8.8) (p<0.001)]. There were more males (63%), than females (57%) with PN but the difference was not significant (p=0.402). The prevalence of PN was significantly different (p<0.01) among the participants with different levels of education whereby PN was more prevalent (69%) among participants with a higher level of education; secondary school and above. A high number (244; 44%) of participants were peasants or involved in farming activities on a small scale. There was a statistically significant (p<0.001) difference in the prevalence of PN among the participants with different occupational activities, in which the PN appeared most in unemployed (72%), followed by employed (69%), self-

employed/business (63%) and least among the farmers (47%). Almost half (46%) were married and PN appeared to be more prevalent among those who were divorced/separated (78%), followed by widow/widowed (67%). This difference in prevalence of PN with marital status was significant (p=0.003). Peripheral neuropathy was highly prevalent among the participants living in the urban setting with 78% compared to 40% among those living in rural settings (p<0.01).

4.7.3.2 Prevalence of PN and its association with the health status characteristics

Health status characteristics included the CD4 cell count levels, duration of HIV infection, the current ARV regimens the participants were on, duration on ARVs, ARV regimen changes the participant had undergone, and the ARV regimen the participant had started with; in terms of containing d4T. Table 10 below illustrates the findings.

Table 10 Prevalence of PN and its association with health status characteristics

		PN n (%) n=507			
Variable		**Without PN (n=207)**	**With PN (n=300)**	**p-value**	**All**
CD4 cell count	<=350	63 (51)	91 (49)		154 (30)
	>350	144(41)	209 (59)	*0.98*	353 (70)
Duration since HIV diagnosis	0 – 3 years ago	72 (46)	84 (54)		156 (31)
	4 – 6 years ago	91(49)	96 (51)	*<0.001**	187 (37)
	7 and above years	44 (27)	120 (73)		164 (32)
Current ARV regimen	Non d4T containing	156 (39)	247 (61)		403 (79)
	d4T containing	51 (49)	53 (51)	0.056	104 (21)
Duration on ARVs (in years)	0 – 1	71 (58)	52 (42)		123 (24)
	1 – 3	58 (36)	101 (64)		159 (32)
	4 – 6	61 (30)	108 (70)		169 (33)
	7 and above	17 (41)	39 (59)	*<0.001**	56 (11)
ARV regimen changes	None	44 (43)	48 (57)		102 (20)
	Once	120 (44)	150 (56)	*0.045*	270 (53)
	Two and more	43 (32)	92 (68)		135 (27)
ARV started with	Non D4T containing	62 (37)	104 (63)		166 (33)
	D4T containing	145 (43)	196 (57)	0.27	341 (67)

* Denotes significant p-value for the association between the PN and the health status characteristic

The majority (70%) of participants had CD4 cell counts of 350ml/m^3 and above. There was no significant difference (p=0.98) in the prevalence of PN among participants with different CD4 cell count levels. A statistically significant difference (p<0.001) was found in the prevalence of PN among participants with different durations of HIV infection; whereby PN was more prevalent (73%) among participants who had the infection for the last seven and above years. Similarly, an association (p<0.001) was observed between PN and the duration on ARVs, in which PN was most prevalent with a duration of (4 – 6) years (70%), followed by (1 – 3) years (64%). In addition to the level of CD4 cell count, other characteristics such as the current ARV regimens and the regimen started with, in terms of containing d4T, did not show differences in PN prevalence.

4.7.3.3 The demographic and health status characteristics, predicting PN

Various demographic and health status characteristics were identified as being associated with PN and were likely predictors of its occurrence. Further analysis with logistic regression models with separate univariate and multivariate analyses were done to determine the magnitude of the association of the characteristics with, and as predictors of PN. Only variables with significant associations on univeriate were included into the multivariate models. Table 11 below illustrates the results with the univariate and multivariate models.

Table 11 Demographic and health status, characteristics associated with PN

Characteristics		Univariate Models		Multivariate Models	
		Odds Ratio (OR)(95% CI)	**p-value**	**Adjusted Odds Ratio (aOR) (95% CI)**	***p-value***
Age		1.1 (1.0, 1.1)	<0.001	1.1 (1.0, 1.1)	<0.001*
Gender	Female				
	Male	1.3 (0.8, 1.9)	0.25		
Education	None	1.0 (ref)		1.0 (ref)	
	Primary	0.6(0.4, 0.9)	0.01	0.6(0.3, 1.0)	0.04*
	>=Secondary	1.2(0.7, 2.0)	0.55	0.6(0.3, 1.3)	0.2
Occupation	Employed	1.0 (ref)		1.0 (ref)	
	Peasant/Farmer	0.4(0.2, 0.8)	0.01	0.9 (0.3, 2.2)	0.76
	Self employed	0.8(0.3, 1.7)	0.5	0.3(0.1, 0.9)	0.03
	Unemployed	1.1(0.5, 2.4)	0.74	0.6(0.2, 1.4)	0.22
Marital status	Single	1.0 (ref)			
	Married	0.9 (0.4, 1.8)	0.75		
	Divorced/Separated	3.3 (1., 4)	<0.01		
	Window/Widower	1. 9 (0.9, 4.)	0.09		
Setting/Residence	Urban				
	Rural	0.2(0.1, 0.3)	<0.001	0.1(0.06, 0.3)	<0.001*
CD4 cell count	<=350				
	>350	1.0(0.7, 1.5)	1.008		
Duration since HIV diagnosis	0 – 3 years ago	1.0 (ref)		1.0 (ref)	
	4 – 6 years ago	0.9(0.6, 1.4)	0.60	0.6(0.3,1.1)	0.08
	7 and above yrs	2.3(1.5, 3.7)	<0.001	1.4 (0.7, 3.0)	0.33
Current ARV regimen	Non D4T containing				
	D4T containing	1.0(0.4, 1.0)	0.06		
Duration on ARVs (in years)	0 – 1	1.0 (ref)		1.0 (ref)	
	1 – 3	2.4(1.5, 3.8)	<0.001	2.6 (1.4, 4.8)	0.001
	4 – 6	2.4(1.5, 3.9)	<0.001	2.0 (10, 4.1)	0.05
	7 and above	3.1(1.6, 6.1)	0.001	2.2 (0.8, 5.9)	0.1
ARV regimen changes	None	1.0 (ref)			
	Once	0.9(0.6, 1.5)	0.80		
	Two and more	1.6(1.0, 2.8)	0.08		
ARV started with	Non D4T containing				
	D4T containing	0.8(0.6, 1.2)	0.27		

*Denotes significant p-value for the association of the characteristics with PN in a multivariable model

Peripheral neuropathy appeared to be associated with demographic characteristics such as; age [OR=1.1; 95% CI(0.1, 1.1); p<0.001], education level [OR = 0.6; 95% CI (0.4, 0.9); p<0.01], occupation [OR=0.4; 95% CI(0.2, 0.8); (p<0.01], rural or urban setting [OR=0.2; 95% CI(0.1, 0.3); p<0.001], and with health status characteristics that

include; duration of HIV infection [OR=2.3; 95% CI(1.5, 3.7); p=0.001], and the duration on ART [OR=2.4; 95% CI(1.5, 3.8); (p<0.001)]. Although, these characteristics were associated with the prevalence of PN in the univariate analysis, some characteristics were not independently associated with PN in the multivariate analysis. Only the age [aOR = 1.06, 95% CI (1.03, 1.08), p<0.001], the education level [aOR = 0.6, 95% CI (0.3, 1.0), p = 0.04] and urban or rural setting [aOR=0.1, 95% CI (0.06, 0.3), p<0.001], were independently and statistically associated with the prevalence of PN. Thus, age, education level and setting predominantly predicated the prevalence of PN in this study.

4.7.4 Association of PN with lower extremity functional limitations

The association of PN and the lower extremity functional limitations of the participants with HIV on ART were assessed. The mean and standard deviations of the scores of each activity for all participants were calculated. Table 12 below illustrates the results of the activity mean and standard deviation scores and the association with PN.

4.7.4.1 The status of functional activity performance and its association with PN

Table 12 below indicates the results of the test.

Table 12: Functional activity performance and its association with PN

	PN mean(±SD) (n=503)			
Functional limitation measures	**Without PN (n=205)**	**With PN (n=298)**	***p-value***	**All participants**
Doing any of your usual work	3.4(±1.0)	2.4(±1.2)	<0.001	2.8(±1.2)
Hobbies, recreational and sporting	3.5 (±1.0)	2.5(±1.3)	<0.001	2.9(±1.3)
Getting into or out of the bath	3.8(±0.7)	3.2(±1.1)	<0.001	3.4(±1.0)
Walking between rooms	3.9(±0.5)	3.3(±1.0)	<0.001	3.5(±0.9)
Putting on any kind of shoes or socks	3.9(±0.5)	2.9(±1.3)	<0.001	3.3(±1.1)
Squatting	3.7(±0.9)	2.7(±1.3)	<0.001	3.1(±1.2)
Lifting an object	3.7(±0.7)	2.9(±1.2)	<0.001	3.2(±1.1)
Doing light activities around home	3.8(±0.7)	3.2(±1.1)	<0.001	3.4(±1.0)
Doing heavy activities around home	3.6(±0.8)	2.7(±1.3)	<0.001	3.1(±1.1)
Getting into or out of a car/taxi.	3.8(±0.8)	3.1(±1.1)	<0.001	3.4(±1.0)
Walking between buildings	3.8(±0.6)	3.2(±1.1)	<0.001	3.4(±1.0)
Walking a Km	3.7(±0.7)	2.9(±1.2)	<0.001	3.2(±1.1)
Going up or down 10 stairs	3.7(±0.7)	2.7(±1.3)	<0.001	3.1(±1.2)
Standing for 1 hour	3.6(±0.8)	2.5(±1.3)	<0.001	3.0(±1.3)
Sitting for 1 hour	3.7(±0.6)	2.8(±1.2)	<0.001	3.2(±1.1)
Fast walking on even ground	3.7(±0.8)	2.6(±1.3)	<0.001	3.1(±1.2)
Fast walking on uneven ground	3.6(±1.0)	2.5(±1.4)	<0.001	3.0(±1.3)
Making sharp turns while walking	3.7(±1.0)	2.6(±1.4)	<0.001	3.1(±1.3)
Standing up fast from squatting	3.7(±0.8)	2.5(±1.4)	<0.001	3.0(±1.3)
Turning in bed	3.8(±0.7)	3.3(±1.0)	<0.001	3.5(±0.9)

Data expressed as mean± standard deviation

There were statistically significant differences (p<0.001) in all of the functional activity performance scores between the participants with PN and those without PN. The participants with PN had lower mean functional ability scores than those without PN.

4.7.4.2 Association of settings with lower extremity functional limitations

Urban and rural settings of the participants indicated differences in terms of association with PN, as indicated in the demographic characteristics and its association with PN,

section. Further testing was done to identify if the settings are also associated with lower extremity functional limitations. Table 13 below illustrates the results.

Table 13: Level and association of Lower extremity functional limitations with participants' settings

	LEFLs mean(±SD) (n=506)			
Functional limitation measures	**Urban (n=258)**	**Rural (n=248)**	***p-value***	**All settings**
Doing any of your usual work	2.8(±1.2)	2.8 (±1.3)	*0.55*	2.8(±1.2)
Hobbies, recreational and sporting	3.0 (±1.3)	2.8 (±1.3)	*0.22*	2.9(±1.3)
Getting into or out of the bath	3.4(±1.0)	3.4(±1.0)	*0.87*	3.4(±1.0)
Walking between rooms	3.8(±1.0)	3.6(±1.9)	*0.14*	3.5(±0.9)
Putting on any kind of shoes or socks	3.1(±1.3)	3.5(±1.0)	*<0.001**	3.3(±1.1)
Squatting	3.0(±1.3)	3.2(±1.1)	*0.08*	3.1(±1.2)
Lifting an object	3.3(±1.1)	3.2(±1.0)	*0.26*	3.2(±1.1)
Doing light activities around home	3.3(±1.1)	3.6(±1.1)	*0.02**	3.4(±1)
Doing heavy activities around home	3.2(±1.1)	3.0(±1.2)	*0.17*	3.1(±1.1)
Getting into or out of a car/taxi.	3.3(±3.3)	3.5(±1.1)	*0.12*	3.4(±1.1)
Walking between buildings	3.4(±1.1)	3.5(±1.0)	*0.35*	3.4(±1.1)
Walking a Km	3.2(±1.1)	3.3(±1.0)	*0.86*	3.2(±1.1)
Going up or down 10 stairs	3.1(±1.1)	3.2(±1.1)	*0.68*	3.1(±1.2)
Standing for 1 hour	2.8(±1.3)	3.0(±1.2)	*0.38*	3.0(±1.3)
Sit for 1 hour	3.1(±1.2)	3.3(±1.0)	*0.10*	3.2(±1.1)
Fast walking on even ground	3.0(±1.2)	3.2(±1.0)	*0.04**	3.1(±1.2)
Fast walking on uneven ground	2.8(±1.4)	3.2(±1.0)	*0.03**	3.0(±1.3)
Making sharp turns while walking fast	2.8(±1.4)	3.3(±1.1)	*<0.001**	3.1(±1.3)
Standing up fast from squatting	2.8(±1.5)	3.2(±1.1)	*<0.01**	3.0(±1.3)
Turning in bed	3.5(±1.0)	3.6(±0.8)	*0.73*	3.5(±0.9)

* Significant values

From Table 13 above, it is observed that participants from urban and rural settings were not different in terms of their lower extremity functional performance abilities. Significant differences were likely in the more complex activities, in which participants from the urban setting demonstrated lower activity performance scores compared to their

counterparts from rural, settings. These activities included (urban vs rural); fast walking on even ground [3.0(±1.2) vs 3.2(±1.0) p=0.04], fast walking on uneven ground [2.8(±1.4) vs 3.2(±1.0) p=*0.03],* making sharp turns while walking fast, [2.8(±1.4) vs 3.3(±1.0) p<*0.001],* and getting up from squatting [2.8(±1.4) vs 3.3(±1.1) p<*0.01]*. Some of the lighter activities that were different between the participants in rural and urban settings were (urban vs rural); putting on socks [3.1(±1.3) vs 3.5(±1.0) p<0.001], and doing light activities around home [3.3(±1.1) vs 3.6(±1.1), p=0.02]. Lower levels of performance ability were seen in participants from the urban setting.

4.7.5 The association of QoL with PN among PLHIV on ART

The level and association of QoL of PLHIV on ART with PN were assessed using the QoL facet scores and domains, as defined in the WHOQOL-BREF tool for assessing the QoL in PLHIV; (as described in chapter 3). The results for each facet score with categories of PN (with PN and without PN) are given (Table 14 below), the computed domain scores (Table 15), and the association of QoL according to the urban and rural settings, were all assessed (Table 17).

4.7.5.1 Rating of QoL facets and association with PN

The level and association of QoL facets among all participants with HIV on ART with PN were computed for mean and standard deviation scores of each facet against the PN categories. Mean and standard deviations were appropriate measures to report the results of QoL scores. These measures are recommended for the calculation of QoL health domain scores as described in the validation and calculation of scores using

WHOQOL-BREF; the tool to assess QoL in PLHIV (Hsiung et al., 2011). Table 14 below illustrates the results of the facet mean and standard deviation scores and the association with PN.

Table 14: Quality of life facet scores and association with PN

	PN mean(±SD) (n=507)			
Quality of life facets in domains	**Without PN**	**With PN**	***p-value***	***Combined***
Overall quality of life				
Rating of quality of life	3.1(±0.9)	2.9(±1.0)	*<0.01*	3.0(±1.0)
Satisfaction with general health	3.2(±1.0)	2.9(±1.0)	*<0.01*	3.0(±1.0)
Physical health domain				
Physical pain and discomfort	3.9(±1.2)	3.7(±1.1)	*0.02*	3.8(±1.0)
Dependence on medication to function	3.7(±1.4)	3.5(±1.3)	*0.24*	3.6(±1.4)
Energy and fatigue	3.8(±1.0)	3.2(±1.1)	*<0.001*	3.4(±1.1)
Ability to get around	3.6(±1.1)	3.3(1.1)	*<0.01*	3.4(±1.1)
Sleep and rest	3.7(±1.1)	3.5(±1.1)	*0.02*	3.7(±1.1)
Ability to perform your daily activities	3.6(±1.1)	3.2(±1.1)	*<0.001*	3.4(±1.1)
Capacity for work	3.6(1.1)	3.2(±1.1)	*<0.001*	3.3(±1.1)
Psychological health domain				
Positive feeling of life	3.4(1.1)	3.1(±1.1)	*<0.01*	3.2(±1.1)
Spirituality or personal beliefs	3.3(±1.1)	3.0(±1.0)	*<0.01*	3.1(±1.0)
Thinking, memory and concentration	3.7(±1.0)	3.2(±1.0)	*<0.001*	3.4(±1.0)
Bodily image and appearance	3.7(±1.0)	3.4(±1.1)	*<0.001*	3.5(±1.0)
Self esteem	3.7(±1.1)	3.5(±1.1)	*<0.05*	3.5(±1.0)
Negative feelings	3.6(±1.3)	3.5(±1.2)	*0.58**	3.5(±1.2)
Social relationship domain				
Personal relationships	3.9(±1.0)	3.5(±1.1)	*<0.001*	3.6(±1.1)
Sexual activity	3.1(±1.4)	2.7(±1.4)	*0.002*	2.9(±1.4)
Social support	3.7(±1.1)	3.3(±1.1)	*<0.01*	3.6(±1.1)
Environmental domain				
Physical safety and security	3.6(±1.1)	3.2(±1.1)	*0.001*	3.5(±1.1)
Financial resources	2.2(±1.3)	2.1(±1.2)	*0.41**	2.2(±1.3)
Healthy physical environment	2.1(±1.3)	24(±1.2)	*<0.01*	2.2(±1.2)
Opportunity for acquiring new information and skills	2.9(±1.2)	2.7(±1.1)	*0.01*	2.8(±1.1)
Participation and opportunity for leisure activities	3.3(±1.4)	2.8(±1.4)	*<0.001*	3.0(±1.4)
Home environment conditions	3.7(±1.0)	3.4(±1.1)	*<0.001*	3.5(±1.1)
Access to health services	3.5(±1.3)	3.0(±1.5)	*<0.001*	3.2(±1.5)
Transport	3.6(±1.2)	3.2(±1.3)	*<0.01*	3.3(±1.3)

*Denotes Non significant association between the PN and the quality of life facet

Table 14 above demonstrates statistically significant differences ($p<0.05$) for most of the facet scores between participants with PN and without PN. The mean scores among the participants with PN were lower than those without PN. However, there were facets in which the differences between participants with and without PN did not differ significantly; namely one from the physical health domain which is the "dependence on medication to function" ($p=0.24$), one from the physiological health domain; the "negative feelings" ($p=0.58$), and one from the environmental domain; "financial resources" ($p=0.41$). The general rating of QoL and life satisfaction was significantly better ($p<0.01$) among the participants without PN than with PN.

4.7.5.2 Rating of QoL domains and the association with PN

For the purpose of knowing the association of QoL health domains and PN, further computations and analysis as described in the WHOQOL-BREF tool, were done for the domains scores, against PN groups. Table 15 below illustrates the results.

Table 15: Quality of life domain scores and the association with PN among PLHIV

Domains	PN mean(±SD)		
	Without PN	With PN	p-value
Physical	14.6(±5.5)	13.4(±5.6)	<0.001
Psychological	14.1(±4.8)	12.9(±3.2)	<0.001
Social relationship	14.0(±2.9)	12.5(±3.1)	<0.001
Environmental	12.2(±6.6)	11.5(±6.7)	0.02
General QoL and health satisfaction	12.4(±1.8)	11.6(±2.0)	0.03

Table 15 above illustrates higher mean scores among PLHIV without PN compared to those with PN, in all the domains of QoL. The differences were statistically significant at p<0.001 for physical, psychological, and social relationship, health domains and at p<0.05 for environmental health, general QoL and health satisfaction.

4.7.5.3 Peripheral Neuropathy as a predictor of PN health domain scores

In previous sections on the association of PN with QoL scores, the observation was that PN is associated with lower QoL scores among participants with PN. Further analysis with a multiple linear regression model to establish PN as a predictive factor for the lower QoL domain scores, among PLHIV on ART was undertaken. Table 16 below illustrates the results.

Table 16: Association of PN with QoL domain

QoL health Domains	Univariate Models		Multivariate Models	
	Unadjusted coef. (95% CI)	p-value	Adjusted coef. (95% CI)	*p-value*
Physical	2.1(1.2, 3.1)	<0.001	2.1(1.2, 3.1)	<0.001
Psychological	1.8 (0.9, 2.6)	<0.001	1.8 (0.9, 2.6)	<0.001
Social relationship	1.2(0.7, 1.7)	<0.001	1.2(0.7, 1.7)	<0.001
Environmental	1.5(0.3, 2.7)	0.01	1.5(0.3, 2.7)	0.01
General QoL & health satisfaction	0.4(0.09, 0.8)	0.01	0.4(0.09, 0.8)	0.01

Each of the QoL domain scores remained significantly different between PLHIV with PN and those without PN, at p<0.001; for physical, psychological and social relationships, while environmental and general QoL and health satisfaction were significant at p<0.05, after adjusting for other domains.

4.7.5.4 Rating of QoL among urban and rural participants, in association with PN

Peripheral neuropathy has been identified in this study, to be more prevalent among urban than rural participants. The influence on the QoL of the participants from the two different settings was assessed; in terms of rating the QoL facets and health domains. The following Tables 17 and 18 illustrate the results for the facets and health domains, respectively.

Table 17: Quality of life facets scores and the association with urban and rural settings

PN mean(±SD) (n=507)				
Quality of life facets	**Urban**	**Rural**	***p-value***	***Combined***
Overall quality of life				
Rating of quality of life	3.0 (±1.0)	2.9 (±1.0)	*0.14*	3.0(±1.0)
Satisfaction with general health	3.0 (±1.0)	2.9 (±1.0)	*0.28*	3.0(±1.0)
Physical health domain				
Physical pain and discomfort	3.8 (±1.1)	3.7 (±1.2)	*0.21*	3.8(±1.0)
Dependence on medication to function	3.5 (±1.4)	3.7 (±1.3)	*0.08*	3.6(±1.4)
Energy and fatigue	3..5 (±1.1)	3.4 (±1.0)	*0.44*	3.4(±1.1)
Ability to get around	3.5 (±1.0)	3.3 (±1.1)	*0.11*	3.4(±1.1)
Sleep and rest	3.7 (±1.1)	3.5 (±1.2)	*0.15*	3.7(±1.1)
Ability to perform your daily activities	3.4 (±1.1)	3.3 (±1.1)	*0.64*	3.4(±1.1)
Capacity for work	3.4 (±1.2)	3.3 (±1.1)	*0.48*	3.3(±1.1)
Psychological health domain				
Positive feeling of life	3.2 (±1.1)	3.2 (±1.1)	*0.46*	3.2(±1.1)
Spirituality or personal beliefs	3.1 (±1.0)	3.2 (±1.1)	*0.43*	3.1(±1.0)
Thinking, memory and concentration	3.4 (±1.1)	3.4 (±1.1)	*0.76*	3.4(±1.0)
Bodily image and appearance	3.5 (±1.1)	3.5 (±1.0)	*0.98*	3.5(±1.0)
Self esteem	3.5 (±1.1)	3.5 (±1.0)	*0.80*	3.5(±1.0)
Negative feelings	3.6 (±1.1)	3.4 (±1.3)	*0.09*	3.5(±1.2)
Social relationship domain				
Personal relationships	3.6 (±1.1)	3.7(±1.0)	*0.69*	3.6(±1.1)
Sexual activity	2.9 (±1.4)	2.8(±1.4)	*0.65*	2.9(±1.4)
Social support	2.5 (±1.1)	3.4(±1.1)	*0.70*	3.6(±1.1)
Environmental domain				
Physical safety and security	3.4 (±1.1)	3.3(±1.2)	*0.65*	3.5(±1.1)
Financial resources	3.3 (±1.2)	2.0(±1.2)	*<0.001**	2.2(±1.3)
Healthy physical environment	2.3 (±1.1)	2.2(±1.1)	*0.08*	2.2(±1.2)
Opportunity for acquiring new information and skills	2.9 (±1.1)	2.7(±1.1)	*0.01**	2.8(±1.1)
Participation and opportunity for leisure activities	3.2 (±1.4)	2.9(±1.4)	*0.02**	3.0(±1.4)
Home environment conditions	3.5 (±1.1)	3.5(±1.1)	*0.44*	3.5(±1.1)
Access to health services	3.2 (±1.5)	3.2(±1.4)	*0.79*	3.2(±1.5)
Transport	3.4 (±1.3)	3.3(±1.2)	*0.24*	3.3(±1.3)

* Denotes Non significant association between the PN and the quality of life facet

Most of the QoL life facets scores were not significantly different between the participants from urban and rural settings. However, some significant differences were

seen with better scores in urban versus rural. The facets with differences included; financial resources; [3.3 (±1.2) vs 2.0(±1.2), p<0.001], opportunity for acquiring new information and skills; [2.9(±1.1) vs 2.7(±1.1), p=0.01] and participation and opportunity for leisure activities; [3.2(±1.4) vs 2.9(±1.4), p=0.02].

Table 18 Quality of life health domain scores and the association participants' settings

	Settings		
Health domains	**Urban**	**Rural**	**p-value**
Physical	14.1(±5.7)	13.8(±5.6)	0.30
Psychological	13.5(±5.0)	13.5(±5.1)	0.84
Social relationship	13.3(±3.1)	13.2(±3.0)	0.88
Environmental	12.2(±6.8)	11.5(±6.7)	0.02*
General QoL and health satisfaction	12.2(±1.9)	11.8(±1.9)	0.20

***Significant value at p<0.05

The QoL health domains did not show differences between the urban and rural participants. The only significant difference was in the environmental health domain where participants from the urban setting had better scores on the QoL in this domain than participants from the rural setting, [urban; 12.2 (±6.8) vs rural; 11.5 (±6.7)], at p=0.02.

4.8 Discussion

HIV has changed from being a terminal illness to a chronic condition in the ART era (Theroux et al., 2013) and PLHIV are now living longer. However, living with a chronic health condition such as HIV and on ART, has its own complications of which some are

disabling (Oshinaike et al., 2012). Peripheral neuropathy has been reported as one of the common neurological complications of HIV infection and in the ART era (Kamerman et al., 2012; Harrison and Smith, 2011). HIV-associated neuropathy is reported as a persistent cause of morbidity among PLHIV due to its effects on their quality of life (Ellis et al., 2010; Theroux et al., 2013). This study identified the prevalence of PN and its association with demographic and health status characteristics, related lower extremity functional limitations and QoL among PLHIV on ART from selected rural and urban ART clinics in Rwanda.

4.8.1 Prevalence of peripheral neuropathy

The overall prevalence of PN was as high as 59%, compared to previous study conducted in Rwanda. A previous study in Rwanda, by Biraguma and Rhoda, (2012) indicated a prevalence of 40.5% from one rural district hospital. The difference in the prevalence between the two studies may be due to the difference in the study setting coverage, in that this study was carried out in various rural and urban health facilities while the former was conducted in only one rural district hospital. However, both studies show similarities in the prevalence in the rural settings. The prevalence in the rural setting in this study is 40% which is the same as the one (40.5%) in the previous study conducted in one hospital in the rural setting. The prevalence in the urban setting in this study is 78%, which eventually contributes to the overall prevalence being high, that is 59%.

Furthermore, the prevalence in this study is higher than other studies carried out in Africa, such as by Luma et al., (2012) in Cameroon with 28%, Mehta et al., (2010) in Kenya with 36%, Oshinaike et al., (2012) in Nigeria with 39% and Maritz et al., (2011) with 49% in South Africa. Almost similar prevalence of PN is found between this study and the study by Wadley et al. (2011) done in South Africa. On the contrary, the prevalence of PN in this study is slightly lower than that found in the study in Brazil by Zanetti et al. (2004) where the prevalence was 69.4%. There might be various reasons for the differences, and these may be due to different methodologies such as study populations, the study area, risk factors of PN; examples being age, types of ARV regimens, disease stages, and different procedures to control PN, different environmental factors and many others. Despite the fact that the prevalence of PN differs from that in other studies in Africa, the prevalence falls into the range of the general reported prevalence of HIV-associated PN that has been identified to range from 30% - 67% (Wulff et al, 2000; Evans et al., 2011; Kamerman et al., 2012). Even so, it is important to note that as about 90% of PLHIV in Rwanda who are eligible for ART are on it, and some ARVs are likely to influence the development of PN (Theroux et al., 2013), the prevalence of PN is likely to continue increasing. This implies that PLHIV with PN are and will likely live longer which has a negative impact on their quality of life (Venkataramana et al., 2005; Ellis et al., 2010; Oshinaike et al., 2012). Thus, efforts need to be made to develop cost effective strategies to reduce the high prevalence that impacts on the QoL of PLHIV on ART.

4.8.2 Association of peripheral neuropathy with demographic characteristics

An older age was associated with PN, those with PN were older (42 years old) than their counterparts without PN (37 years old). This is similar to other studies in which age has been consistently identified as a risk factor for developing PN (Cherry et al., 2009; Oshinaike et al., 2012). It is known that aging is susceptible to various neuromuscular disorders (Hyldahl and Hubal, 2013) including PN. Identifying and monitoring PN occurrence is important for possible early detection and appropriate management of PN in this group. Haanpää et al. (2009) and colleagues highlighted that early identification and management of the neuropathic pain symptoms is important in primary care to improve the quality of life.

There is a high prevalence of PN in PLHIV on ART living in urban compared to rural, settings in Rwanda. The very big difference between rural and urban prevalence rates is puzzling. A possible reason for the difference may be that people living in an urban setting are more likely to be physically inactive and physical inactivity has been reported as a risk factor for neuromuscular conditions (which may include PN) in PLHIV (Masterson Creber et al., 2010; Schuelter-Trevisol et al., 2012). Similarly, increased body weight which is usually common among people who are physically inactive has been identified in one of the studies conducted in Rwanda, as a risk factor for neuropathy (Mutimura et al., 2007), although weight was not measured in this study. Again, the literature shows that physical exercise reduces weight and other co-morbidities (Botros et al., 2012), such as lipodystrophy which is a potential mediator for PN in HIV (Jayakumar et al., 2012). Despite the fact that this study did not assess weight

and lipodystrophy, Mutimura et al. (2007) indicated that lipodystrophy was more prevalent among PLHIV in urban than rural settings in Rwanda. Routine monitoring and assessment of PN with its association with physical inactivity and body weight would be useful so as to advise on the appropriate strategies for the management of PN among PLHIV, particularly in urban settings.

4.8.3 Association of PN and health status characteristics

The CD4 cell count was not associated with PN. Similar findings of non-associated CD4 cell counts with PN have been demonstrated in the studies by Morgello et al. (2004), Schifitto et al. (2005) and Oshinaike et al. (2012). This implies CD4 cell count might not be a measure of risk once on ART (Ellis et al., 2010). The results are contrary to what has been found in other studies done in Africa, such as the study by (Millogo et al., 2008) in Burkina Faso, and the study by Luma et al., (2012) in Cameroon. Possible reasons for the differences might include that this study was cross sectional and all participants were outpatients and most of them (70%) had CD4 cell counts of 350m//m^3 and above. Yet, decreased CD4 cell count has been shown to be associated with co-morbidities including PN in PLHIV (Ances et al., 2009).

Likewise, the d4T containing regimen was not associated with PN, which is contrary to the findings in the study by Forna et al. (2007), but is similar to the study by Luma et al. (2012) which showed no association of d4T use with PN. A possible reason being that people who experience PN as a result of d4T usually experience it in the initial stages of the therapy (Hung et al., 2008; Kampira et al., 2013). In their study, Hung and

colleagues (2008) demonstrated that the continuation of the use of the so called “d-drugs” such as d4T among patients who persist with PN from the initial stages did not show a significant difference with the use of non d-drugs, in worsening the neuropathy. It is common practice that in cases of PN suspected to occur as a result of d4T, the medication is usually discontinued. The experience of PN at later stages of therapy is likely attributable to factors other than d4T.

The time since HIV diagnosis and duration on ART, did not independently predict the occurrence of PN after adjusting for other confounders in a multivariate model with the exception of the duration of 1 – 3 years that appeared as a predictor of PN. To the author’s knowledge, it is not yet clear as to why being on ART in the first three years predicts PN rather than longer periods of 4 – 6 or 7 and above years. Possible reasons might be that people who experience PN as a result of ART particularly regimens containing toxic “d” drug usually experience it in the initial stages of the therapy (Hung et al., 2008; Kampira et al., 2013). Additionally, individual susceptable to develop PN, regardless of the cause, they do so early. However, further investigation into this with longitudinal studies to identify the trend should be done. Otherwise, similar findings in other studies in Africa such as by Oshinaike et al., (2012) indicated the same trend of ART duration and non - association with PN. Conversely, studies such as the one by Robinson-Papp et al (2012), highlighted the duration of HIV infection as a risk factor for PN. It is important to note that there is a likelihood that the duration the patient has been HIV positive and on ART, may influence the occurrence of PN, but different intervals of the duration need to be specifically identified.

4.8.4 The lower extremity functional limitations and the association with PN

Pain and its associated body functional disturbances or limitations are common in PLHIV (Sandoval et al., 2013). The common cause of chronic pain in HIV is sensory neuropathy (Robinson-Papp et al., 2010), and the pain usually affects the physical, psychological, social, and functional abilities of the affected person (Van As et al., 2009). Sensory neuropathy in HIV, of which the common one is DSP (Luma et al., 2012), affects the lower and upper extremities (Robert P. Fellows et al., 2012). This study assessed the lower extremity functional limitations and their association with PN.

The findings demonstrated that the functional ability of the lower extremity among PLHIV with PN was lower than those without PN. The differences between the two groups were observed in all of the functional activities of the lower extremities assessed. It is noted that having peripheral neuropathy likely caused limitations in mobility of the lower extremities in the group with the neuropathy. Such limitations in mobility eventually impacted on the functional activities of the lower extremities of the affected participants. For example, participants with PN had difficulties in walking fast, standing and sitting for a period of an hour and squatting in toilets (as many people particularly in rural areas still use pit latrines), compared to their counterparts without PN. It is obvious that PN specifically the neuropathic pain such as burning pain, tingling sensations and paraesthesia limit movements that later result in tight muscles, stiff joints and spasms and hence limited mobility. This is likely to cause muscle weakness of the affected lower extremity due to inactivity. These findings are similar to the study by Van As et al., (2009) which found body impairments including neurological, in PLHIV as

“predictors of mobility”. Physiologically, neurological impairments influence the daily physical functional activities and have been demonstrated as the common cause of mobility dysfunction among PLHIV (Meholjić-Fetahović, 2005; Harrison and Smith, 2011). It is important therefore to note that most cases of HIV related physical body impairments affect mobility, and because PN affects the lower extremity, thus the functional activities of the lower extremity are more affected.

The lower extremity functional performance abilities of the participants from the urban and rural settings were mostly the same. Only significant differences were observed in some of the more difficult physical activities, in which there were lower activity performance scores, among participants from the urban setting compared to the rural one. Physical activities are common in the daily activities of the Rwandans living in rural settings because they earn their living through doing hard physical work. Their work usually include activities such as farming, cultivation, walking long distances to fetch or gather food, firewood, and water, socialisation and other public activities like attending church, and going to market. Although such activities are hard, it is likely that they help people keep strong physically maintain their flexibility and hence are protective against some of the effects of PN on their functional ability. Physical activity or exercise has been shown to improve physical functioning and reduce functional limitations (Graham et al., 2007), but this was not specifically tested in this study. Further studies could look into this relationship. Additionally, the literature indicates that physical activity has a protective effect on neurodegenerative disorders (Foster et al., 2011), which might result in reduced effects of PN thereby reducing functional limitations among the

physically active rural population. The latter might be one of the reasons for having less PN related functional limitations among the rural dwellers compared to the urban ones.

The urban participants also had more difficulty in some of the lighter activities namely; “putting on socks” and “doing light activities around the home”, than the rural participants. The difficulty in putting on socks may have been due to superficial sensory pain that is a common symptom in PN (Cettomai et al., 2013). The difficulty of putting on socks is one of the functional activities related to the sensory hypersensitivity disorders among PLHIV with PN assessed in this study. But there are other related difficulties faced by PLHIV with PN which likely affect their daily living. For instance, people with allodynia encounter problems with sleep difficulties whereby a light touch with a bed sheet, for example causes pain, and the person feels as if “there is a touch on a wound” (Verma et al., 2005).

4.8.5 The association of PN with QoL

Quality of life is a measure of people’s wellbeing and any disruption of QoL affects their wellbeing. It was found that PLHIV with PN have a lower quality of life compared to those without PN. However, the participants did not differ in some facets of QoL; as all participants equally demonstrated that they depend on the medication such as ARVs, experience negative feelings and are financially poor. Poverty, and their dependency on medication sometimes result in negative feelings which impact on their quality of life (Skevington, 2012). This implies that in addition to the effects of PN for some PLHIV, there are other life challenges that impact on them, as demonstrated equally by both groups of participants; those with and without PN.

Generally, the rating of QoL and life satisfaction was lower among participants with PN than without. The low rating of QoL and life satisfaction might have been in this group with PN simply because the QoL is generally affected with functional activity limitations as a result of compromised mobility, pain and discomfort (Hughes et al., 2004) of which all have been identified among PLHIV with PN. People with limited mobility are unable to do most of their daily activities and this affects their QoL and life satisfaction (de França et al., 2013). A person with limited mobility may have difficulty doing active work that usually earns an income in environments like in this study. Activities like sitting or standing for at least an hour, lifting loads, walking long distances, were identified in this study to be limited in PLHIV with PN. These findings are similar to the study conducted in one district hospital in Rwanda by Biraguma and Rhoda (2012) which showed a lower QoL with PLHIV with PN compared to a group of people without PN symptoms in the physical and psychological domains. But the studies differ in the study area and participant coverage. This study was conducted among both urban and rural participants, while the previous one considered only rural participants. To my knowledge, this study is the first of its kind to identify the relationship between PN and quality of life at a national level coverage of eight health facilities in Rwanda. The results from this study may thus be generalised to Rwanda and possibly to other resource limited countries, particularly in Africa where some of the social and environmental influences are similar (Conn, 2012).

Peripheral neuropathy was a predictor of low QoL among PLHIV in all QoL domains. The domains of QoL include; physical and psychological health, social relationships and

environmental domains. Peripheral neuropathy which is described with symptoms that include neuropathic pain, numbness, tingling and, “pins and needle” sensations, and signs such as reduced or no vibration sense, and ankle tendon reflex, are all likely to affect all the domains of QoL. This is one of the reasons that people with PN confirmed low QoL compared to those without. The results are similar to those of Ellis et al. (2010) except that Ellis and colleagues tested PN as a predictive factor of QoL among pre-ART participants. Furthermore, the study by Ellis et al. (2010) used neuropathic pain as a measure for PN, and the effects of PN on physical and mental subscales of the measure of the QoL, were assessed.

On the other hand, PLHIV with PN in urban areas showed better financial resources, opportunities for acquiring new information and skills, and participation opportunities for leisure activities, compared to their counterparts from rural areas. This difference is likely to be related to environmental factors rather than to the PN. For example in the urban areas there is easy access to information through radio and TV, opportunities to access recreational centres, good road networks and easy public transport. Furthermore, it is possible that some people in the urban areas were employed, although this was not assessed. These factors might have contributed to the urban dwellers having better accessibility to information, recreational services and having better financial resources than those in the rural areas. The Rwanda Demographic and Health Survey [RDHS] (2010) has reported that households in urban areas are wealthier by 12% than those in the rural areas. This also might have resulted in the reporting of better financial resources in the urban dwellers. It has been reported that financial resources are one of the most common facets in the environmental domain

that influences lower QoL (de França et al., 2013). A study conducted in Singapore highlighted that the financial resources were “intimately linked to environmental and living conditions” and impacted on the QoL (Leow et al., 2013).

4.8.5.1 Importance of understanding PN in relation to QoL

Although the introduction of ART has improved the QoL in PLHIV by reducing the impact of HIV, the adverse effects of ART including PN, still affect the QoL of PLHIV (Abdella et al., 2011). The QoL is affected in its various domains that include; physical, psychological and environmental and this may interfere with the benefits of ART, hence impacting on ART adherence (Abdella et al., 2011). It is important therefore to have initiatives for complementary management of the neuropathy, particularly in Rwanda and other resource limited countries, where the PN prevalence is high.

4.8.6 Strengths and limitations of the study

The strength of this study is demonstrated in the large sample size and inclusion of randomly selected ART clinics. The use of a rigorous PN assessment tool ensured reliable data to determine the prevalence of PN in Rwanda. The data can be used in developing strategies for the comprehensive management of the condition, particularly among urban and in the older, PLHIV on ART in Rwanda. In addition, the findings can be generalized for both rural and urban dwellers in Rwanda and possibly poorly resourced nations where the lifestyle of the populations is similar.

The study's major limitation is that it is cross sectional and participants were outpatients who were likely not in the advanced stages of HIV, which might have influenced the level of CD4 cell count in the sample. Additionally, few participants in the sample were on d4T containing regimens which may have limited the associations tested for d4T and PN. Occupational activities were used to identify the lifestyle of the participants but a more rigorous assessment procedure to identify the lifestyle activities, and demonstrate the influence of the lifestyle activities on occurrence of PN could be done. Also the study recruited participants from public ART clinics, which is a limitation on generalisation of results to the private PLHIV, though the number of people who attend the private ART services is likely very low.

4.8.7 Conclusions

This study identified a high prevalence of PN in Rwanda and this can form the basis for designing strategies for managing the problem and to prevent or minimise the effects of PN that compromise the quality of life of PLHIV. Older PLHIV and those living in urban settings and on ART should have their PN status monitored so as to maintain and improve their quality of life appropriately. However, further investigation into lifestyle behaviour and other factors that may influence the occurrence of PN need to be assessed in a longitudinal study.

CHAPTER 5

5.0 STUDY 3: METHODOLOGY OF THE EXERCISE INTERVENTION (RCT)

THE EFFECTS OF PHYSIOTHERAPEUTIC EXERCISES ON PERIPHERAL NEUROPATHY, RELATED FUNCTIONAL LIMITATIONS OF THE LOWER EXTREMITY AND QUALITY OF LIFE, AMONG PLHIV ON ART IN RWANDA

5.1 Introduction

The aim of study 3 was to establish the effects of physiotherapeutic exercise (PTEx) on PN, its related lower extremity functional limitations and QoL, among PLHIV on ART in Rwanda. The study was a RCT and this chapter describes the methodology used. The methodology includes; the objectives participants and their selection, the randomisation process, exercise programme protocol, assessment procedures and finally the data analysis tests done.

5.2 Objectives

1. To test the effects of PTExs on PN, related lower extremity functional limitations and QoL, in PLHIV on ART,
2. To assess the effects of a PTExs programme post 12 weeks of its intervention in PLHIV on ART,
3. To identify factors associated with and influencing the improvement of PN, related lower extremity functional limitations and QoL, in PLHIV on ART

5.3 Study setting, participants, sample size and selection

5.3.1 Study setting and participants

This study was carried out in Kigali city Rwanda and the setting for the intervention was located near the city centre, at the Kigali Health Institute (KHI)'s physiotherapy clinic and fitness centre, located about 200 metres from the main road to the city centre. This location was convenient for participants travelling with public transport and was easily accessible for participants from the three districts that constitute Kigali city.

As described in chapter four, the study participants were PLHIV on ART, who were systematically randomly screened from four simple randomly selected ART clinics at health centres and hospitals in the Kigali districts; namely; Kicukiro Health Centre in Kicukiro district, Kimironko Health Centre and Kacyiru Hospital both in Gasabo district, and Biryogo Health Centre commonly known as Kwa-Nyiranuma in the Nyarugenge district. Kigali city was considered to be the most appropriate study site due to the fact that being a city and an urbanised area, the populations' life style was likely to be more homogeneous than in rural areas where people have a range of different life styles. Also Kigali being a city with a large population living close together in the three districts of the city, made it convenient for participants to travel to the intervention site. In addition transport in the city is better than in rural areas as it is more accessible making it easier for participants to reach the centre easily.

5.3.2 Inclusion and exclusion criteria of the participants

The following inclusion and exclusion criteria were considered in addition to what is listed in Chapter four (prevalence; Study 2).

5.3.2.1 Inclusion criteria

Only participants screened with obvious PN in Study 2 were invited to participate in the intervention; Study 3.

5.3.2.2 Exclusion

- Any clinical history that would be an exercise contraindication ; according to the American College of Sports Medicine guidelines for exercise prescription for PLHIV (Sonya and Anderson, 2006).
- Unwilling to participate in the PTExs and the rest of the follow up programme, very weak patients who could not walk without support, other neuromusculoskeletal impairments such as, musculoskeletal deformity, amputation, scoliosis, and inability to actively and functionally move ankle and knee joints, lower extremity arthritis, and central neuropathies like hemiparesis and central paralyses.
- PLHIV with a known history of diabetes, and substance abuse, Vitamin B12 deficiency, TB or taking TB medication such isoniazide, renal failure, hypothyroidism and other pathologies that may be associated with neuropathy.

5.3.3 Sample size and selection

The sample for the exercise intervention was one hundred and twenty (120) participants. The participants in the sample were consecutively invited from one hundred and sixty four (164) PLHIV on ART who were randomly screened with PN in Kigali, during the prevalence study (Study 2; Chapter four) with the methodology described in chapter four. The 164 participants were invited from respective selected

ART clinics in Kigali, to the Kigali Health Institute physiotherapy clinic where screening for eligibility and baseline assessment took place prior to the start of the exercise intervention. One hundred and thirty nine (139) out of the 164 participants responded to the invitation at the clinic, and only 120 were eligible for the exercise intervention, according to the eligibility criteria discussed in the above section. Thus, 60 participants were allocated to each group. The statistical power with an allowance for a dropout of 30% per group demonstrated that the sample of 120 participants would give the desired effect with a power of more than 80% and detect a difference in the of pain improvement (effect size) for p=0.05, from the exercise intervention.

5.3.4 Randomisation and concealed allocation to the groups

The 120 participants assessed for baseline data were randomised into two groups of 60 in the experimental group and 60 participants in the control group, with random computer generated numbers. An independent research assistant put the numbers into opaque sealed envelopes which were randomly given to the eligible participants by another research assistant who did not participate in putting the numbers into the opaque sealed envelopes. This ensured concealed allocation of the participants into the groups. The study was a single blinded RCT design, whereby the assessor was blinded to which group was experimental or control, until after the last assessments.

5.4 Procedure for the exercise intervention

The experimental group of 60 participants continued receiving Routine Health Care (RHC) from the respective ART clinics plus PTExs (RHC+PTExs). The control group continued receiving only the RHC without PTExs (RHC–PTExs), that is the ARVs and

other prophylactic medications such as the ones that were used to reduce/treat pain; including antidepressants, multivitamins, as well as routine medical consultations, CD4 testing and counselling services.

5.4.1 Physiotherapeutic exercise protocol (Appendix 2)

The PTExs protocol was mainly comprised of exercises for the extremities that were identified in the literature (Gale, 2003; White, 2004; Hess and Woollacott, 2005; Nixon et al., 2005; O'Brien et al., 2010) and were recommended as safe and beneficial to PLHIV.

The exercises included aerobic exercises that constituted a start of 15 minutes warm up by walking (slow then to brisk walk plus full range of upper and lower limb flexibility exercises), 15 minutes of mobility training with self-stretching in standing, lying and long sitting, positions, 10 minutes of muscle conditioning with isometric exercises in various starting positions, 10 minutes of balance exercises and finally 10 minutes of cooling down exercises (stretching and deep breathing) among others. Systematic reviews of effectiveness of PTExs of an aerobic nature for various patient conditions indicate that a combination of the above exercises is safe, affordable and is recommended (Smidt et al., 2005; O'Brien et al., 2010). The PTExs were given for 60 minutes per session three times a week for a period of 12 weeks.

In addition, the participants in the exercise intervention were educated on how to exercise on their own as a home exercise programme. This was so that after the supervised and guided exercise sessions of 12 weeks at the centre, the participants

were expected to continue exercising on their own at home. The participants were encouraged to continue exercising at home and were assessed again at 12 weeks after the supervised and guided exercise intervention at the centre. At the centre, the exercise intervention was conducted in a room suitable for aerobic and therapeutic exercises. A qualified physiotherapist with a master's degree and who had experience in conducting aerobic exercise programme, conducted and supervised the intervention exercise programme with the experimental group. The research assistant was also trained by the author to conduct the exercise sessions, with emphasis on the exercise protocol guide designed for the intervention.

5.4.2 Outcome measures and assessment procedure

The blinded assessor, that is the author did the assessments for both groups and was blinded to the group allocation (experimental or control) prior to the beginning of the exercise programme (baseline), after 12 weeks (end of exercise programme) and after 12 weeks post intervention. The outcome measures described and adapted in Study 1 and used in Study 2 were also used in this study (Study 3); namely, the checklist for demographic and health status characteristics, BPNS & DN4 for PN, LEFS-M for LEFLs, & WHOQOL-BREF, for the QoL. All the procedures and protocols used in the assessment for this study were described in Chapter four (Study 2).

5.4.4 Precautions and follow up of the participants during the intervention

During the exercise sessions, precautions were taken to prevent fatigue, check for abnormal heart rate and any other clinical signs such as blood pressure or symptoms contraindicated to exercises. Participation at each session was registered and followed

up with telephone calls to those who had mobile phones, to establish the reasons as to why any participant missed session(s). Also monthly, calls were made to the control group, to remind them of the schedules for the assessment after 12 weeks and after 24 weeks. They were only reminded of the assessment schedules during these calls.

5.5 Data management and analysis

All the questionnaires and other data collection material were kept in a well locked room reserved at the Kigali Health Institute physiotherapy clinic where the intervention and assessments took place. The data entry took place at the same place. Questionnaire variables were coded with numbers and the codes were entered into an Excel spread sheet by two research assistants trained by a statistician on how to enter data. The variables were re-checked and verified by the author before and after entry for correctness and any errors. The data were transferred into a STATA programme for cleaning of any errors that might have occurred during the data entry process. Any error identified was rectified from the questionnaires and from recording spread sheets. The author was blinded to the data of which group was the experimental or control, until after the analysis.

Using descriptive analysis such as tabulations for frequencies and percentages for categorical variables and measures of central tendency (means) and measures of variability (standard deviations) for continuous variables such as age and the measures of lower extremity functional limitations and QoL, were done with Wilcoxon rank-sum (Mann-Whitney) test. A bivariate analysis using Pearson's Chi-square test for significant

differences between the experimental and control groups, at baseline, after 12 weeks of PTExs and after 12 weeks post intervention, was done. A generalised linear model with generalised estimating equations (GEE) and logit link function, was used to identify the significant factors associated with, and influencing improvement changes, their magnitude, for the outcome measures of interest for PN and lower extremity functional limitations. While analysis for the overall QoL was done with multilevel mixed effects linear regression. The factors tested for the association with, and influence of improvement changes of PN, lower extremity functional limitations and QoL, included the demographic and health status related characteristics; such as age, gender, level of education, marital status, occupation, duration since HIV diagnosis, CD4 cell count levels, duration on ART, treatment regime (ARVs) the participants were taking, ARV regimen changes, and whether PN started before or after the start on ARVs. Adjusted odds ratios and their 95% confidence level were reported to have a magnitude of association and influence for PN and lower extremity functional limitations, as binomial outcomes, while coefficient correlations were reported for QoL as a linear outcome in the model. Significance level acceptance was set at p-value ≤0.05. Data were analysed using STATA (version 11, Stata Corp, College Station, Texas, USA). All analyses were done with an intention-to-treat analysis, whereby all analyses included all the participants who were randomised according to each group assignment (the baseline observation carry forward analysis). The results of the intervention are presented in Chapter six.

CHAPTER 6

6.0 STUDY 3: RESULTS OF THE INTERVENTION

6.1 Introduction

Chapter six presents the results of Study 3 which was an intervention using a RCT, to test the effects of PTExs on PN, related lower extremity functional limitations and the QoL in PLHIV on ART. During the intervention, three interval assessments were done; namely at; 1) baseline, 2) after twelve (12) weeks of PTExs and 3) after twelve weeks post intervention. The results are presented for all three interval assessments.

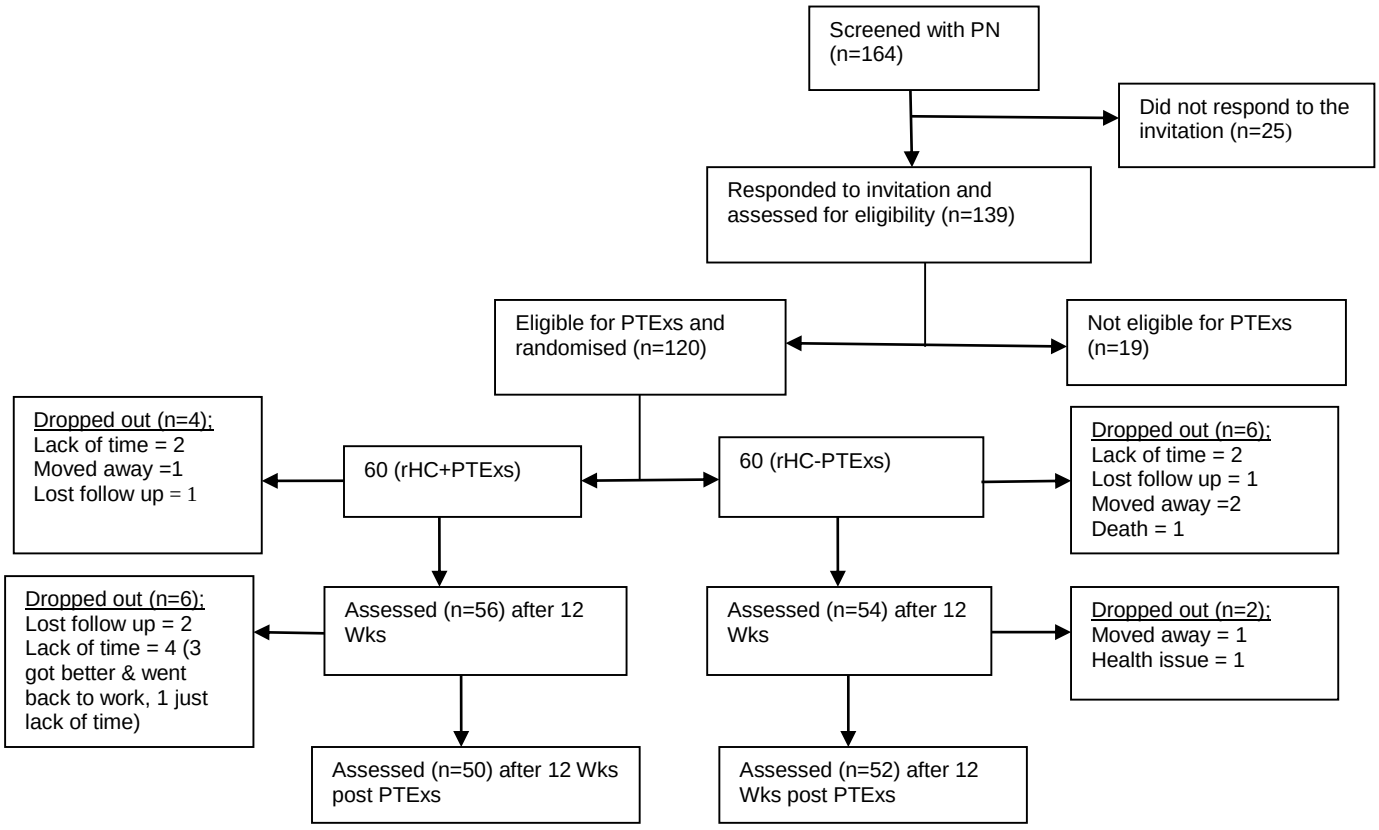


Figure 2: Flow diagram of the participants randomised into the intervention and control, groups

Out of 164 participants who were screened with PN and invited for the intervention study, 25 did not respond to the invitation, and 19 were not eligible for exercises due to a known clinical condition that was contraindicated for exercise, such as cardiovascular abnormalities, and any neuromusculoskeletal disorder that is exacerbated by exercise (Kisner and Colby, 2007). Four people dropped out of the exercise intervention during the 12 weeks of PTExs. Reasons for dropout being; one participant was a primary school administrator and because of her work demands she was unable to get enough time for exercising at the site, another person moved to one of the other provinces, two other participants were unable to attend because also of work related reasons. This brings the adherence to the exercise intervention in the experimental group during the 12 weeks to 93%, with approximately 7% dropout.

In the control group, six participants dropped out during the first 12 weeks. Common reasons were lack of time (n=two), moving away from Kigali (n=two), one participant died of meningitis, one participant lost to follow up. The follow up of the control during the 12 weeks was 90% with a 10% drop out.

After 12 weeks post exercise intervention, six participants did not return for assessment in the experimental group, giving a follow up of 89%. Three participants improved sufficiently and returned to work and were unable to come back during the time of the assessment; one was a driver, another a night watchman and the third was a business woman who had gone to neighbouring country for business reasons. The reasons for two people (lost to follow up) were unknown and one person also reported lack of time to come back for the third assessment. Only two participants did not come for the third

assessment (after 24 weeks) for the control group and the follow up at this stage was calculated as 96%. The reasons for the drop out being that one had moved away from Kigali and the second one was sick and could not make it for the last round of the assessments.

6.2 Objectives

Objectives for the intervention study (Study 3) were set to guide the analysis and presentation of the results appropriately. The objectives were;

6.2.1 Specific objectives

1. To test the effects of PTExs on PN as the primary outcome,
2. Test effect of PTEs on PN related lower extremity functional limitations and QoL, in PLHIV on ART, as the secondary outcomes.
3. To assess the effect of a physiotherapeutic exercises programme post 12 weeks of its intervention in PLHIV on ART
4. To identify factors associated with and influencing the improvement of PN, related lower extremity functional limitations and QoL, in PLHIV on ART

6.2.2 Demographic and health status differences between the groups at baseline

Participants in the intervention group were adult women and men, living with HIV, attending ART programmes at selected ART clinics in Kigali Rwanda, and who were screened with PN during the prior prevalence study (Study 2; chapter four). Table 19 below compares the demographic and health status characteristics between the experimental and control groups at baseline.

Table 19: Demographic and health status characteristics of the participants: comparison between the experimental and control groups at baseline (n=120)

Characteristics	Experimental group (n=60) n (%)	Control group (n=60) n (%)	Group differences n(%)	p-value
Age (mean±SD years)	41.2 ±7.8 CI: 95% (40,45)	40.4±7.7 CI: 95% (39, 43)	1.01± CI: 95% (1,2)	0.59
Gender				
Female	48 (80)	50 (83)	2(3)	0.64
Male	12 (20)	10 (17)	2(3)	
Education				
No schooling	11 (18)	13 (22)	3(4)	
Some primary school	3 (58)	29 (48)	6(10)	0.54
Some secondary and university education	14 (24)	18 (30)	4(6)	
Occupation				
Employed	5 (8)	6 (10)	1(2)	
Self-employed/Peasant/farmers	13 (21)	18 (30)	5(9)	0.51
Unemployed	4 (70)	36 (60)	6(10)	
Marital status				
Single	1 (2)	2 (3)	1(1)	
Married	16 (26)	18 (30)	2(4)	0.10
Separated/Divorced	4 (7)	12 (20)	7(13)	
Widow/Widower	39 (65)	28 (48)	11(17)	
Duration since HIV diagnosis				
Less or equal to 3 years ago	8(13)	3 (5)	5(8)	
4 to 6 years ago	18 (30)	19 32)	1(2)	0.31
7 and above years ago	34 (57)	38 (63)	4(6))	
CD4 cell count				
≤ 350	22 (37)	15 (25)	7 (12)	0.17
351 >	38 (63)	45 (75)	7(12	
Duration on ARVs				
Less or equal to 3 years ago	15 (25)	18 (30)	3(5)	
4 to 6 years ago	36 (60)	34 (54)	2(6)	0.82
7 and above years ago	9 (15)	8 (13)	1(2)	
ARV regimen combination started with				
None D4T including	33 (55)	40(66)	7 (11)	
D4T including	27 (45)	20 (34)	7 (11)	0.78
Current ARV regimens' combination				
None D4T including	53 (88)	50 (83)	3(5)	0.60
D4T including	7 (12)	10 (17)	3(5)	
ARV regimen changes since started on ART				
No change	18 (30)	16 (27)	2 (3)	0.69
One or more changes	42 (70)	44 (73)	2 (3)	
The onset of PN symptoms and/Signs				
Before starting on ARVs	5 (8)	12 (20)	7 (12)	0.07
After starting on ARVs	55 (92)	48 (80)	7 (12)	
After how long on ARVs when PNS started				
Within the 1st 12 months	25 (45)	14 (29)	11 (16)	0.09
After the 1st 12 months	30 (55)	34 (61)	4 (6)	

The results of the comparison of the demographic and health status characteristics indicated non-significant differences between the two groups at baseline.

6.3 The effect of the physiotherapeutic exercises on the PN, lower extremity functional limitations and QoL

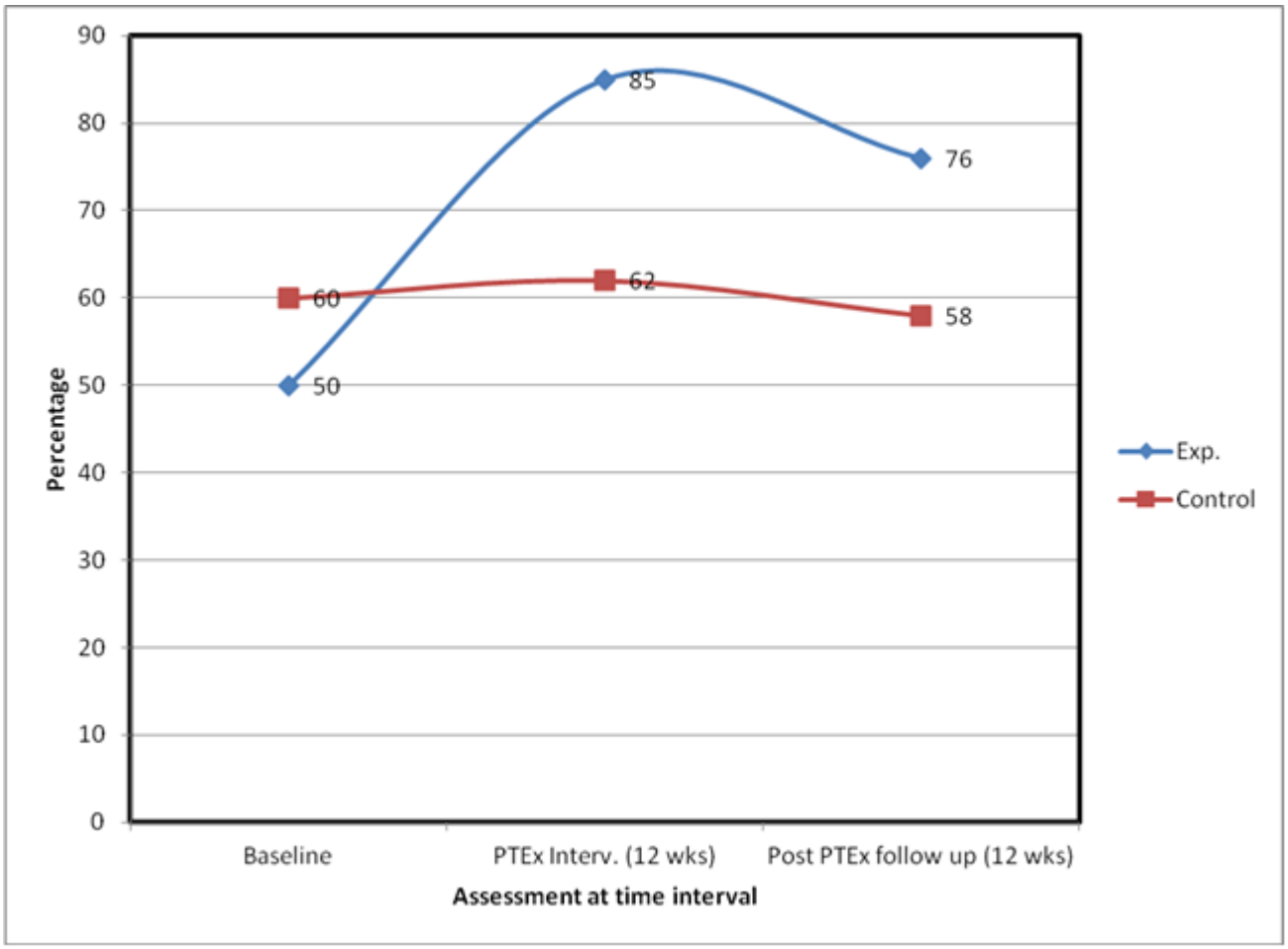
The following sections present the results for each of the three major outcomes of interest in regard to the effects of PTExs.

6.3.1.1 The effects of physiotherapeutic exercises on the PN

Peripheral neuropathy characteristics included more than one symptom and sign which were; PN symptom grades or severity, distribution of PN to different locations of the lower extremity, sense of vibration and ankle tendon reflex. The results on the effect of the PTExs on each characteristic are presented with respective figures that show the trend of differences and changes over time during the 12 weeks of intervention and 12 weeks post intervention. Finally, the results on the overall diagnosis of PN are also shown.

6.3.1.1 The effect of physiotherapeutic exercises on the PN symptoms

Peripheral neuropathy symptoms were measured at three time intervals; at baseline, after 12 weeks of the PTExs intervention and 12 weeks post intervention. The PN symptoms were measured as none, mild or moderate to severe. Figure 3 below indicates how PN symptoms changed from severe to none and or mild PNS through the three assessments



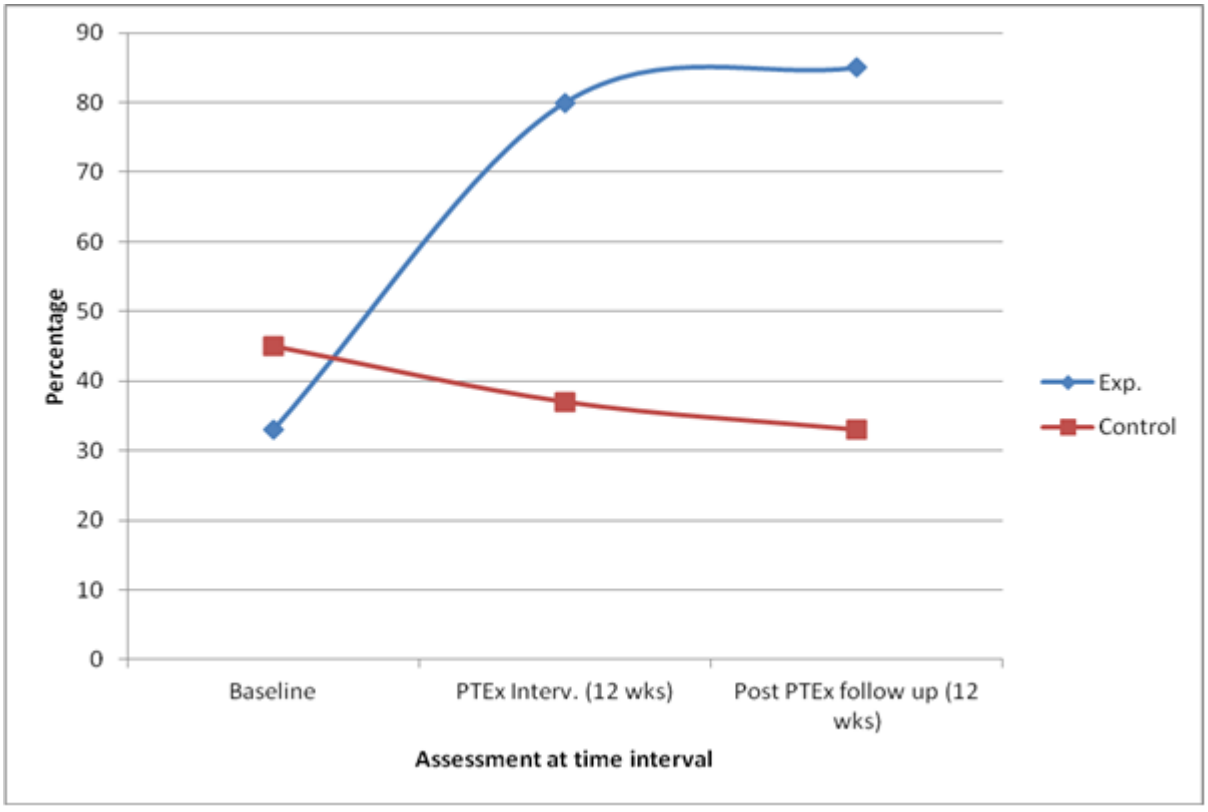
Differences in PN symptom severity: baseline; p= 0.20, at 12 weeks; p<0.001, and 24 weeks; p<0.001.

Figure 3: The difference and change in percentage of participants who improved from severe to mild/none PN symptoms, between the groups

The participants improved from severe PN symptoms to mild or none. The above figure demonstrates the percentage increase of participants who improved. At baseline, there were 60% and 55% of participants with PN symptoms for control and experimental groups, respectively. There were statistically significant differences between the groups, with improvement in the intervention group compared to the control group after 12 weeks of PTExs (85% vs 62%; p<0.001) and 12 weeks post intervention (76% vs 58%; p<0.001).

6.3.1.2 Effect of PTExs on the distribution of PN symptoms to parts of the lower extremity

Usually the PN symptoms of DSP type are distributed to the lower extremity in a "stocking" pattern, however in cases of severe symptoms; the participants had radiation of symptoms above the common region of distribution, such as the lower leg and knee, above the knee and sometimes to the hip region. Figure 4 below indicates the percentage of participants who had an improvement of the radiating PN symptoms above the ankle region, after 12 weeks of PTExs intervention and after 12 weeks post intervention.



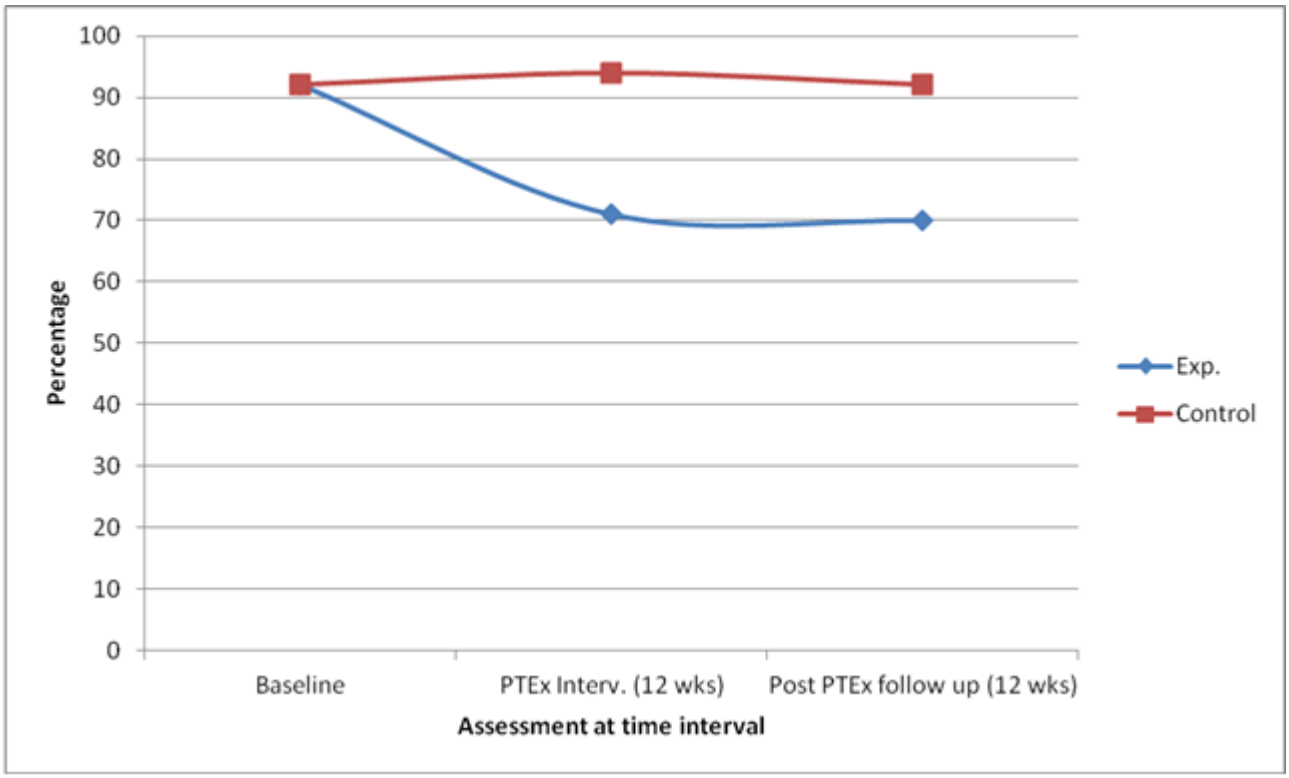
Differences in PN symptoms distribution: baseline; p= 0.190, at 12 weeks; p<0.001, and 24 weeks; p<0.001

Figure 4: Change in percentage of participants who improved in terms of PN symptoms distribution to various parts of the lower extremity

There were significant differences between the groups with an improvement in the experimental group after 12 weeks of PTExs and 12 weeks post intervention; (80% vs 37%; p<0.001) and (85% vs 33%; p<0.001) respectively.

6.3.1.3 The effect of PTExs on the neuropathic pain

Neuropathic pain includes sensations such as; burning, pins & needles and tingling sensations, numbness, painful cold, pains in the form of “electric shocks” hyper and hypo-aesthesia to touch and pin prick, among people with PN. Figure 5 below indicates the differences between the groups and change in percentage of participants with neuropathic pain from baseline to 12 weeks of intervention and 12 weeks post intervention.



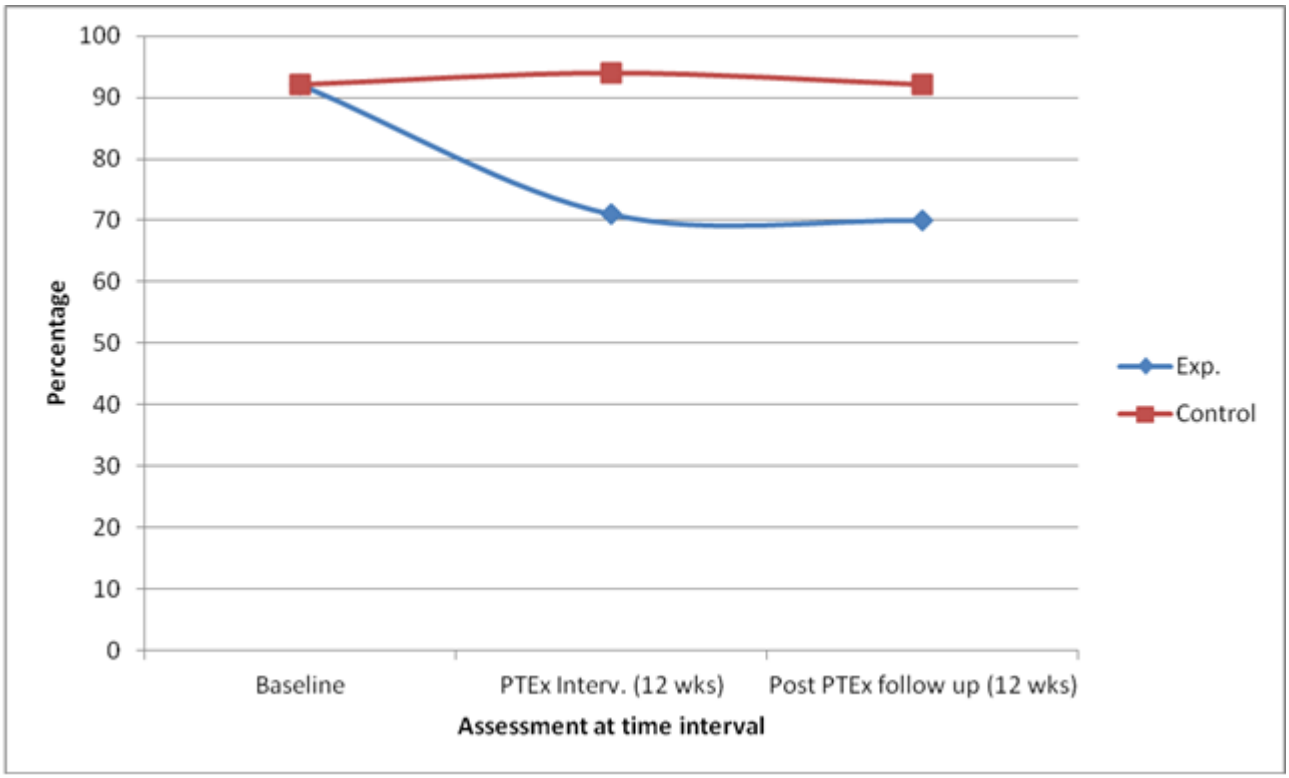
Differences in neuropathic pain; at 12 weeks; p<0.005, and 24 weeks; p<0.005

Figure 5: The change from higher to lower percentages of participants with neuropathic pain for the intervention group

There was a statistically significant difference in improvement of the peripheral neuropathic pains in the intervention group compared to the control group, which is evident with the reduced percentages of participants still presenting with pain, after 12 weeks of the PTExs (71% vs 94; $p<0.005$) and 12 weeks post intervention (70% vs 92%; $p<0.005$).

6.3.1.4.1 The effect of physiotherapeutic exercises on sense of vibration

Sense of vibration was one of the objective measures for the diagnosis of PN. Figure 6 below indicates whether there was a change in terms of improvement of the sense of vibration from none/severely reduced to normal or minimally reduced.



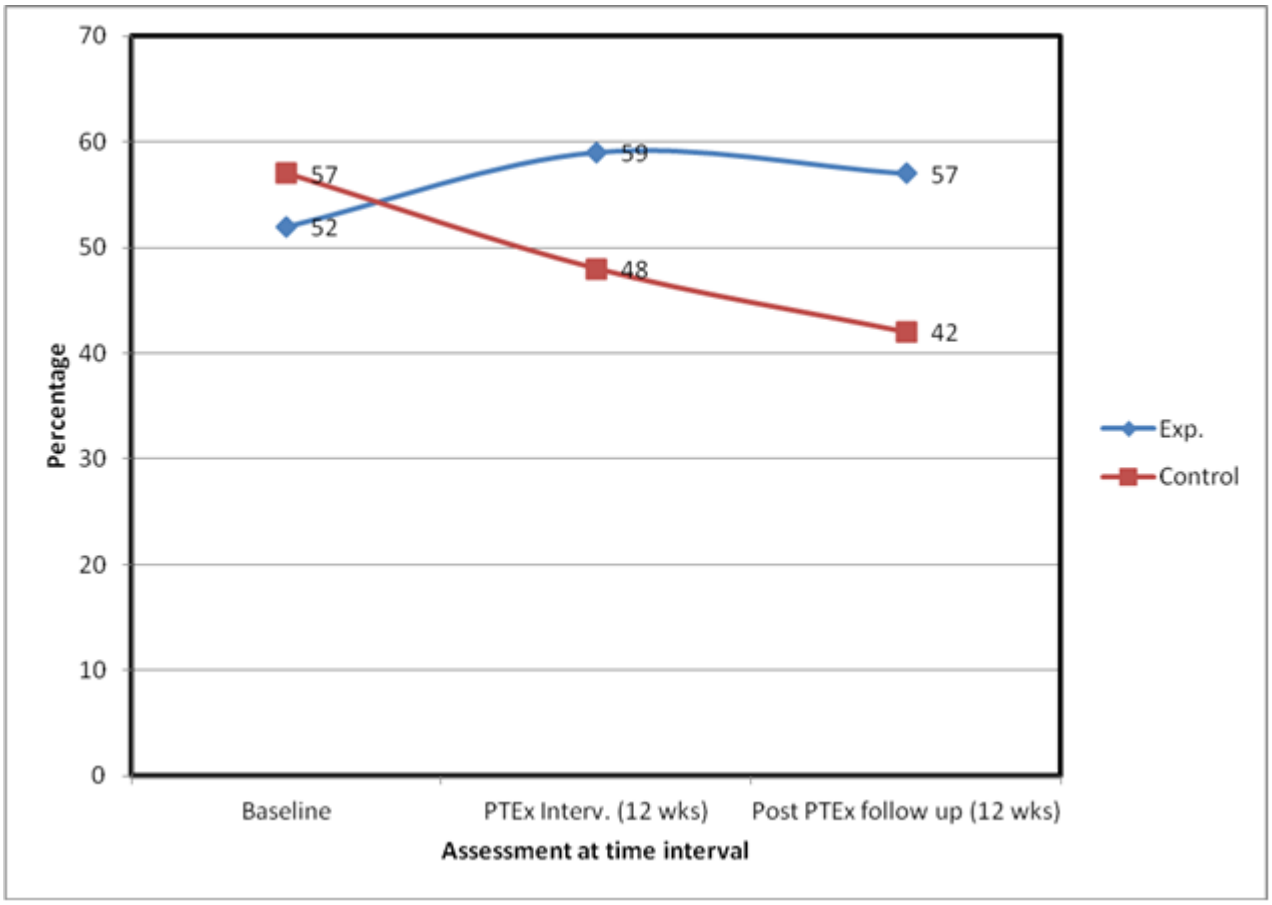
Differences in sense of vibration; baseline; p= 0.58, at 12 weeks; p =0.26, and 24 weeks; p = 0.16.

Figure 6: Changes from severely reduced/none, to normal/minimally reduced vibration sense

There were no significant differences in improvement in the sense of vibration from severely reduced/none to minimally reduced or normal sense of vibration, between the two groups after 12 weeks of PTExs intervention and 12 weeks post intervention, (59% vs 48%, p=0.26) and (57% vs 42%, p=0.16)

6.3.1.4.2 The effects of PTExs on ankle tendon reflex

Figure 7 below indicates the results of the changes in terms of improvement of the ankle tendon reflex from no reflex to reduced /normal reflex.



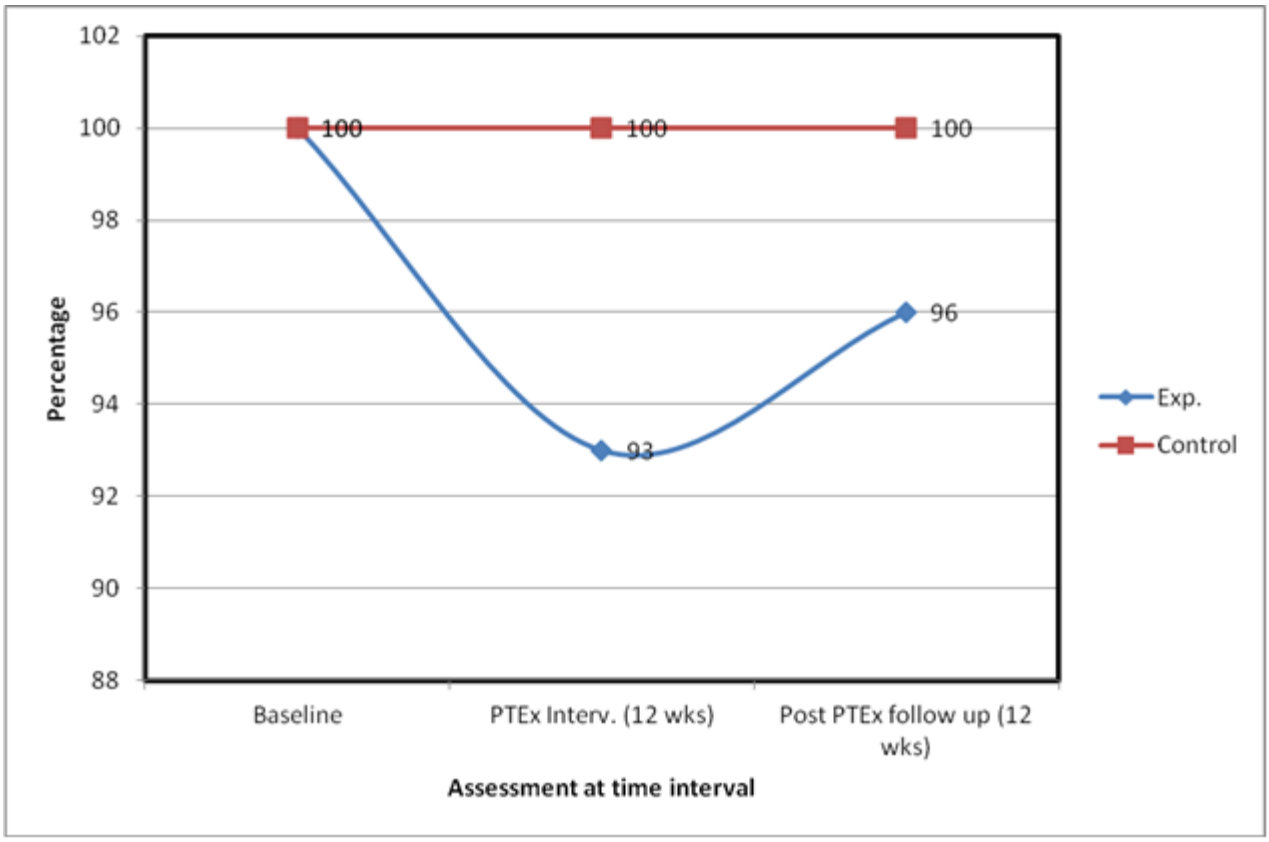
Differences in the ankle tendon reflex; baseline; p= 0.54, at 12 weeks; p=0.10, and 24 weeks; p=0.06.

Figure 7: Improvement in ankle tendon reflex from "no reflex" to "minimal or normal"

The measure of improvement in the ankle tendon reflex was based on the improvement from "no reflex" to "reduced/normal" because of slight changes that were observed within the reflex scores. There were very few participants who gained back the reflex from "none" and or "reduced", to "normal" reflex hence reduced and normal reflex was used to define improvement/change for the reflex. There were no differences in improvement between the two groups, (87% vs 75%; p=0.10) after 12 weeks and (83% vs 68%; p=0.06) after 12 weeks post intervention.

6.3.1.6 The effect of physiotherapeutic exercises on the overall diagnosis of PN

Figure 8 below indicates the changes in the percentages of participants who were still diagnosed with PN at the three assessments.



PN differences; at 12 weeks; p<0.05, and 24 weeks; p = 0.13

Figure 8: Change in the percentages of participants still with PN

Every participant who entered into the intervention study was diagnosed with PN. Seven percent of the participants in the experimental group were no longer diagnosed with PN post intervention. There were differences after 12 weeks between the experimental and control group; whereby 93% still had PN vs 100% (p<0.05), respectively. There was a non-statistically significant change observed between the intervention and the control group 12 weeks post intervention (96% vs 100%; p=0.13),

6.3.2 The effect of PTExs on the lower extremity functional limitations measures

The results for each activity score of the lower extremity functional limitations in means and standard deviations are presented in Table 20 and the overall measure of function is presented in Table 21 below.

Table 20: Comparison of participants' Lower Extremity Functional Limitations; at baseline, 12 weeks of PTExs and 12 post the PTExs intervention (n=120)

Activity limitation	At baseline			At 12 weeks of PTExs for exp group			At 12 weeks post PTExs intervention		
	Experimental	Control	p-value	Experimental	Control	p-value	Experimental	Control	p-value
Doing any usual work	1.8(±0.8)	2.1 (±0.9)	0.16	3.1(±0.7)	1.7 (±0.9)	<0.001	3.3(±0.7)	1.6 (±0.9)	<0.001
Hobbies, Recreational and sporting	1.9 (±0.9)	2.1 (±0.9)	0.15	3.1 (±0.7)	1.7 (±0.9)	<0.001	3.3 (±0.8)	1.6 (±1.0)	<0.001
Getting into or out of the bath	1.9(±0.9)	2.1(±1.0)	0.36	3.1(±0.8)	1.7 (±0.9)	<0.001	3.2(±0.8)	1.6(±1.0)	<0.001
Walking between rooms	2.5(±0.9)	2.7(±0.7)	0.32	3.2(±0.8)	2.1 (±0.6)	<0.001	3.2(±0.8)	2.1(±0.8)	<0.001
Putting on any kind of shoes or socks	1.8(±0.9)	1.9(±0.9)	0.37	3.1(±0.8)	1.6(±1.0)	<0.001	3.2(±0.8)	1.5(±1.0)	<0.001
Squatting	1.7(±1.0)	2.0(±1.0)	0.13	3.1(±0.8)	1.7(±1.0)	<0.001	3.2(±0.7)	1.4(±0.9)	<0.001
Lifting an object	1.9(±0.9)	1.9(±0.9)	0.77	3.0(±0.8)	1.7 (±0.9)	<0.001	3.2(±0.8)	1.6(±1.1)	<0.001
Doing light activities around home	1.9(±1.0)	2.0(±1.0)	0.80	3.2(±0.8)	1.7 (±1.0)	<0.001	3.3(±0.8)	1.6(±1.0)	<0.001
Doing heavy activities around home	1.9(±1.0)	2.0(±0.9)	0.71	3.1(±0.8)	1.7 (±1.0)	<0.001	3.3(±0.8)	1.5(±1.0)	<0.001
Getting into or out of a car/taxi.	2.0(±1.0)	1.9(±1.0)	0.85	3.1(±0.8)	1.6 (±0.9)	<0.001	3.3(±0.9)	1.5(±1.0)	<0.001
Walking across between buildings	2.1(±1.0)	2.2(±0.8)	0.97	3.1(±0.7)	1.6 (±0.9)	<0.001	3.3(±0.7)	1.5(±0.9)	<0.001
Walking a Km	1.9(±0.9)	1.9(±0.9)	0.64	3.1(±0.8)	1.6 (±0.9)	<0.001	3.2(±1.0)	1.5(±1.0)	<0.001
Going up or down 10 stairs	1.7(±0.9)	2.0(±0.9)	0.78	3.1(±0.8)	1.5 (±0.9)	<0.001	3.2(±0.9)	1.4(±0.9)	<0.001
Standing for 1 hour	1.7(±0.9)	0.8(±1.0)	0.47	3.0(±0.8)	1.5 (±0.9)	<0.001	3.1(±0.9)	1.4(±1.0)	<0.001
Sitting for 1 hour	1.6(±0.9)	1.7(±0.9)	0.44	3.0(±0.8)	1.5 (±0.8)	<0.001	3.2(±0.8)	1.4(±0.9)	<0.001
Fast walking on even ground	1.7(±0.9)	1.9(±0.9)	0.56	3.1(±0.8)	1.7 (±0.9)	<0.001	3.2(±0.9)	1.4(±0.9)	<0.001
Fast walking on uneven ground	1.6(±0.8)	1.7(±0.9)	0.37	3.0(±0.8)	1.4 (±0.8)	<0.001	3.2(±0.9)	1.4(±0.9)	<0.001
Making sharp turns while walking	1.6(±0.9)	1.7(±0.9)	0.59	3.0(±0.8)	1.4 (±0.8)	<0.001	3.1(±0.8)	1.4(±0.9)	<0.001
Standing up fast from squatting	1.7(±0.9)	1.9(±0.9)	0.21	3.0(±0.9)	1.5 (±0.9)	<0.001	3.2(±0.9)	1.6(±1.0)	<0.001
Turning in bed	2.4(±0.9)	2.6(±0.9)	0.37	3.3(±0.8)	2.2 (±0.7)	<0.001	3.4(±0.7)	1.8(±0.8)	<0.001

Data presented in means (±SD)

Table 20 above demonstrates that there were no differences in the activities of the LEFLs at the baseline assessment ($p>0.05$). Statistically significant differences ($p<0.001$) were observed in the average scores of all activities between the experimental and control groups after 12 weeks of PTExs and after 12 weeks post intervention. Improvements in function were seen in the experimental group after 12 weeks of PTExs intervention and 12 weeks post intervention.

6.3.2.2 Comparison of the lower extremity functional measure between the experimental and control groups

The overall measure of the function of the lower extremity is functional levels of abilities, namely; extremely difficult or unable to perform activity, quite a bit of difficulty, moderate difficulty, a little bit of difficulty and no difficulty. Table 21 below compares the percentages of the participants at the three time interval measurements between the experimental and control groups.

Table 21: Comparison of participants' functional ability at baseline, 12 weeks of PTExs and 12 weeks post PTExs intervention (n=120)

	At baseline			At 12 weeks of PTExs for exp group			At 12 weeks post PTExs intervention		
Measure of function	Experimental	Control	p-value	Experimental	Control	p-value	Experimental	Control	p-value
Extremely difficulty	0(0)	1 (2)		0(0)	6 (10)		0(0)	8 (13)	
Quite a bit of difficulty	35(58)	32 (53)		14(23)	37 (62)		13(21)	35 (58)	
Moderate difficulty	17(28)	20 (33)	0.67	14(23)	12 (20)	<0.001	7(12)	11(19)	<0.001
A little a bit of difficulty	7(12)	7 (12)		28(47)	5 (8)		31(52)	6(10)	
No difficulty	1(2)	0(0)		4(7)	0(0)		9(15)	0(0)	

Table 19 above indicates that there were no significant differences (p=0.67) in the lower extremity functional level between the experimental and control groups of the participants at the baseline assessment. Significant differences were observed for the functional ability level after 12 weeks of PTExs intervention and after 12 weeks post PTExs intervention; (p<0.001). A higher percentage of participants in the experimental group presented higher levels of function "a little or a bit of difficulty" in performing the activities compared to the control. Higher percentages among the participants in the control group presented with a lower level of "quite a bit of difficulty" throughout all three assessments.

6.3.3 The effect of PTExs on the QoL

The facets were categorised (according to the guidelines of WHO; in Chapter 3) into the domains; physical health, psychological health, social relationships, environmental and overall QoL, domains (Table 22).

6.3.3.1 The effects of PTExs on the facets of QoL

The results on the effects of PTExs on the facets indicated in Table 20 below.

Table 22: Comparison of participants' facets of QoL; at baseline, Comparison of participants' facets of QoL; at baseline, after 12 and 24 weeks post of intervention (n=120)

	At baseline			At 12 weeks of PTExs for exp group			At 12 weeks post PTExs intervention		
Items / Responses	Experimental	Control	p-value	Experimental	Control	p-value	Experimental	Control	p-value
Physical health domain									
Physical pain and discomfort	3.0 (±0.8)	2.9(±0.8)	0.58	3.5 (±0.9)	3.0(±0.9)	0.01	3.7(±0.8)	3.0 (±1.0)	0.001
Dependence on medication to function	3.1(±0.7)	3.2 (±0.7)	0.54	3.8 (±0.9)	3.5(±0.7)	0.03	3.9 (±0.7)	3.4(±0.8)	0.007
Energy and fatigue	2.6 (±0.6)	2.7(±0.7)	0.50	3.3 (±0.8)	2.7(±0.7)	<0.001	3.4 (±0.8)	2.7(±0.7)	<0.001
Ability to get around	2.6 (±0.7)	2.7(±0.7)	0.32	3.4 (±0.7)	2.6(±0.7)	<0.001	3.6 (±0.7)	2.7(±0.7)	0.001
Sleep and rest	2.6 (±0.7)	2.7(±0.7)	0.43	3.4 (±0.8)	2.5(±0.9)	<0.001	3.6 (±0.8)	2.7(±0.8)	<0.001
Ability to perform your daily activities	2.6 (±0.7)	2.7(±0.7)	0.53	3.5 (±0.7)	2.7(±0.7)	<0.001	3.5 (±0.8)	2.7(±0.8)	0.001
Capacity for work	2.7 (±0.7)	2.8(±0.7)	0.49	3.4 (±0.7)	2.7(±0.7)	<0.001	3.5 (±0.8)	2.7(±0.8)	<0.001
Psychological health domain									
Positive feeling of life	2.6 (±0.6)	2.7(±0.7)	0.50	3.3 (±0.8)	2.7(±0.7)	<0.001	3.4 (±0.8)	2.7(±0.7)	<0.001
Spirituality or personal beliefs	2.9 (±0.7)	2.7(±0.7)	0.84	3.5 (±0.7)	2.6(±0.7)	<0.001	3.4 (±0.8)	2.6(±0.7)	<0.001
Thinking, memory and concentration	2.6 (±0.6)	2.7(±0.7)	0.87	3.4 (±0.7)	2.6(±0.7)	<0.001	3.4 (±0.8)	2.7(±0.7)	<0.001
Bodily image and appearance	2.7 (±0.8)	2.8(±0.7)	0.58	3.5 (±0.8)	2.7(±0.7)	<0.001	3.6 (±0.7)	2.7(±0.7)	<0.001
Self esteem	2.7 (±0.7)	2.7(±0.6)	1.00	3.5 (±0.7)	2.6(±0.7)	<0.001	3.6 (±0.8)	2.7(±0.8)	0.001
Having negative feelings	3.1 (±0.6)	3.1(±0.8)	0.64	4.2 (±0.7)	3.1 (±0.7)	<0.001	4.1 (±0.7)	3.0(±0.7)	0.001
Social relationship domain									
Personal relationships	2.7 (±0.7)	2.7(±0.7)	0.80	3.5 (±0.5)	2.6(±0.7)	<0.001	3.5 (±0.8)	2.8(±0.8)	<0.001
Sexual activity	2.6 (±0.8)	2.6(±0.8)	0.54	3.4 (±0.8)	2.6(±0.7)	<0.001	3.5 (±0.9)	2.7(±0.7)	<0.001
Social support	2.7 (±0.7)	2.8(±0.7)	0.424	3.5 (±0.8)	2.7(±0.7)	<0.001	3.6 (±0.8)	2.7(±0.7)	<0.001
Environmental domain									
Physical safety and security	2.6 (±0.6)	2.7(±0.7)	0.53	3.3 (±0.7)	2.7(±0.7)	<0.001	3.4 (±0.8)	2.7(±0.7)	<0.001
Financial resources	1.7 (±0.7)	1.8(±0.7)	0.61	2.4 (±0.5)	2.3(±0.6)	0.75*	2.4 (±0.5)	2.1(±0.5)	0.002
Healthy physical environment	2.6 (±0.6)	2.7(±0.7)	0.80	2.8 (±0.6)	2.5(±0.5)	0.01	2.8(±0.7)	2.4 (±0.5)	0.003
Opportunity for acquiring new information and skills	2.7 (±0.7)	2.7(±0.7)	0.65	3.5 (±0.8)	2.6(±0.7)	<0.001	3.5(±0.8)	2.7 (±0.7)	<0.001
Participation and opportunity for leisure activities	2.6 (±0.7)	2.7(±0.7)	0.51	3.6 (±0.7)	2.6(±0.6)	<0.001	3.6 (±0.7)	2.7(±0.7)	<0.001
Home environment conditions	2.7 (±0.7)	2.7(±0.6)	0.75	3.5 (±0.7)	2.7(±0.7)	<0.001	3.5 (±0.7)	2.7(±0.7)	<0.001
Access to health services	2.7 (±0.7)	2.7(±0.5)	0.24	3.5 (±0.7)	2.7(±0.7)	<0.001	3.6 (±0.7)	2.7(±0.7)	<0.001
Transport facility	2.7 (±0.7)	2.8(±0.7)	0.35	3.6 (±0.7)	2.8(±0.8)	<0.001	3.7 (±0.7)	2.7(±0.7)	<0.001
Overall quality of life									
Rating of quality of life	2.6 (±0.7)	2.6(±0.8)	0.76	3.4 (±0.8)	2.6(±0.8)	<0.001	3.4 (±0.8)	2.7(±0.6)	<0.001
Satisfaction with general health	2.6 (±0.7)	2.8(±0.7)	0.11	3.3 (±0.8)	2.6(±0.7)	<0.001	3.4 (±0.8)	2.6(±0.7)	<0.001

*Data presented in mean (±SD), * Denotes Non-statistically significant difference in the compared facets between the groups at interval assessments.*

Table 22 above indicates that there were no significant differences for all the facets of QoL between the experimental and control groups, at the baseline assessment. However, significant differences ($p<0.05$) for almost all the facets were observed between the groups after 12 weeks of exercising and 12 weeks post PTExs, with improvement for the intervention group in most of the facets of QoL. The only non-significant difference was in the facet of "financial resources", which appeared at baseline, after 12 weeks ($p=0.75$).

6.3.3.2 Comparison of the QoL domains between the experimental and control groups

The QoL domains were calculated from the total mean scores of the facets (procedures described in Chapter 5) and the results are indicated in Table 23 below.

Table 23: Comparison of participants' QoL; at baseline, after 12 of PTExs and after 12 weeks post intervention (n=120)

Items / Responses	At baseline			At 12 weeks of PTExs for exp group			At 12 weeks post PTExs intervention		
	Experimental	Control	p-value	Experimental	Control	p-value	Experimental	Control	p-value
Physical health domain	11.1(±3.0)	11.1(±2.7)	0.46	14.1(±3.8)	11.3(±3.1)	<0.001	14.5(±3.9)	11.4(±3.3)	<0.001
Psychological health domain	11.4(±2.9)	11.6(±3.2)	0.81	14.3(±3.3)	11.5(±3.3)	<0.001	14.5(±3.8)	11.5(±3.3)	<0.001
Social relationship domain	10.7(±2.0)	10.8(±2.0)	0.87	13.7(±2.0)	10.7(±2.0)	<0.001	14.1(±2.2)	10.9(±2.1)	<0.001
Environmental domain	10.2(±4.1)	10.5(±3.7)	0.30	12.1(±3.5)	10.7(±3.9)	0.10*	13.3(±3.7)	10.4(±4.0)	<0.001
Overall quality of life	10.6(±4.8)	10.8(±5.0)	0.36	13.4(±1.4)	10.4(±1.4)	<0.001	13.6(±1.6)	10.4(±1.3)	<0.001

*Data presented in mean (±SD), * Denotes non statistically significant difference in the compared values*

It was observed that there were no differences ($p>0.05$) at baseline between the groups for all domains, but significant differences in improvements appeared at 12 weeks after PTExs and after 12 weeks post intervention for the experimental group, with the exception for the environmental domain at 12 weeks of PTExs ($p=0.10$). However, this domain (environmental) indicated a difference ($p<0.001$) with improvement for the experimental group at 12 weeks post PTExs intervention

6.4 Factors associated and influencing the change on PN, lower extremity functional limitations and QoL, during and post the PTExs intervention

The effect of PTExs on different measures of PN, lower extremity functional limitations, and QoL, was measured in terms of changes and differences between the experimental and the control groups. The changes and differences observed were the improvements in the PN, lower extremity functional limitations, and QoL, among the experimental group compared to the control group. It is likely that most of the changes were due to the PTExs intervention; however there might be other factors that influenced the changes in the outcomes of PN, lower extremity functional limitations & QoL, during and after the intervention. The influencing factors on the changes in the improvement are described for each outcome of PN, lower extremity functional limitations and QoL, in the sections below;

6.4.1 Factors associated and influencing the changes in improvement of PN, during and post the exercise intervention.

The improvement of PN assessed by the positive changes in the symptoms of the PN. Some factors likely influenced the improvement. The factors tested included; age, gender, marital status, occupation, level of education, duration since HIV diagnosis, CD4 cell count, duration on ARV, ARV combination started with, current ARV regimen combination, ARV regimen changes since started on ART, and the onset of PN symptoms and/signs. Table 24 below illustrates the associated and influencing factors for the change in the improvement of PN.

Table 24: Generalised linear regression with general estimating equation (GEE) for the associated and influencing factors of improvement on PN

Factors	Univariate analysis		Multivariate analysis	
	Univariable (OR)(95% CI)	p-value	Adjusted Odds Ratio (aOR) (95% CI)	p-value
Age/years (Mean±SD)	1.0 (1.0, 1.1)	0.12		
Gender				
Male	0.9(0.5,1.7)	0.75		
Female				
Marital status				
Non married	1.0(ref)			
Married	1.2(0.3, 5.1)	0.77		
Separated/Divorced/Widowed	1.6(0.4, 5.9)	0.51		
Occupation				
Employed	1.0(ref)			
Self-employed/peasant	1.5 (0.6, 3.7)	0.35		
Unemployed	1.7(0.8, 4.0)	0.20		
Level of Education				
No schooling	1.0(ref)			
Primary	0.9 (0.5, 1.7)	0.73		
>=Secondary	0.6(0.3, 1.2)	0.15		
Duration since HIV diagnosis				
Less or equal to 3 years	1.0(ref)			
4 to 6 years	0.5(0.2, 1.2)	0.12	0.4(0.2, 1.0)	0.06
7 and above years	0.4(0.2, 1.0)	0.05	0.4(0.2, 0.9)	0.02*
CD4 cell count				
≤ 350				
351 >	1.4(0.8, 2.3)	0.24		
Duration on ARV				
Less or equal to 3 years	1.0(ref)			
4 to 6 years	0.8(0.5, 1.3)	0.39		
7 and above years	1.1(0.5,2.1)	0.89		
ARV regimen combination started with				
Non D4T containing				
D4T containing	0.7(0.4, 1.2)	0.14		
Current ARV regimens' combination				
Non D4T containing				
D4T containing	0.6(0.3, 1.3)	0.21		
ARV regimen changes since started on ART				
No change				
One or more changes	1.6(1.0, 2.7)	0.05	1.7(1.0, 3.0)	0.04*
The onset of PN symptoms and/Signs				
Before starting on ARVs				
After starting on ARVs	2.1(1.1, 3.8)	0.01	2.2(1.2, 4.2)	<0.01*

* Statistically significant for the factors associated and influencing improvement of PN

Table 24 above indicates the results of factors associated and influencing improvement of PN after 12 weeks and 12 weeks post, PTExs intervention. A univariate analysis was done to determine the factors associated with improvements. There were no demographic factors associated with the improvement. Associated factors were observed among the health related characteristics; such as duration since the participant was diagnosed with HIV, regimen changes and at which point the PN symptoms started (before or after start on ARVs). These factors which were statistically significant in the univariate model reporting odds ratio (OR) were further confirmed with multivariate analysis models with adjusted odds ratios (aOR). The participants who were diagnosed with HIV for seven years and above were likely to have less improvement [OR=0.4, 95%CI (0.2, 1.0); p=0.05 & aOR = 0.4, 95% CI (0.2, 0.9); p=0.02], compared to less or equal to 3 years since the diagnosis. Having changed the ARV regimen was likely to predict improvement (OR=1.6, 95%CI(1.0, 2.7) p=0.05; aOR=1.7, 95%CI(1.0, 3.0) p=0.04) compared to no change and the participants who developed PNS after the start on ARVs were likely to have faster improvements [OR=2.1, 95%CI(1.1, 3.8); p=0.01; & aOR = 2.2, 95%CI(1.2, 4.2); (p<0.01)].

6.4.2 Factors associated and influencing the changes in improvement of lower extremity functional limitations, during and post the exercise intervention

Factors associated with lower extremity functional limitations were also tested in a univariate analysis and confirmed with multivariate analysis models. Table 25 below indicates the results of the associated and influencing factors for the change in the improvement of lower extremity functional limitations

Table 25: Generalised linear regression with general GEE for the associated and influencing factors of improvement on lower extremity functional limitations

Factors	Univariate analysis		Multivariate Analysis	
	Univariate (OR)(95% CI)	p-value	Adjusted Odds Ratio (aOR) (95% CI)	p-value
Age/years (Mean ±SD)	1.0(0.9, 1.0)	0.84		
Gender				
Female				
Male	3.5(1.0, 6.2)	<0.001	3.9(2.0, 7.5)	<0.001*
Marital status				
Non married	1.0(ref)			0.34
Married	3.1(1.7, 5.8)	<0.001	1.4(0.7, 2.9)	
Separated/Divorced/ Widowed	1.7(1.0, 3.0)	0.07	1.0(0.5, 1.8)	0.98
Occupation				
Employed	1.0(ref)			
Self-employed/peasant	0.5 (0.2, 1.0)	0.08		
Unemployed	0.6(0.2, 1.0)	0.11		
Education				
No schooling	1.0(ref)			
Primary	1.5 (0.8, 2.6)	0.17		
>=Secondary	1.2(0.6, 2.2)	0.86		
Duration since HIV diagnosis				
Less or equal to 3 years	1.0(ref)			
4 to 6 years	0.8(0.3, 1.7)	0.49		
7 and above years	0.6(0.3, 1.2)	0.11		
CD4 cell count				
≤ 350				
351 >	0.7(0.2, 0.5)	0.23		
ARV regimen combination started with				
Non D4T containing				
D4T containing	0.6(0.4, 1.0)	0.03	1.0(0.5, 2.0)	0.98
Current ARV regimens' combination				
Non D4T containing				
D4T containing	1.0(0.5, 1.9)	0.95		
ARV regimen changes since started on ART				
No change				
One or more changes	1.4(0.9, 2.3)	0.15		
The onset of PNS and/Signs				
Before starting on ARVs				
After starting on ARVs	1.9(0.9, 4.00)	0.11		
PNS				
Severe				
Mild	4.3(2.7, 6.9)	<0.001	4.8(2.8, 8.0)	<0.001*

* **Statistically significant for the factors associated and influencing improvement of LEFLs**

Gender and PN symptoms significantly predicted the improvement of lower extremity functional limitations during and after the intervention, confirmed with univariate model reporting odds ratio (OR) and were further confirmed with multivariate analysis models with adjusted odds ratios (aOR). The results demonstrate males improved faster [OR=3.5, 95%CI (1.0, 6.2); p<0.001; & aOR = 3.9; 95%CI (2.0, 7.5); p<0.001], compared to females. The odds ration of the participants with mild PNS were 4.8 times greater than the odds ratio of the the participant with severe PNS, in improving; [OR=4.3, 95%CI (2.7, 6.9); p<0.001; & aOR = 4.8, 95%CI (2.8, 8.0) p<0.001].than the ones with severe PN symptoms.

6.4.3 Factors associated and influencing the changes in improvement of QoL overall measure, during and post the exercise intervention

Factors predicting improvement changes in the QoL were tested on the overall measure of QoL, which was calculated from the sum scores of the domains of QoL; the physical, psychological, social relationship and environmental, health domains plus the outcomes on the facets of the overall QoL and health status. A single continuous variable to take the total scores of all the domains of QoL was created, and tested with a multilevel mixed effects linear regression model, against the predicting factors. Table 26 below illustrates the results.

Table 26: Multilevel mixed effects linear regression for the associated and influencing factors of improvement changes on the overall QoL

Predicting factors	Univariate analysis		Multivariate Analysis	
	Unadjusted coef. Corr. (uCC.)(95% CI)	p-value	Adjusted coef. Corr. (aCC.) (95% CI)	p-value
Age/years (Mean±SD)	1.0 (-0.1, 0.3)	0.36		
Gender				
Female				
Male	6.7(3.3, 10.2)	<0.001	6.9(3.5, 10.4)	<0.001*
Marital status				
Non married	1.0(ref)			
Married	0.4(-8.0, 8.8)	0.92		
Separated/Divorced/Widowed	-5.6(-14.0, 3.3)	0.22		
Occupation				
Employed	1.0(ref)			
Self-employed/peasant	-7.0(-12.2,-1.8)	0.008		
Unemployed	-6.8(-10.6,-1.0)	0.018	0.03(-0.8, 0.9)	0.95
Education				
No schooling	1.0(ref)			
Primary	0.8(-2.9, 4.6)	0.65		
>=Secondary	1.4(-2.8, 5.6)	0.51		
Duration since HIV diagnosis				
Less or equal to 3 years	1.0(ref)			
4 to 6 years	-9.2(-14.2, -4.2)	<0.001		
7 and above years	-10.4(-15.2,-5.7)	<0.001	-3.0(-5.0,-1.0)	0.003*
CD4 cell count				
≤ 350				
351 >	1.1(-2.0, 4.2)	0.48		
ARV regimen combination started with				
Non D4T containing				
D4T containing	-3.4(-6.2,-0.6)	0.02	-1.8(-4.5, 1.0)	0.195
Current ARV regimens' combination				
Non D4T containing				
D4T containing	-1.2(-5.3, 2.9)	0.56		
ARV regimen changes since started on ART				
No change				
One or more changes	0.3(-2.8, 3.3)	0.86		
The onset of PN symptoms and/Signs				
Before starting on ARVs				
After starting on ARVs	4.2(-0.6, 9.0)	0.09	3.5(-1.0, 8.0)	0.129
PNS				
Severe				
None/mild	7.0(3.9, 10.0)	<0.001	5.9(2.9, 8.8)	<0.001*

**** Statistically significant for the factors associated and influencing improvement of QoL***

Gender, duration since diagnosis of HIV and PN symptoms are associated with and predict the improvement changes in the overall QoL during and after the intervention

of PTExs. With the multilevel mixed linear regression model, the results show that in terms of gender, males improved faster [uCC=6.7, 95%CI (3.3, 10.2); p<0.001; & aCC = 6.9, 95%CI (3.5, 10.4); p<0.001], compared to females. The participants who were diagnosed with HIV for 7 years and above were likely to have less improvement [uCC=-10.4, 95%CI(-15.2, -5.7); p<0.001; & aCC = -3.0; 95%CI(-5.0, -1.0); p=0.003], compared with those who had been diagnosed in the last 3 or less years, and participants with mild PN symptoms improved their QoL faster [uCC=7.0; 95%CI(3.9, 10.0); p<0.001; & aCC = 5.9; 95%CI(2.9, 8.8); p<0.001] than those with severe PN symptoms.

CHAPTER 7

7.0 DISCUSSION OF RESULTS OF THE INTERVENTION (STUDY 3)

7.1 Introduction

Physical exercise is considered to be a key strategy, by rehabilitation professionals to address the disabling health-related consequences of HIV (O'Brien et al., 2010); (Maharaj and Chetty, 2011). But rehabilitation professionals still lack evidence on the effects of exercise on the management of PN, and the related functional limitations that compromise the QoL of PLHIV, particularly, in resource-limited settings (Apker et al., 2006). Several studies with exercise interventions on PLHIV have been conducted, including studies identified in systematic reviews by Nixon et al., (2002), Nixon et al., (2005) O'Brien et al., (2008), and O'Brien et al., (2010). However, in all of those studies there is a dearth of evidence on the effects of exercise on PN among PLHIV on ART.

The aim of study 3 was to test the effects of physiotherapeutic exercise on PN, related lower extremity functional limitations, and QoL, in PLHIV on ART in Rwanda. A RCT was used to test the effects of the exercise intervention. The intervention included the physiotherapeutic exercises that were identified from the systematic reviews (Nixon et al., 2005); O'Brien et al., 2008 and O'Brien et al., 2010) and that have been used and described as safe for PLHIV.

The overall effect in this study was that the exercise reduced PN symptoms, improved lower extremity functional ability and QoL among PLHIV on ART who exercised for 12 weeks. It is known from the literature and common physiotherapy

practice that therapeutic exercises have beneficial effects in the management of painful neuromuscular conditions, functional activity limitations and improve QoL through enhancing participation in daily life activities (Taylor et al., 2007; Adeniyi et al., 2010), but there is insufficient data from studies that might have tested the effects of exercise on PN symptoms in PLHIV on ART. The few that attempted were pilot studies, which did not use a controls and the results were not conclusive (Sandoval et al., 2010).

The PN symptoms that limited functional mobility and activity of PLHIV in this study were improved with exercise that included stretching as one of the important techniques used (appendix 2; exercise protocol). This resulted in improved activity participation and improved QoL. To my knowledge, this study with RCT is the first one to show that physiotherapeutic exercise can reduce PN symptoms and improve the lower extremity functional ability and QoL in PLHIV on ART in Rwanda and most likely in the whole of Sub Saharan Africa. The findings are similar to the few existing studies, particularly the study by Graham et al. (2007) who found that a community exercise intervention reduced activity limitations among PLHIV with inflammatory peripheral neuropathy type of peripheral neuropathy, however their study was not a RCT.

The significant effects of the physiotherapeutic exercises on the PN symptoms, related lower extremity functional limitations and QoL in PLHIV on ART, are therefore discussed in detail in this chapter. The factors that may have influenced the effects of the exercise during the intervention are highlighted.

7.2 The effects of physiotherapeutic exercise on peripheral neuropathy

There were remarkable improvements in the PN symptoms among PLHIV on ART, who exercised for 12 weeks. Specifically, there were improvements in the neuropathic pain, numbness, paraesthesia and distribution of the symptoms along the lower extremities. The reduced symptoms led to the overall reduced percentage of participants diagnosed with PN at the end of the intervention. This implies that the improvements of PN symptoms observed in the experimental group after 12 weeks of exercise are attributable to the exercise intervention as there were no improvements in the control group (Sandoval et al., 2010).

The mechanism of how exercise reduces symptoms of PN is not yet clear. Nevertheless, the antidepressant effect that has been reported as one of the exercise effects (Schroder et al., 2013; Schuch et al., 2013; Eng and Reime, 2014) might play a role. An antidepressant effect is one of the treatments of choice for neuropathic pain in PLHIV (Lana et al., 2008; Brix Finnerup et al., 2013). Exercise has been known to have effects such as; antidepressant, reduction of anxiety, inducement of sleep in people with insomnia, among others (Salmon, 2001; Suna et al., 2014). The antidepressant effect of exercise is likely a result of the increased blood circulation that enhances the discharge of neuro-chemical pain inhibitors. The discharged pain inhibitors, inhibit the pain receptors by enhancing the closing of the pain gate at the spinal dorsal horn of the small diameter nerves (Baron et al., 2010), thus, relieving the pain.

Additionally, exercise leads to a feeling of relaxation by exercising participants hence improving their mood. In cases of pain, the psychologically feeling of good mood as

a result of exercise inhibits the nociceptive mechanism and release of the neuro-chemical pain inhibitors hence modifying pain perception (Dworkin et al., 2003). Similarly, exercise has been recommended as a complementary non pharmacological treatment for postoperative pain (Topcu and Findik, 2012).

The exercises were prescribed and supervised by a physiotherapist, and the usual therapeutic exercise techniques were applied. These included stretching for joint mobility, isometric strengthening, as well as aerobic exercises for “warm-up” and finally “cool down” at the end of the every session (appendix 2). Stretching exercises after warming-up are known for their effect on improving flexibility (Zakas et al., 2006; O’Sullivan et al., 2009) and enhancing pain free range of movements about a joint to promote better performance (Marek et al., 2005). Neuromuscular flexibility has been reported as a benefit of stretching before performing strength training exercises (Rubini et al., 2007). The stretching exercises might have induced muscle relaxation, nerve stretching and its flexibility, consequently improving pain free movements. For example, most of the participants were able to do squatting activities such as sitting on a pit latrine, and walk up and down stairs, more easily after the intervention which they had found very difficult before the intervention. Therefore, with the participants able to achieve pain free movements they reported reduced PN symptoms.

Furthermore, stretching exercises are reported to improve neural tissue flexibility. The stretching mechanism includes the “sliding and tensioning techniques, which are thought to enhance nerve gliding and restore neural tissue mobility” (Oskay et al., 2010). This may have induced nerve flexibility and mobility (Oskay et al., 2010) that resulted in reduced pain during the performance of activities. Pain is one of the common symptoms that limits the ability to perform activities of daily living (Dorsey

and Morton, 2006). The reduction of the pain as a result of the exercise intervention in this study was a considerable beneficial effect for PLHIV with PN.

Exercise interventions that include mobility and stretching exercises are commonly used to increase the neuromuscular flexibility and hence improve mobility (Stanziano et al., 2009; Sobolewski et al., 2013). A study that used stretching techniques for improvement of a non–flexible piriformis nerve and strengthening of the lower extremity muscles, reported an improvement of the nerve pain and resulted in pain-free movement, and improved functional activity (Tonley et al., 2010). Thus, peripheral nerve injury or compression may make the nerve lose its flexibility which later causes pain on movement. This results in muscle weakness and muscle spasm that further leads to more nerve and muscle pain (Parlak et al., 2014). Therefore, increasing the nerve flexibility with stretching or mobility exercises and muscle strengthening improves the pain, consequently allowing free movement and improved functional activity (Tonley et al., 2010).

To my knowledge, the only study so far that has tested the effects of exercise on neuropathic pain in PLHIV is a pilot study by Sandoval et al. (2010). However, it did not significantly show changes in the pain. The differences in the results of these two studies may be because of the differences in the methodologies. The study by Sandoval and colleagues was a pilot study with few participants (17), and without a control group.

There were no significant improvements found in the PN signs, namely; sense of vibration and ankle tendon reflex. Sense of vibration and tendon reflexes are mediated by large sensory nerves, unlike PN symptoms such as neuropathic pain

which result from small sensory nerve fibre damage (Devigili et al., 2008). In addition, the development of PN signs is progressive and takes some time, though the time frame is uncertain. Consequently, it is possible that the treatment and relief or recovery of PN signs may occur after a longer exercise intervention than the one conducted in this study. The improvements shown with the PN symptoms, may be because the recovery is quicker in small nerve fibres than in large fibres. Hence, the change in the improvement of the PN signs may need to be evaluated after a longer period of intervention.

It appears that the improvement of the PN symptoms was as a result of the improvement in the neuro-tissue flexibility and in mobility, and possibly an improvement in the nerve regeneration or growth. However, as stated above further studies need to investigate and test exercise interventions over prolonged periods of time, to establish if there is an improvement in the recovery of the larger nerve fibres for an improvement in PN signs.

7.4 The effects of exercise on the lower extremity functional limitations

Lower extremity functional ability was one of the outcome measures of interest in this study. There were trends of changes in improvement of the functional ability in the experimental group. Prior to the exercise intervention, the participants in both the experimental and control groups had similar levels of functional abilities; described as “quite a bit of difficulty” in performing the various activities assessed with the LEFS. All functional activity measures in the experimental group after 12 weeks of exercise improved from “quite a bit of difficulty” to a “little a bit of difficulty” and some

to “no difficulty” in performing their daily activities. No change in functional activity measures was observed in the control group. Improvement was maintained in the experimental group at 12 weeks post intervention.

The improvement of the functional ability among the participants in the experimental group may have been as a result of improved lower extremity movements which were earlier restricted/limited by the neuropathic pain and other PN symptoms. For example, after the exercise intervention the participants reported that they were able to move around more, walk longer distances, sit and stand for longer periods because of reduced or no neuropathic pain. The participants with severe PN symptoms had more difficulty in performing their daily activities as measured by the LEFS, than the ones who had mild PN symptoms. This implies that the severely affected PLHIV were almost unable to carry out their routine activities of living, such as walking distances, before the intervention. Similarly, Ellis et al. (2010) found that neuropathic pain was significantly associated with functional limitations in the form of disability and hence affected people’s QoL. The prevention and treatment of neuropathic pain is inadequate and in addition some drugs used for treatment have side effects (Brix Finnerup et al., 2013). For example the long term use of the tricyclic antidepressants is associated with “nausea, sedation, dry mouth, drowsiness, dizziness, blurred vision, weight gain, urinary retention, peripheral oedema, and constipation” (Dworkin et al., 2007). Thus the management of the neuropathic pain to prevent functional limitations and, or disability in PLHIV needs a multidisciplinary approach that specifically includes a non-pharmacological approach. Thus, reducing PN symptoms and especially the neuropathic pain with exercises is a fundamental approach to improve the functional ability, with the aim of promoting functional

independence and reducing the side effects of the pharmacological treatments, in PLHIV with PN.

Although muscle strength was not measured in this study, there is evidence that therapeutic exercise moderately improves muscle strength and stamina in people with PN associated to diabetes (White et al., 2004), and muscle strength in PLHIV (O'Brien et al., 2010). The exercise intervention in this study provided a combination of exercises that included isometric strengthening, mobility and aerobic activities. There is a possibility that this intervention improved their lower extremity muscle strength and endurance, which might have contributed to their improved functional activities. For instance, the participants improved in activities such as getting up from sitting to standing, squatting on pit latrines and walking up stairs, which were difficult to perform prior to the intervention. These findings are similar to other studies which found that exercise improved muscle strength, flexibility and mobility of soft tissues, and stamina among PLHIV (Taylor et al., 2007; O'Brien et al., 2008; O'Brien et al., 2010). Equally, exercise has been shown to improve physical function (Mbada et al., 2013), and strength in the elderly (Souza et al., 2011). However, there has been limited literature specifically on the effects of exercises on functional activities among PLHIV with PN, such as those found in this study. To the author's knowledge this study might be one of the first studies to establish the effects of exercise on functional limitations related to PN in PLHIV on ART.

7.5 The effects of physiotherapeutic exercises on quality of life

The participants who exercised for 12 weeks, improved in most of the facets that comprise the QoL domains. The domains of QoL according to the WHOQOL-BREF, are; physical, psychological, social relationship, environmental, health domains, plus

overall life satisfaction (Gholami et al., 2013). The improvements were observed in all the physical and social relationship domain facets and the overall QoL measures, in the experimental group after the 12 weeks intervention and 12 weeks post intervention.

The improvements in the physical domain included; physical pain and discomfort, dependence on medication to function, energy and fatigue, ability to get around, sleep and rest, ability to perform daily activities, and capacity for work. The possible explanations for the improvement include; improvements in neuropathic pain and other PN symptoms that caused discomfort, as well as reduced severity and distribution of PN symptoms. With such improvements in the PN symptoms and specifically neuropathic pain, participants were able to feel comfortable in their daily activities. For instance, participants reported that were able do their usual work at home, put on socks and “closed shoes”, walk around the home and have a good night’s sleep and rest. The participants with less pain and fewer PN related functional limitations might have felt more independent and less likely to depend on medication to relieve pain.

With improved pain and fewer functional activity limitations, participants were able to perform their usual activities and felt more energetic. As a result, the improved activities enhanced their mobility and their ability to participate in social activities. For example, participants reported that they were able to move around, walk long distances, sit and stand for longer when attending social events such as weddings, funerals, church, and going to markets, visiting friend and relatives, more easily than before the exercise programme. These activities are important in the lives of people in Rwanda as well as elsewhere, and if an individual is unable to participate in such

activities or events, she/he feels disassociated from the community and it affects their QoL. As a result, the participants achieved their lost or reduced former activities and these achievements likely restored their QoL in most of the domains.

Furthermore, participants had less sleep disturbances likely from the neuropathic pain at night and this may have contributed to their improved capacity to work during the day. In addition, the improved mobility that resulted in improved functional activities may have contributed to the improved capacity to work as assessed in the physical domain of their QoL. Such improved activities might have contributed to their working and doing activities on their own leading to improving their income and hence improving their independence. Maharaj and Chetty (2011) similarly showed that rehabilitation with exercise to maximise patients' functional independence, minimises their functional limitations, and increases their functional status, thus improving their QoL.

Although some components of the social domain of QoL such as the social interaction of the participants during the intervention were not assessed, but an improvement as a result of the social interaction and support to each other may have occurred. Possible reasons being that during the exercise sessions, participants might have enjoyed and benefited from the interactions with their peers. They may have shared their life experiences and might have started supporting each other. Social interactions and support for each other are some of the influences that improve psychological well-being (Jia et al., 2004). The interactions and sharing of experiences might have relieved some of the psychological depression, negative feelings, and promoted positive feelings, self-esteem and person beliefs (Skevington, 2002). According to the WHO (2003) psychological well-being is

improved with socialisation, support from peers, friends, family and spouses. Additionally, the improved functional activities such as walking long distances to attend social events, namely; weddings, funerals, church, and going to other public places such as markets, improved their social domain.

Moreover, the improved physical health domain facets such as mobility might have resulted in improved psychological health domain facets. For example, the exercise improved positive feelings about their body image, appearance, and function and this improved their self-esteem. It has been reported in previous studies that physical exercise programmes improve physical health, and improve life satisfaction perceptions in PLHIV (Mutimura et al., 2008; Gomes et al., 2010).

There was improvement in almost all QoL health domains, with the exception of the overall environmental health domain that did not show a significant improvement, at the end of 12 weeks of exercise. This is probably because there was no improvement demonstrated for the financial resources which is one of the important facets of the environmental health domain. According to Skevington (2002) environmental health domain assesses “the influence of factors like financial resources, the work environment, accessibility to health and social care, freedom, security, participation and opportunities for leisure activities”. People would like to have the financial resources that they need to meet their daily needs (WHO, 2003). Participants in this study demonstrated poor financial resources at the end of 12 weeks of exercise, simply because these QoL facets cannot be improved with exercise and are dependent on other social factors.

7.6 The effects of physiotherapeutic exercises at 12 weeks post intervention

The improvement attained by the participants during the 12 weeks of exercise was maintained and could still be demonstrated 12 weeks post exercise, although there was a slight decline compared to the previous improvements at 12 weeks of exercising. The improvement of PN symptoms was maintained and is likely attributable to the probable continuation of exercises by the participants after the structured exercise programme at the centre, though this was not examined. As the participants went through the exercise sessions at the centre, the physiotherapist conducting the sessions educated and encouraged them to continue exercising after the intervention. The main goal of the education was to empower them such that after the intervention the participants would continue exercising on their own. Thus, it was important to evaluate if the exercises taught to the participants, were maintained and still beneficial at 12 weeks post intervention. Importantly, the participants maintained the improvements and further studies could evaluate a home exercise programme among PLHIV with PN. This could encourage PLHIV to continue exercising as a life time strategy to prevent and reduce the impact of PN (Silberberg and Katabira, 2006).

Surprisingly, it was shown in the 12 weeks post intervention evaluation that the financial facet had improved, hence the whole environmental domain also improved. It is not clear how this facet improved. However, although this study did not assess the return to work of the participants after the exercise intervention some participants who did not come back for the assessment at 12 weeks post intervention revealed during the follow up telephone calls that they had gone back to their former activities

and were not able to get time to come back for the follow up assessment at the centre. One of the participants mentioned that he had started up a new business and was unable to get time to come back for the assessment. Another one highlighted that he had gone back to his former employment in a security company and could not get permission to come back for the assessment, while another was a driver and started up again after getting relief from the “pins and needle” symptoms that had disturbed him when driving. It is therefore possible that some participants, who improved during the 12 weeks of exercise, and who did come back for the 12 weeks post intervention assessment had also started gainful employment. Again, among the participants who were re-assessed after the 12 weeks post intervention some reported their improved work activities; for example some reported being able to continue their usual business activities such as those working in public markets. Consequently, such earnings likely improved the financial resources of those who were able to come for assessment, hence demonstrating a significantly improved environmental domain.

Furthermore, improved financial resources might have resulted from the reduced severity of PN symptoms and the improved functional ability. Severity of HIV-related symptoms have been reported to be associated with economic costs and low QoL in PLHIV compared to asymptomatic PLHIV (Lopez-Bastida et al., 2009). This suggests that an exercise intervention to reduce HIV-related disorders such as PN might have an impact on reducing the costs participants might have been incurring for treatment of pain and other PN symptom management, consequently improving their QoL.

7.7 Factors that influenced the improvement during the exercise intervention

There were factors that likely influenced the improvement and these were assessed. Some factors significantly predicted the improvement. These factors include health related characteristics namely; the duration of HIV infection, ART regimen changes and the PN that developed post ART initiation.

The participants diagnosed with HIV for seven and above years were likely to have less improvement as a result of the exercise intervention. Since HIV infection might be one of the causes of PN (Dubey et al., 2013; Gabbai et al., 2013), this implies that living with the infection for a long time results in more severe PN or that prolonged exposure to HIV may render the nerve damage permanent. Robinson-Papp et al. (2012) reported that a long duration of HIV infection is one of the risks for PN. This implies that the duration of HIV infection is a risk for developing PN and hampers the improvement of PN during treatment. Early screening of the PN immediately after a person is diagnosed and treating appropriately is important. This is supported by the participants who had PN for a relatively short period, for example three years and below, improving more than those with PN for four and above years. This means that managing a chronic health condition at an early stage has benefits to the individual in terms of a quicker improvement of the treated condition and thus, is cost-effective, rather than interventions when the health problem is at an advanced stage (Armbruster and Brandeau, 2010; Hutton et al., 2010). PN is a chronic and disabling condition and early management including physiotherapeutic exercises might give relief and better health outcomes.

The participants who developed PN after the start on ART had significantly greater improvements compared to those who developed PN before starting on ART. The participants who developed PN before starting on ART had a longer period with PN than those who developed it later after starting on ART. This means that the longer the duration the person has had PN the longer it takes for the intervention to have health benefits (Armbruster and Brandeau, 2010) such as the improvement of PN symptoms and function. Alternatively, the PN that develops after the start on ART is more likely to be related to ART than HIV. A change in the drug regimen will facilitate improvement of the pain, and with exercise as a supplementary treatment the improvement may be quicker. It is therefore, important to include exercise in addition to drug regimen changes in the management of PN that occurs as a result of ART.

Likewise, the participants in whom the ARV regimen was not changed had more improvement. This is likely because in cases where there were no regimen changes;

- it is either that the PN was not severe or,
- it was not suspected to be augmented with a particular toxic ARV type (Woldemedhin and Wabe, 2012) or,
- the PN had just started.

Usually changing the ARV regimen is one of the strategies used to deal with PN (Sarah and Nath, 2012). However, in some cases, the changing of the regimen does not show an improvement (Gabbai et al., 2013). The probable reasons for non-improvement might be that the neuropathy is not a result of the neurotoxic ART type (Robinson-Papp et al., 2012), and changing the suspected offending drug is not helpful. On the other hand, the neuropathy might have already contributed to other physical impairments such as reduced mobility and muscle weakness. In such cases, the reduced mobility is as result of reduced flexibility of the soft tissues, and

muscle weakness due to the limited active use of muscles because of the neuropathic pain. The treatment approach should include pain management modalities and exercise rehabilitation of the reduced flexibility and muscle weakness.

Gender was associated with and predicted an improvement during and after exercise. Males improved their lower extremity functional ability faster compared to females. It is not clear why males improved faster as this study did not assess the reasons, however, it has been reported that females are affected by PN more severely than males (Mehta et al., 2011), and this may delay their improvement. A related explanation is that females probably have a high body mass index (BMI) which is likely a risk factor for PN. Body mass index is one of the established risk factors for PN among people with diabetes (Tesfaye et al., 2005). In their study, Mutimura et al., (2008) also found that HIV–positive women had higher BMI than men. Additionally, it was hypothesised that females are more likely affected with lower haemoglobin levels than males, in which case this could be an influencing factor for having PN (Mehta et al., 2011). Although this study did not assess the haemoglobin levels, a previous study in Rwanda indicated that haemoglobin levels are lower in HIV-positive women (Munyazesa et al., 2012). However, this study cannot give conclusive reasons as to why gender predicted improvements in PN, as the above factors, namely BMI and haemoglobin levels were not measured.

7.8 Summary, conclusions and implications of the physiotherapeutic exercise effects

The manegement of PN – related to HIV has commoly depended on the use pharmacological agents but they have not yieded substantial relief of the neuropathy. The findings of this study add to the existing body of knowledge in that exercises

prescribed and supervised by physiotherapists are effective in reducing PN symptoms, improving functional ability and related QoL among PLHIV in this era of ART, where people likely live with such complications for their lifetime. Additionally, this study adds to the results of other studies that tested the effects of exercise in PLHIV (Nixon et al., 2002; Nixon et al., 2005; O'Brien et al., 2008 ; O'Brien et al., 2010) for the management of the HIV and ART-related conditions. Specifically, the findings are similar to the study by Mutimura et al. (2008), who evaluated the effects of exercise training on lipodystrophy and QoL in PLHIV in Rwanda. Mutimura and colleagues demonstrated that exercises are safe and cost – effective in improving QoL among PLHIV on ART.

The findings from these two studies can be used to establish exercise programmes that can be integrated into the routine health care and management of HIV and ART-related co-morbidities particularly, PN and lipodystrophy. The exercise programme can be conducted at health facility level (ART clinics) in Rwanda and probably in other resource limited countries, where neurological disorders as a result of HIV are reported to be high (Silberberg and Katabira, 2006).

Functional limitations as results of PN and poor QoL are common challenges for PLHIV, and this study showed improvement of function and QoL with exercise. It should be emphasised that exercise is an important management approach that should be introduced and be used as supplementary PN management in the routine health care of PLHIV.

7.9 Strengths and limitations of the intervention study

7.9.1 Strengths

The outcomes measures used in this intervention were re-validated and adapted to the African culture and environment, particularly the Rwandan. This made the strength of the results which were well captured in the exact local context particularly the functional activities done, and were evaluated with the re-validated LEFS.

The intervention used simple aerobic exercises that are safe, inexpensive and need little equipment other than a room and an instructor. The approach can be easily extended to the community for the prevention of disabling complications associated with HIV.

The use of a RCT, with concealed allocation, blinded assessor and standardised appropriate outcome measures, and a good sample size, were all strengths of this study.

Again, the participation in the exercise intervention study was high with a 93% follow up of participants. This was good compared to most RCTs, in which high rates of dropouts and low adherence rates have been reported (O'Brien et al., 2010). The good adherence rate in this study is possibly attributable to; having a strategic location for the exercise intervention that is in the centre of Kigali city, and from which participants could easily access public transport. Secondly, the scheduled time for the exercise was convenient for most of the participants, both working and non-working, being in the afternoon from 3pm to 5pm. A probable reason for the good follow up of the participants was the regular phone calls to remind them of the

exercise and assessment dates, ensuring that participants felt they were part of an important study.

The study also assessed the sustainability of the exercise benefits at 12 weeks post intervention. Participants maintained the improvements they had achieved during the 12 week exercise period. They were able to demonstrate the improvement at the 12 weeks post intervention assessment, although the improvement had dropped a little from the end of the 12 weeks of the exercise intervention.

7.7.2 Limitations

Participants in the exercise intervention were educated and encouraged to exercise back home after the structured exercises programme at the centre. However, this study did not assess or monitor the exact exercises and frequency of the home-based exercise.

The intervention group might have had more interractions with the investigators than the control group, which may influence the possiblility of “care effect”, thus the intervention group getting greater improvements compared to the control group. It is known and sometimes unavoidable that the therapist lead intervention might lead to participants feel better (Hojat et al., 2011). This study recognises the limitation.

The exercise intervention was conducted in the urban setting and results may be more applicable to participants from urban settings than rural settings.

CHAPTER 8

8.0 SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

8.1 Introduction

This chapter restates the aims and methods of the three studies in summary, and highlights the conclusions drawn from the main findings of the three studies in the thesis. The recommendations specifically focus on suggesting clinical approaches and further research regarding improving the management of PN, the related lower extremity functional limitations and the QoL, among PLHIV on ART.

8.2 Summary of the aims and methods

The primary aim of the study was to establish the effects of physiotherapeutic exercises on PN, related lower extremity functional limitations and the QoL, among PLHIV on ART. However, prior to establishing the effects, two studies namely; study 1 and study 2 were conducted.

Study 1 aimed at re-establishing the validity and reliability of the outcome measures used in the three studies and adapted the measures to the Rwandan environment and cultural contexts. The reliability establishment included the intra and inter-assessor reliability of the LEFS. The lower extremity functional scale was the only outcome measure re-validated and tested for intra and inter-assessor reliability. The re-validation included contextual validation and translating the LEFS from English to Kinyarwanda, the local language in Rwanda. The intra and inter-assessor reliability was carried out in a cross-sectional study of 50 PLHIV on ART attending an ART clinic at an urban health centre. The other outcome measures that included the BPNS and DN4 were piloted and adapted to the local context during the same cross-

sectional study. The re-validated and adapted outcome measures were used in the rest of the studies in this thesis.

Study 2 established the prevalence of PN and its associated functional limitations of the lower extremities and the QoL in PLHIV. Studies 1 and 2, prepared for study 3, which was a randomised controlled trial to test the effects of physiotherapeutic exercises on PN, the associated lower extremity functional limitations and QoL, in PLHIV on ART in Rwanda. The prevalence of PN, its association with the lower extremity functional ability and QoL, were identified through a cross sectional study (Study 2) of 507 PLHIV on ART who were attending eight randomly selected ART clinics from rural and urban health facilities across the provinces and city of Kigali.

The effects of physiotherapeutic exercises were established through an RCT (Study 3). One hundred and twenty (120) PLHIV attending four ART clinics in Kigali were randomly invited from those identified with PN in Study 2. The 120 participants were equally randomised to exercise and control groups. The exercise group underwent 12 weeks of exercise intervention and the post exercise assessment results were compared with the baseline, for both groups. In addition, at 12 weeks post exercise intervention, an assessment was also carried out for both groups to examine the sustainability of the exercise benefits, in the intervention group.

8.3 Conclusions

The conclusions highlight the major findings from each of the three studies that comprised the whole thesis.

8.3.1 Re-established validity and adapted outcome measures for PN, lower extremity functional limitations and QoL, among PLHIV in Rwanda

The LEFS was tested and re-validated to evaluate the lower extremity functional limitations related to PN in PLHIV in Rwanda. The re-validated and test re-tested reliability of LEFS yielded optimal and good reliability. Thus, this study represents the first validation of the LEFS in PLHIV on ART, from English into Kinyarwanda and appropriate adaptation to a specific cultural context. The study demonstrated the importance of validating tools derived from developed world contexts to the African environmental setting.

In addition, the BPNS which is a well-used and considered gold standard tool to assess PN associated with HIV, and DN4 to screen for neuropathic pain, were also adapted for use in Rwanda. WHOQOL-BREF was not re-validated as it had already been adapted and used among PLHIV in Rwanda.

8.3.2 Established prevalence of peripheral neuropathy in Rwanda

The overall prevalence of PN was very high at 59% but differently distributed; higher (78%) in the urban than (40%) in the rural, settings. An older age and living in an urban setting, were the demographic characteristics significantly associated with PN. The findings demonstrate that older aged PLHIV, and those living in urban settings are likely more vulnerable to having PN. The findings can be generalized for both rural and urban dwellers in Rwanda and possibly in other poorly resource-limited settings where the lifestyle of the populations is similar.

8.3.3 Peripheral neuropathy is associated with the functional limitations of the lower extremities and quality of life in PLHIV on ART

Peripheral neuropathy was significantly associated with low performance of functional activities of the lower extremities, and thus resulted in poorer QoL. The functional ability of the lower extremities among PLHIV with PN was lower than those without PN. Having PN likely caused limited mobility of the lower extremities in the group with the neuropathy. Such limitations in mobility eventually contributed to the limitations in the functional activities and eventually led to lower QoL.

Furthermore, participants with PN from urban settings had more difficulty in performing their daily functional activities, than their counterparts from rural settings. This is likely because the PN in urban PLHIV was more prevalent and probably more severe than in rural participants.

8.3.4 The physiotherapeutic exercises benefited PLHIV on ART with PN

Physiotherapeutic exercises improved all the clinical PN symptoms among the participants who exercised for 12 weeks. This implies that the improvements of PN symptoms observed in the experimental group after 12 weeks of exercise are attributable to the exercise intervention as there were no improvements in the control group. Importantly, the improvement of the PN symptoms attained by the participants during the exercise intervention was maintained during the 12 weeks post intervention. This is likely a result of the probable continuation of exercises by the participants after the structured exercise programme at the centre. During the intervention the participants were educated and encouraged to continue exercising after the intervention.

8.3.5 The physiotherapeutic exercises improved the functional ability and QoL of PLHIV on ART with PN

There were trends of changes in improvement of the functional ability among the participants who exercised. No improvement was observed in the functional ability measures among the control group. The change in the improvement was maintained in the exercise group at 12 weeks post exercise intervention. The reduced PN symptoms such as neuropathic pain, muscle tightness and improved flexibility, might have played a role in the improvement of the functional ability. The same effects that began with improved PN symptoms improved functional ability might have resulted in the improved QoL of the exercised group. Thus, the improved QoL was demonstrated in this group after 12 weeks of exercising and at 12 weeks post exercise intervention.

8.3.6 Factors that influenced the improvement during the exercise intervention

The participants, who had HIV infection for the last seven and above years, were likely to have less improvement. Living with the infection for a long time may result in more severe PN, and this negatively affects the improvement of the PN during treatment.

The participants, who had not undergone any change in the ART regimen and those who developed PN after the start on ART, improved more. More males improved their lower extremity functional ability, compared to females. Other studies have shown that females have more severe PN than males, but the findings of this study could not fully explain why males improved faster than females,

8.4 Recommendations and implications

The recommendations are based on the findings of the study and are in two parts, namely; clinical and for further research.

8.4.1 Clinical recommendations

Due to the fact that there is a high prevalence of PN, there is a need for routine screening and evaluation for possible early detection of PN and to plan appropriate management. The re-validated outcome measures in this study are simple and can be used in the screening and evaluations of PN and its related functional activities limitations. The older group (40 years and above years) and those living in urban settings should be prioritised during screening as they are vulnerable to developing PN.

Additionally, as there is poor availability of clinically – oriented evidence on tools to use in routine management of HIV related functional limitations, the validated tools in this study may not only help in the Rwandan setting but also this type of research can be conducted in other settings, specifically in African countries.

As the management of HIV – PN has been commonly depending mainly on pharmacological, the findings of this study open new ways of evidence – informed thinking about treatment option. The study therefore introduces discussions on the role of physiotherapy and rehabilitations in general within the HIV health care. Thus, the study provides a specific guidance on the role of particular physiotherapeutic exercises in the management of HIV – PN. There is therefore a need to start exercise programmes and integrate them into clinical settings such as at ART clinics

in the health facilities, and make exercise part of the routine management for PLHIV identified with PN. The PLHIV on ART should be educated and encouraged to exercises at home. Periodical monitoring and evaluation of the exercise efficiency and sustainability will be needed.

Also this study demonstrates that there is a need for further discussions about making the management of HIV – related conditions beyond the medical model. Thus, there is essential need for Inter-collaboration between the health care professionals who are involved in health care management of PLHIV at the ART clinics and the rehabilitation professionals such as physiotherapists. This will make it possible for early referral and appropriate management for interdisciplinary management. If possible, every ART clinic should have a rehabilitation professional, specifically a physiotherapist who will be in charge of any rehabilitation needs of PLHIV particularly those identified with PN and educate them for the lifestyle changes.

8.4.2 Further Research

Lifestyle, social and behaviour research in longitudinal studies needs to establish the exact factors predicting the occurrence of PN, examples include being physically active versus being inactive, living in urban versus rural areas, or being male or female.

There is a need for further research to establish the mechanism of how exercise improves PN symptoms such as neuropathic pain. This may lead to a better understanding of how important exercises are, in the management of PN, and the associated functional limitations that compromise the QoL of PLHIV.

Furthermore, for the need of better understanding the effects of exercises on the PN and its development in this era of ART, where possible, it is important to carry out a study on the physiological effects of exercise on the toxicity of the ARVs, particularly at the mitochondrial level.

Finally, there is a need to investigate and test the exercise interventions over prolonged periods of time, to establish if there is an improvement in nerve recovery, in particular the larger nerve fibres for the improvement of PN signs.

REFERENCES

A. Casado, X. Badia, E. Consiglio, E. Ferrer, A. González, E. Pedrol, J.M. Gatell, C. Azuaje, J.M. Llibre, M. Aranda, P. Barrufet, J. Martínez-Lacasa, D. Podzamczer, 2004. Health-Related Quality of Life in HIV-Infected Naive Patients Treated with Nelfinavir or Nevirapine Associated with ZDV/3TC (the COMBINE-QoL Substudy). HIV Clin. Trials 5, 132–139. doi:10.1310/EACX-1RFX-41R5-VH45

Abdella, S.H., Wabe, N.T., Yesuf, E.A., 2011. Management of common adverse effects in the era of highly active antiretroviral therapy in south east Ethiopia. North Am. J. Med. Sci. 3, 499–502. doi:10.4297/najms.2011.3499

Adeniyi, A.F., Fasanmade, A.A., Sanya, A.O., Borodo, M., 2010. Neuromusculoskeletal disorders in patients with type 2 diabetes mellitus: outcome of a twelve-week therapeutic exercise programme. Niger. J. Clin. Pract. 13, 403–408.

Adewuya, A.O., Afolabi, M.O., Ola, B.A., Ogundele, O.A., Ajibare, A.O., Oladipo, B.F., Fakande, I., 2008. Relationship between Depression and Quality of Life in Persons with HIV Infection in Nigeria. Int. J. Psychiatry Med. 38, 43–51. doi:10.2190/PM.38.1.d

Agu, K.A., Oparah, A.C., 2013. Adverse drug reactions to antiretroviral therapy: Results from spontaneous reporting system in Nigeria. Perspect. Clin. Res. 4, 117–124. doi:10.4103/2229-3485.111784

Ahmad, M., Goucke, C.R., 2002. Management strategies for the treatment of neuropathic pain in the elderly. Drugs Aging 19, 929–945.

Alfahad, T.B., Nath, A., 2013. Update on HIV-associated neurocognitive disorders. Curr. Neurol. Neurosci. Rep. 13, 387. doi:10.1007/s11910-013-0387-7

Ances, B.M., Vaida, F., Rosario, D., Marquie-Beck, J., Ellis, R.J., Simpson, D.M., Clifford, D.B., McArthur, J.C., Grant, I., McCutchan, J.A., 2009. Role of Metabolic Syndrome Components in HIV Associated Sensory Neuropathy. AIDS Lond. Engl. 23, 2317–2322. doi:10.1097/QAD.0b013e328332204e

Anderson, P.L., Lamba, J., Aquilante, C.L., Schuetz, E., Fletcher, C.V., 2006. Pharmacogenetic Characteristics of Indinavir, Zidovudine, and Lamivudine Therapy in HIV-Infected Adults: A Pilot Study. JAIDS J. Acquir. Immune Defic. Syndr. 42, 441–449. doi:10.1097/01.qai.0000225013.53568.69

Apker, J., Propp, K.M., Zabava Ford, W.S., Hofmeister, N., 2006. Collaboration, Credibility, Compassion, and Coordination: Professional Nurse Communication Skill Sets in Health Care Team Interactions. J. Prof. Nurs. 22, 180–189. doi:10.1016/j.profnurs.2006.03.002

Arcury, T.A., Weir, M.M., Summers, P., Chen, H., Bailey, M., Wiggins, M.F., Bischoff, W.E., Quandt, S.A., 2012. SAFETY, SECURITY, HYGIENE AND

PRIVACY IN MIGRANT FARMWORKER HOUSING. New Solut. J. Environ. Occup. Health Policy NS 22, 153–173. doi:10.2190/NS.22.2.d

Arendt, G., Nolting, T., 2012. [Neuro-AIDS in the cART era]. Fortschr. Neurol. Psychiatr. 80, 450–457. doi:10.1055/s-0032-1313191

Armbruster, B., Brandeau, M.L., 2010. Cost-Effective Control of Chronic Viral Diseases: Finding the Optimal Level of Screening and Contact Tracing. Math. Biosci. 224, 35–42. doi:10.1016/j.mbs.2009.12.006

Arseniou, S., Arvaniti, A., Samakouri, M., 2014. HIV infection and depression. Psychiatry Clin. Neurosci. 68, 96–109. doi:10.1111/pcn.12097

Baigis, J., Korniewicz, D.M., Chase, G., Butz, A., Jacobson, D., Wu, A.W., 2002. Effectiveness of a home-based exercise intervention for HIV-infected adults: a randomized trial. J. Assoc. Nurses AIDS Care JANAC 13, 33–45.

Balducci, S., Iacobellis, G., Parisi, L., Di Biase, N., Calandriello, E., Leonetti, F., Fallucca, F., 2006. Exercise training can modify the natural history of diabetic peripheral neuropathy. J. Diabetes Complications 20, 216–223. doi:10.1016/j.jdiacomp.2005.07.005

Baron, R., Binder, A., Wasner, G., 2010. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 9, 807–819. doi:10.1016/S1474-4422(10)70143-5

Basavaraj, K.H., Navya, M.A., Rashmi, R., 2010. Quality of life in HIV and AIDS. Indian J. Sex. Transm. Dis. 31, 75–80. doi:10.4103/0253-7184.74971

Bhat, V.G., Ramburuth, M., Singh, M., Titi, O., Antony, A.P., Chiya, L., Irusen, E.M., Mtyapi, P.P., Mofoka, M.E., Zibeke, A., Chere-Sao, L.A., Gwadiso, N., Sethathi, N.C., Mbondwana, S.R., Msengana, M., 2010. Factors associated with poor adherence to anti-retroviral therapy in patients attending a rural health centre in South Africa. Eur. J. Clin. Microbiol. Infect. Dis. Off. Publ. Eur. Soc. Clin. Microbiol. 29, 947–953. doi:10.1007/s10096-010-0949-4

Binkley, J.M., Stratford, P.W., Lott, S.A., Riddle, D.L., 1999. The Lower Extremity Functional Scale (LEFS): Scale Development, Measurement Properties, and Clinical Application. Phys. Ther. 79, 371–383.

Biraguma, J., Rhoda, A., 2012. Peripheral neuropathy and quality of life of adults living with HIV and AIDS in the Rulindo district of Rwanda. SAHARA J J. Soc. Asp. HIVAIDS Res. Alliance SAHARA Hum. Sci. Res. Counc. 9, 88–94. doi:10.1080/17290376.2012.683582

Bitran, R.A., Giedion, U., Muñoz, R.A., 2003. The Impact of HIV AND AIDS on Rwanda's Health Sector. Bitran & Associates.

Black, K., 2011. Business Statistics: For Contemporary Decision Making. John Wiley & Sons.

Blalock, A.C., McDaniel, J.S., Farber, E.W., 2002. Effect of employment on quality of life and psychological functioning in patients with HIV AND AIDS. Psychosomatics 43, 400–404.

Botros, D., Somarriba, G., Neri, D., Miller, T.L., 2012. Interventions to Address Chronic Disease and HIV: Strategies to Promote Exercise and Nutrition Among HIV-Infected Individuals. Curr. HIV and AIDS Rep. 9, 351–363. doi:10.1007/s11904-012-0135-7

Bouhassira, D., Letanoux, M., Hartemann, A., 2013. Chronic Pain with Neuropathic Characteristics in Diabetic Patients: A French Cross-Sectional Study. PLoS ONE 8, e74195. doi:10.1371/journal.pone.0074195

Boulle, A., Ford, N., 2007. Scaling up antiretroviral therapy in developing countries: what are the benefits and challenges? Sex. Transm. Infect. 83, 503–505. doi:10.1136/sti.2007.027748

Brix Finnerup, N., Hein Sindrup, S., Staehelin Jensen, T., 2013. Management of painful neuropathies. Handb. Clin. Neurol. 115, 279–290. doi:10.1016/B978-0-444-52902-2.00017-5

Cacchio, A., De Blasis, E., Necozione, S., Rosa, F., Riddle, D.L., di Orio, F., De Blasis, D., Santilli, V., 2010. The Italian version of the Lower Extremity Functional Scale was reliable, valid, and responsive. J. Clin. Epidemiol. 63, 550–557. doi:10.1016/j.jclinepi.2009.08.001

Cade, W.T., Peralta, L., Keyser, R.E., 2004. Aerobic Exercise Dysfunction in Human Immunodeficiency Virus: A Potential Link to Physical Disability. Phys. Ther. 84, 655–664.

Cambiano, V., Lampe, F.C., Rodger, A.J., Smith, C.J., Geretti, A.M., Lodwick, R.K., Puradiredja, D.I., Johnson, M., Swaden, L., Phillips, A.N., 2010. Long-term trends in adherence to antiretroviral therapy from start of HAART: AIDS 24, 1153–1162. doi:10.1097/QAD.0b013e32833847af

Cettomai, D., Kwasa, J.K., Birbeck, G.L., Price, R.W., Cohen, C.R., Bukusi, E.A., Kendi, C., Meyer, A.-C.L., 2013. Screening for HIV-associated peripheral neuropathy in resource-limited settings. Muscle Nerve 48, 516–524. doi:10.1002/mus.23795

Chen, H., Clifford, D.B., Deng, L., Wu, K., Lee, A.J., Bosch, R.J., Riddler, S.A., Ellis, R.J., Evans, S.R., 2013. Peripheral neuropathy in ART-experienced patients: prevalence and risk factors. J. Neurovirol. 19, 557–564. doi:10.1007/s13365-013-0216-4

Chen, W.-T., Shiu, C.-S., Yang, J.P., Simoni, J.M., Fredriksen-Goldsen, K.I., Lee, T.S.-H., Zhao, H., 2013. Antiretroviral Therapy (ART) Side Effect Impacted on Quality of Life, and Depressive Symptomatology: A Mixed-Method Study. J. AIDS Clin. Res. 4, 218. doi:10.4172/2155-6113.1000218

Cherry, C.L., Affandi, J.S., Imran, D., Yunihastuti, E., Smyth, K., Vanar, S., Kamarulzaman, A., Price, P., 2009. Age and height predict neuropathy risk in patients with HIV prescribed stavudine. Neurology 73, 315–320. doi:10.1212/WNL.0b013e3181af7a22

Cherry, C.L., Wesselingh, S.L., Lal, L., McArthur, J.C., 2005. Evaluation of a clinical screening tool for HIV-associated sensory neuropathies. Neurology 65, 1778–1781. doi:10.1212/01.wnl.0000187119.33075.41

Choi, Y., Townend, J., Vincent, T., Zaidi, I., Sarge-Njie, R., Jaye, A., Clifford, D.B., 2011. Neurologic manifestations of human immunodeficiency virus-2: dementia, myelopathy, and neuropathy in West Africa. J. Neurovirol. 17, 166–175. doi:10.1007/s13365-011-0022-9

Ciccolo, J.T., Jowers, E.M., Bartholomew, J.B., 2004. The Benefits of Exercise Training for Quality of Life in HIV and AIDS in the Post-HAART Era. Sports Med. 34, 487–499. doi:10.2165/00007256-200434080-00001

Conn, C., 2012. Young African women must have empowering and receptive social environments for HIV prevention. AIDS Care 1–8. doi:10.1080/09540121.2012.712659

Conradie, F., Mabiletsa, T., Sefoka, M., Mabaso, S., Louw, R., Evans, D., Van Rie, A., 2014. Prevalence and incidence of symmetrical symptomatic peripheral neuropathy in patients with multidrug-resistant TB. South Afr. Med. J. Suid-Afr. Tydskr. Vir Geneeskd. 104, 24–26.

Crystal, S., Fleishman, J.A., Hays, R.D., Shapiro, M.F., Bozzette, S.A., 2000. Physical and role functioning among persons with HIV: results from a nationally representative survey. Med. Care 38, 1210–1223.

Da Silva, J., Bunn, K., Bertoni, R.F., Neves, O.A., Traebert, J., 2013. Quality of life of people living with HIV. AIDS Care 25, 71–76. doi:10.1080/09540121.2012.686594

Dalakas, M.C., 2001. Peripheral neuropathy and antiretroviral drugs. J. Peripher. Nerv. Syst. 6, 14–20. doi:10.1046/j.1529-8027.2001.006001014.x

De França, I.S.X., Coura, A.S., de Sousa, F.S., de Almeida, P.C., Pagliuca, L.M.F., 2013. [Quality of life in patients with spinal cord injury]. Rev. Gaúcha Enferm. EENFUFRGS 34, 155–163.

Deli, G., Bosnyak, E., Pusch, G., Komoly, S., Feher, G., 2013. Diabetic neuropathies: diagnosis and management. Neuroendocrinology 98, 267–280. doi:10.1159/000358728

Devigili, G., Tugnoli, V., Penza, P., Camozzi, F., Lombardi, R., Melli, G., Broglio, L., Granieri, E., Lauria, G., 2008. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. Brain 131, 1912–1925. doi:10.1093/brain/awn093

Dolan, S.E., Frontera, W., Librizzi, J., Ljungquist, K., Juan, S., Dorman, R., Cole, M.E., Kanter, J.R., Grinspoon, S., 2006. Effects of a supervised home-based aerobic and progressive resistance training regimen in women infected with human immunodeficiency virus: a randomized trial. Arch. Intern. Med. 166, 1225–1231. doi:10.1001/archinte.166.11.1225

Dorfman, D., George, M.C., Schnur, J., Simpson, D.M., Davidson, G., Montgomery, G., 2013. Hypnosis for treatment of HIV neuropathic pain: a preliminary report. Pain Med. Malden Mass 14, 1048–1056. doi:10.1111/pme.12074

Dorsey, S.G., Morton, P.G., 2006. HIV peripheral neuropathy: pathophysiology and clinical implications. AACN Clin. Issues 17, 30–36.

Driscoll, S.D., Meininger, G.E., Lareau, M.T., Dolan, S.E., Killilea, K.M., Hadigan, C.M., Lloyd-Jones, D.M., Klibanski, A., Frontera, W.R., Grinspoon, S.K., 2004. Effects of exercise training and metformin on body composition and cardiovascular indices in HIV-infected patients. AIDS Lond. Engl. 18, 465–473.

Dubey, T.N., Raghuvanshi, S.S., Sharma, H., Saxena, R., 2013. HIV neuropathy in pre-HAART patients and it's correlation with risk factors in Central India. Neurol. India 61, 478–480. doi:10.4103/0028-3886.121912

Dudgeon, W.D., Phillips, K.D., Bopp, C.M., Hand, G.A., 2004. Physiological and psychological effects of exercise interventions in HIV disease. AIDS Patient Care STDs 18, 81–98. doi:10.1089/108729104322802515

Dworkin, R.H., O'Connor, A.B., Backonja, M., Farrar, J.T., Finnerup, N.B., Jensen, T.S., Kalso, E.A., Loeser, J.D., Miaskowski, C., Nurmikko, T.J., Portenoy, R.K., Rice, A.S.C., Stacey, B.R., Treede, R.-D., Turk, D.C., Wallace, M.S., 2007. Pharmacologic management of neuropathic pain: Evidence-based recommendations. PAIN 132, 237–251. doi:10.1016/j.pain.2007.08.033

Dworkin RH, Backonja M, Rowbotham MC, et al, 2003. Advances in neuropathic pain: Diagnosis, mechanisms, and treatment recommendations. Arch. Neurol. 60, 1524–1534. doi:10.1001/archneur.60.11.1524

Ellis, R.J., Rosario, D., Clifford, D.B., McArthur, J.C., Simpson, D., Alexander, T., Gelman, B.B., Vaida, F., Collier, A., Marra, C.M., Ances, B., Atkinson, J.H., Dworkin, R.H., Morgello, S., Grant, I., CHARTER Study Group, 2010. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study. Arch. Neurol. 67, 552–558. doi:10.1001/archneurol.2010.76

Eng, J.J., Reime, B., 2014. Exercise for depressive symptoms in stroke patients: a systematic review and meta-analysis. Clin. Rehabil. doi:10.1177/0269215514523631

Evans, S.R., Ellis, R.J., Chen, H., Yeh, T., Lee, A.J., Schifitto, G., Wu, K., Bosch, R.J., McArthur, J.C., Simpson, D.M., Clifford, D.B., 2011. Peripheral

neuropathy in HIV: prevalence and risk factors. AIDS Lond. Engl. 25, 919–928. doi:10.1097/QAD.0b013e328345889d

Fellows, R.P., Byrd, D.A., Elliott, K., Robinson-Papp, J., Mindt, M.R., Morgello, S., 2012. Distal Sensory Polyneuropathy is Associated with Neuropsychological Test Performance among Persons with HIV. J. Int. Neuropsychol. Soc. 18, 898–907. doi:10.1017/S1355617712000707

Ferrari, S., Vento, S., Monaco, S., Cavallaro, T., Cainelli, F., Rizzuto, N., Temesgen, Z., 2006. Human immunodeficiency virus-associated peripheral neuropathies. Mayo Clin. Proc. 81, 213–219. doi:10.4065/81.2.213

Forna, F., Liechty, C.A., Solberg, P., Asiimwe, F., Were, W., Mermin, J., Behumbiize, P., Tong, T., Brooks, J.T., Weidle, P.J., 2007. Clinical toxicity of highly active antiretroviral therapy in a home-based AIDS care program in rural Uganda. J. Acquir. Immune Defic. Syndr. 1999 44, 456–462. doi:10.1097/QAI.0b013e318033ffa1

Fortson, J.G., 2010. Mortality Risk and Human Capital Investment: The Impact of HIV and AIDS in Sub-Saharan Africa. Rev. Econ. Stat. 93, 1–15. doi:10.1162/REST_a_00067

Foster, P.P., Rosenblatt, K.P., Kuljiš, R.O., 2011. Exercise-Induced Cognitive Plasticity, Implications for Mild Cognitive Impairment and Alzheimer's Disease. Front. Neurol. 2. doi:10.3389/fneur.2011.00028

Gabbai, A.A., Castelo, A., Oliveira, A.S.B., 2013a. HIV peripheral neuropathy. Handb. Clin. Neurol. 115, 515–529. doi:10.1016/B978-0-444-52902-2.00029-1

Gaidhane, A.M., Zahiruddin, Q.S., Waghmare, L., Zodpey, S., Goyal, R.C., Johrapurkar, S.R., 2008. Assessing self-care component of activities and participation domain of the international classification of functioning, disability and health (ICF) among people living with HIV and AIDS. AIDS Care 20, 1098–1104. doi:10.1080/09540120701808820

Gakhar, H., Kamali, A., Holodniy, M., 2013. Health-related quality of life assessment after antiretroviral therapy: a review of the literature. Drugs 73, 651–672. doi:10.1007/s40265-013-0040-4

Galantino, M.L., Shepard, K., Krafft, L., Laperriere, A., Ducette, J., Sorbello, A., Barnish, M., Condoluci, D., Farrar, J.T., 2005. The effect of group aerobic exercise and t'ai chi on functional outcomes and quality of life for persons living with acquired immunodeficiency syndrome. J. Altern. Complement. Med. N. Y. N 11, 1085–1092. doi:10.1089/acm.2005.11.1085

Galantino, M.L.A., Eke-Okoro, S.T., Findley, T.W., Condoluci, D., 1999. Use of Noninvasive Electroacupuncture for the Treatment of HIV-Related

Peripheral Neuropathy: A Pilot Study. J. Altern. Complement. Med. 5, 135–142. doi:10.1089/acm.1999.5.135

Gallant, J.E., 2012. Antiretroviral therapy in resource-limited settings: is there still a role for stavudine? Antivir. Ther. 17, 1507–1509. doi:10.3851/IMP2498

Gholami, A., Jahromi, L.M., Zarei, E., Dehghan, A., 2013. Application of WHOQOL-BREF in Measuring Quality of Life in Health-Care Staff. Int. J. Prev. Med. 4, 809–817.

Gomes, R.D., Borges, J.P., Lima, D.B., Farinatti, P.T.V., 2010. Effects of physical exercise in the perception of life satisfaction and immunological function in HIV-infected patients: Non-randomized clinical trial. Rev. Bras. Fisioter. São Carlos São Paulo Braz. 14, 390–395.

Gonzalez-Duarte, A., Robinson-Papp, J., Simpson, D.M., 2008. Diagnosis and Management of HIV-Associated Neuropathy. Neurol. Clin. 26, 821–832. doi:10.1016/j.ncl.2008.04.001

Gore, M., Brandenburg, N.A., Dukes, E., Hoffman, D.L., Tai, K.-S., Stacey, B., 2005. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. J. Pain Symptom Manage. 30, 374–385. doi:10.1016/j.jpainsymman.2005.04.009

Graham, R.C., Hughes, R.A.C., White, C.M., 2007. A prospective study of physiotherapist prescribed community based exercise in inflammatory peripheral neuropathy. J. Neurol. 254, 228–235. doi:10.1007/s00415-006-0335-4

Greeff, M., Uys, L.R., Wantland, D., Makoae, L., Chirwa, M., Dlamini, P., Kohi, T.W., Mullan, J., Naidoo, J.R., Cuca, Y., Holzemer, W.L., 2010. Perceived HIV stigma and life satisfaction among persons living with HIV infection in five African countries: a longitudinal study. Int. J. Nurs. Stud. 47, 475–486. doi:10.1016/j.ijnurstu.2009.09.008

Haanpää, M.L., Backonja, M.-M., Bennett, M.I., Bouhassira, D., Cruccu, G., Hansson, P.T., Jensen, T.S., Kauppila, T., Rice, A.S.C., Smith, B.H., Treede, R.-D., Baron, R., 2009. Assessment of neuropathic pain in primary care. Am. J. Med. 122, S13–21. doi:10.1016/j.amjmed.2009.04.006

Hahn, K., Husstedt, I.W., Arendt G für die Deutsche Neuro-AIDS-Arbeitsgemeinschaft (DNAA), 2010. [HIV-associated neuropathies]. Nervenarzt 81, 409–417. doi:10.1007/s00115-010-2931-x

Hakuzimana A, 2005. Quality of life assessment in adults with HIV infection in the treatment and research aids center (trac) HIV clinic of Kigali. A cross-sectional study. National University of Rwanda, Rwanda.Unpublished Thesis

Hammersla, M., Kapustin, J.F., 2012. Peripheral neuropathy: evidence-based treatment of a complex disorder. Nurse Pract. 37, 32–39; quiz 39–40. doi:10.1097/01.NPR.0000413482.44379.ff

Harmon, J.L., Barroso, J., Pence, B.W., Leserman, J., Salahuddin, N., 2008. Demographic and Illness-Related Variables Associated With HIV-Related Fatigue. J. Assoc. Nurses AIDS Care 19, 90–97. doi:10.1016/j.jana.2007.08.005

Harrison, T.B., Smith, B., 2011a. Neuromuscular manifestations of HIV and AIDS. J. Clin. Neuromuscul. Dis. 13, 68–84. doi:10.1097/CND.0b013e318221256f

Harrison, T.B., Smith, B., 2011b. Neuromuscular manifestations of HIV AND AIDS. J. Clin. Neuromuscul. Dis. 13, 68–84. doi:10.1097/CND.0b013e318221256f

Herrmann, S., McKinnon, E., Hyland, N.B., Lalanne, C., Mallal, S., Nolan, D., Chassany, O., Duracinsky, M., 2013. HIV-related stigma and physical symptoms have a persistent influence on health-related quality of life in Australians with HIV infection. Health Qual. Life Outcomes 11, 56. doi:10.1186/1477-7525-11-56

Hess, J.A., Woollacott, M., 2005. Effect of high-intensity strength-training on functional measures of balance ability in balance-impaired older adults. J. Manipulative Physiol. Ther. 28, 582–590. doi:10.1016/j.jmpt.2005.08.013

Hill, A., Ruxrungtham, K., Hanvanich, M., Katlama, C., Wolf, E., Soriano, V., Milinkovic, A., Gatell, J., Ribera, E., 2007. Systematic review of clinical trials evaluating low doses of stavudine as part of antiretroviral treatment. Expert Opin. Pharmacother. 8, 679–688. doi:10.1517/14656566.8.5.679

Hogan, C., Wilkins, E., 2011. Neurological complications in HIV. Clin. Med. Lond. Engl. 11, 571–575.

Hosegood, V., 2009. The demographic impact of HIV and AIDS across the family and household life-cycle: implications for efforts to strengthen families in sub-Saharan Africa. AIDS Care 21, 13–21. doi:10.1080/09540120902923063

Hou, W.-L., Chen, C.-E., Liu, H.-Y., Lai, Y.-Y., Lee, H.-C., Lee, N.-Y., Chang, C.-M., Chen, P.-L., Ko, W.-C., Shu, B.-C., Ko, N.-Y., 2014. Mediating effects of social support on depression and quality of life among patients with HIV infection in Taiwan. AIDS Care. doi:10.1080/09540121.2013.873764

Hsiung, P.-C., Fang, C.-T., Chang, Y.-Y., Chen, M.-Y., Wang, J.-D., 2005. Comparison of WHOQOL-BREF and SF-36 in patients with HIV infection. Qual. Life Res. 14, 141–150. doi:10.1007/s11136-004-6252-z

Hsiung, P.-C., Fang, C.-T., Wu, C.-H., Sheng, W.-H., Chen, S.-C., Wang, J.-D., Yao, G., 2011. Validation of the WHOQOL-HIV BREF among HIV-infected patients in Taiwan. AIDS Care 23, 1035–1042. doi:10.1080/09540121.2010.543881

Hughes, J., Jelsma, J., Maclean, E., Darder, M., Tinise, X., 2004. The health-related quality of life of people living with HIV and AIDS. Disabil. Rehabil. 26, 371–376. doi:10.1080/09638280410001662932

Hung, C.F., Gibson, S.A., Letendre, S.L., Lonergan, J.T., Marquie-Beck, J.A., Vaida, F., Ellis, R.J., 2008. Impact of long-term treatment with neurotoxic dideoxynucleoside antiretrovirals: implications for clinical care in resource-limited settings. HIV Med. 9, 731–737. doi:10.1111/j.1468-1293.2008.00615.x

Hutton, D.W., So, S.K., Brandeau, M.L., 2010. Cost-Effectiveness of Nationwide Hepatitis B Catch-up Vaccination Among Children and Adolescents in China. Hepatol. Baltim. Md 51, 405–414. doi:10.1002/hep.23310

Hyldahl, R.D., Hubal, M.J., 2013. Lengthening our perspective: Morphological, cellular and molecular responses to eccentric exercise. Muscle Nerve. doi:10.1002/mus.24077

Imam, M.H., Karim, M.R., Ferdous, C., Akhter, S., 2011. Health related quality of life among the people living with HIV. Bangladesh Med. Res. Counc. Bull. 37, 1–6.

Iwuji, C.C., Mayanja, B.N., Weiss, H.A., Atuhumuza, E., Hughes, P., Maher, D., Grosskurth, H., 2011. Morbidity in HIV-1-infected individuals before and after the introduction of antiretroviral therapy: a longitudinal study of a population-based cohort in Uganda. HIV Med. 12, 553–561. doi:10.1111/j.1468-1293.2011.00923.x

Jang, Y., Hsieh, C.-L., Wang, Y.-H., Wu, Y.-H., 2004. A validity study of the WHOQOL-BREF assessment in persons with traumatic spinal cord injury. Arch. Phys. Med. Rehabil. 85, 1890–1895.

Jayakumar, P., Shankar, E.M., Karthikeyan, M., Ravikannan, P., 2012. Lipodystrophy and adrenal insufficiency: potential mediators of peripheral neuropathy in HIV infection? Med. Hypotheses 78, 373–376. doi:10.1016/j.mehy.2011.12.003

Jelsma, J., 2009. Use of the International Classification of Functioning, Disability and Health: A Literature Survey. J. Rehabil. Med. 41, 1–12. doi:10.2340/16501977-0300

Jenkin, P., Koch, T., Kralik, D., 2006. The experience of fatigue for adults living with HIV. J. Clin. Nurs. 15, 1123–1131. doi:10.1111/j.1365-2702.2006.01343.x

Jia, H., Uphold, C.R., Wu, S., Reid, K., Findley, K., Duncan, P.W., 2004. Health-related quality of life among men with HIV infection: effects of social support, coping, and depression. AIDS Patient Care STDs 18, 594–603.

Jin, C., Zhao, G., Zhang, F., Feng, L., Wu, N., 2010. The psychological status of HIV-positive people and their psychosocial experiences in eastern China. HIV Med. 11, 253–259. doi:10.1111/j.1468-1293.2009.00770.x

Kalemli-ozcan, S., 2005. Reversal of the Demographic Transition and Economic Development: Evidence from Africa.

Kallianpur, A.R., Hulgan, T., 2009. Pharmacogenetics of nucleoside reverse-transcriptase inhibitor-associated peripheral neuropathy. Pharmacogenomics 10, 623–637. doi:10.2217/pgs.09.14

Kamerman, P.R., Wadley, A.L., Cherry, C.L., 2012. HIV-associated sensory neuropathy: risk factors and genetics. Curr. Pain Headache Rep. 16, 226–236. doi:10.1007/s11916-012-0257-z

Kampira, E., Kumwenda, J., van Oosterhout, J.J., Dandara, C., 2013. Mitochondrial DNA subhaplogroups L0a2 and L2a modify susceptibility to peripheral neuropathy in Malawian adults on stavudine containing highly active antiretroviral therapy. J. Acquir. Immune Defic. Syndr. 1999. doi:10.1097/QAI.0b013e3182968ea5

Karlsson, M., Nilsson, T., Lyttkens, C.H., Leeson, G., 2010. Income inequality and health: importance of a cross-country perspective. Soc. Sci. Med. 1982 70, 875–885. doi:10.1016/j.socscimed.2009.10.056

Kayirangwa, E., Hanson, J., Munyakazi, L., Kabeja, A., 2006. Current trends in Rwanda's HIV and AIDS epidemic. Sex. Transm. Infect. 82, i27–i31. doi:10.1136/sti.2006.019588

Keswani, S.C., Jack, C., Zhou, C., Höke, A., 2006. Establishment of a rodent model of HIV-associated sensory neuropathy. J. Neurosci. Off. J. Soc. Neurosci. 26, 10299–10304. doi:10.1523/JNEUROSCI.3135-06.2006

Keswani, S.C., Pardo, C.A., Cherry, C.L., Hoke, A., McArthur, J.C., 2002. HIV-associated sensory neuropathies. AIDS Lond. Engl. 16, 2105–2117.

Kim, A.A., Wanjiku, L., Macharia, D.K., Wangai, M., Isavwa, A., Abdi, H., Marston, B.J., Ilako, F., Kjaer, M., Chebet, K., Cock, K.M.D., Weidle, P.J., 2007. Adverse Events in HIV-Infected Persons Receiving Antiretroviral Drug Regimens in a Large Urban Slum in Nairobi, Kenya, 2003-2005. J. Int. Assoc. Physicians AIDS Care JIAPAC 6, 206–209. doi:10.1177/1545109707304494

Kinghorn, A., Kgosidintsi, Schierhout, Gatete, Bwandinga, Rugeiyamu, 2003. Assessment of the Impact of AIDS on the Education Sector in Rwanda. Johannesburg, South Africa.

Kisner, C., Colby, L., 2007. Therapeutic Exercise: Foundations and Techniques, 5 edition. ed. F.A. Davis Company.

Kluding, P.M., Pasnoor, M., Singh, R., Jernigan, S., Farmer, K., Rucker, J., Sharma, N.K., Wright, D.E., 2012. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. J. Diabetes Complications 26, 424–429. doi:10.1016/j.jdiacomp.2012.05.007

Kohli, R.M., Sane, S., Kumar, K., Paranjape, R.S., Mehendale, S.M., 2005. Assessment of quality of life among HIV-infected persons in Pune, India. Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil. 14, 1641–1647.

Kranick, S.M., Nath, A., 2012. Neurologic Complications of HIV-1 Infection and Its Treatment in the Era of Antiretroviral Therapy. Contin. Lifelong Learn. Neurol. 18, 1319–1337. doi:10.1212/01.CON.0000423849.24900.ec

Laast, V.A., Shim, B., Johanek, L.M., Dorsey, J.L., Hauer, P.E., Tarwater, P.M., Adams, R.J., Pardo, C.A., McArthur, J.C., Ringkamp, M., Mankowski, J.L., 2011. Macrophage-Mediated Dorsal Root Ganglion Damage Precedes Altered Nerve Conduction in SIV-Infected Macaques. Am. J. Pathol. 179, 2337–2345. doi:10.1016/j.ajpath.2011.07.047

Lana, R., Lérida, A.I., Mendoza, J.L., 2008. [Treatment of neuropathic pain in HIV-infected patients]. Enfermedades Infecc. Microbiol. Clínica 26, 348–355.

Leow, M.K.-S., Griva, K., Choo, R., Wee, H.-L., Thumboo, J., Tai, E.S., Newman, S., 2013. Determinants of Health-Related Quality of Life (HRQoL) in the Multiethnic Singapore Population – A National Cohort Study. PLoS ONE 8, e67138. doi:10.1371/journal.pone.0067138

Lopez-Bastida, J., Oliva-Moreno, J., Perestelo-Perez, L., Serrano-Aguilar, P., 2009. The economic costs and health-related quality of life of people with HIV and AIDS in the Canary Islands, Spain. BMC Health Serv. Res. 9, 55. doi:10.1186/1472-6963-9-55

Louwagie, G.M., Bachmann, M.O., Meyer, K., Booysen, F.R., Fairall, L.R., Heunis, C., 2007. Highly active antiretroviral treatment and health related quality of life in South African adults with human immunodeficiency virus infection: A cross-sectional analytical study. BMC Public Health 7, 244. doi:10.1186/1471-2458-7-244

Luciano, C.A., Pardo, C.A., McArthur, J.C., 2003. Recent developments in the HIV neuropathies. Curr. Opin. Neurol. 16, 403–409. doi:10.1097/01.wco.0000073943.19076.98

Luma, H.N., Tchaleu, B.C.N., Doualla, M.S., Temfack, E., Sopouassi, V.N.K., Mapoure, Y.N., Djientcheu, V.-P., 2012. HIV-associated sensory neuropathy in HIV-1 infected patients at the Douala General Hospital in Cameroon: a cross-sectional study. AIDS Res. Ther. 9, 35. doi:10.1186/1742-6405-9-35

Magrinelli, F., Zanette, G., Tamburin, S., 2013. Neuropathic pain: diagnosis and treatment. Pract. Neurol. 13, 292–307. doi:10.1136/practneurol-2013-000536

Mahajan, A.P., Sayles, J.N., Patel, V.A., Remien, R.H., Ortiz, D., Szekeres, G., Coates, T.J., 2008. Stigma in the HIV and AIDS epidemic: A review of the literature and recommendations for the way forward. AIDS Lond. Engl. 22, S67–S79. doi:10.1097/01.aids.0000327438.13291.62

Maharaj, S.S., Chetty, V., 2011. Rehabilitation program for the quality of life for individuals on highly active antiretroviral therapy in KwaZulu-Natal, South Africa: a short report. Int. J. Rehabil. Res. Int. Z. Für Rehabil. Rev. Int. Rech. Réadapt. 34, 360–365. doi:10.1097/MRR.0b013e32834d2bab

Marek, S.M., Cramer, J.T., Fincher, A.L., Massey, L.L., Dangelmaier, S.M., Purkayastha, S., Fitz, K.A., Culbertson, J.Y., 2005. Acute Effects of Static and Proprioceptive Neuromuscular Facilitation Stretching on Muscle Strength and Power Output. J. Athl. Train. 40, 94–103.

Margalho, R., Pereira, M., Ouakinin, S., Canavarro, M.C., 2011. [Adherence to HAART, quality of life and psychopathological symptoms among HIV and AIDS infected patients]. Acta Médica Port. 24 Suppl 2, 539–548.

Maritz, J., Benatar, M., Dave, J.A., Harrison, T.B., Badri, M., Levitt, N.S., Heckmann, J.M., 2010. HIV neuropathy in South Africans: frequency, characteristics, and risk factors. Muscle Nerve 41, 599–606. doi:10.1002/mus.21535

Maschke, M., Kastrup, O., Esser, S., Ross, B., Hengge, U., Hufnagel, A., 2000. Incidence and prevalence of neurological disorders associated with HIV since the introduction of highly active antiretroviral therapy (HAART). J. Neurol. Neurosurg. Psychiatry 69, 376–380. doi:10.1136/jnnp.69.3.376

Masterson Creber, R.M., Smeeth, L., Gilman, R.H., Miranda, J.J., 2010. Physical activity and cardiovascular risk factors among rural and urban groups and rural-to-urban migrants in Peru: a cross-sectional study. Rev. Panam. Salud Pública Pan Am. J. Public Health 28, 1–8.

Mbada, C., Onayemi, O., Ogunmoyole, Y., Johnson, O., Akosile, C.O., 2013. Health-related quality of life and physical functioning in people living with HIV and AIDS: a case–control design. Health Qual. Life Outcomes 11, 106. doi:10.1186/1477-7525-11-106

McArthur, J.C., Brew, B.J., Nath, A., 2005. Neurological complications of HIV infection. Lancet Neurol. 4, 543–555. doi:10.1016/S1474-4422(05)70165-4

McGrath, C.J., Njoroge, J., John-Stewart, G.C., Kohler, P.K., Benki-Nugent, S.F., Thiga, J.W., Etyang, A., Chung, M.H., 2012. Increased incidence of symptomatic peripheral neuropathy among adults receiving stavudine- versus zidovudine-based antiretroviral regimens in Kenya. J. Neurovirol. 18, 200–204. doi:10.1007/s13365-012-0098-x

Meholjić-Fetahović, A., 2005. [Complex functional test in juvenile rheumatoid arthritis]. Med. Arh. 59, 373–375.

Mehta, S.A., Ahmed, A., Kariuki, B.W., Said, S., Omasete, F., Mendillo, M., Laverty, M., Holzman, R., Valentine, F., Sivapalasingam, S., 2010. Implementation of a Validated Peripheral Neuropathy Screening Tool in Patients Receiving Antiretroviral Therapy in Mombasa, Kenya. Am. J. Trop. Med. Hyg. 83, 565–570. doi:10.4269/ajtmh.2010.09-0629

Mehta, S.A., Ahmed, A., Laverty, M., Holzman, R.S., Valentine, F., Sivapalasingam, S., 2011. Sex differences in the incidence of peripheral neuropathy among Kenyans initiating antiretroviral therapy. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 53, 490–496. doi:10.1093/cid/cir432

Meyer-Hamme, G., Friedemann, T., 徐莲薇 L.X., Epplée, S., Schroeder, S., 2012. Structured literature review of acupuncture treatment for peripheral neuropathy. J. Acupunct. Tuina Sci. 10, 235–242. doi:10.1007/s11726-012-0611-z

Millogo, A., Lankoandé, D., Yaméogo, I., Yaméogo, A.A., Sawadogo, A.B., 2008. [Polyneuropathies in patients treated with HAART in Bobo-Dioulasso hospital, Burkina Faso]. Bull. Société Pathol. Exot. 1990 101, 11–13.

Minzi, O.M.S., Irunde, H., Moshiro, C., 2009. HIV patients presenting common adverse drug events caused by highly active antiretroviral therapy in Tanzania. Tanzan. J. Health Res. 11, 5–10.

Miranda, J.J., Kinra, S., Casas, J.P., Davey Smith, G., Ebrahim, S., 2008. Non-communicable diseases in low- and middle-income countries: context, determinants and health policy. Trop. Med. Int. Health 13, 1225–1234. doi:10.1111/j.1365-3156.2008.02116.x

Misfeldt, R., Linder, J., Lait, J., Hepp, S., Armitage, G., Jackson, K., Suter, E., 2014. Incentives for improving human resource outcomes in health care: overview of reviews. J. Health Serv. Res. Policy 19, 52–61. doi:10.1177/1355819613505746

Mitro, P., Kotianova, A., Bodnar, J., Skorodensky, M., Valocik, G., 2008. Quality of life and psychological well-being in patients with various pacing modes. Bratisl. Lekárske Listy 109, 260–266.

Mkandla, K., 2013. The effects of progressive resisted exerxcises on performance-oriented mobility in persons with Hiv related poly-Neuropathy (Thesis).

Mkanta, W.N., Uphold, C.R., 2006. Theoretical and methodological issues in conducting research related to health care utilization among individuals with HIV infection. AIDS Patient Care STDs 20, 293–303. doi:10.1089/apc.2006.20.293

Morgello, S., Estanislao, L., Simpson, D., Geraci, A., DiRocco, A., Gerits, P., Ryan, E., Yakoushina, T., Khan, S., Mahboob, R., Naseer, M., Dorfman, D., Sharp, V., Manhattan HIV Brain Bank, 2004. HIV-associated distal sensory polyneuropathy in the era of highly active antiretroviral therapy: the

Manhattan HIV Brain Bank. Arch. Neurol. 61, 546–551. doi:10.1001/archneur.61.4.546

Munyazesa, E., Emile, I., Mutimura, E., Hoover, D.R., Shi, Q., McGinn, A.P., Musiime, S., Muhairwe, F., Rutagengwa, A., Dusingize, J.C., Anastos, K., 2012. Assessment of haematological parameters in HIV-infected and uninfected Rwandan women: a cross-sectional study. BMJ Open 2. doi:10.1136/bmjopen-2012-001600

Mutimura, E., Crowther, N.J., Cade, T.W., Yarasheski, K.E., Stewart, A., 2008a. Exercise training reduces central adiposity and improves metabolic indices in HAART-treated HIV-positive subjects in Rwanda: a randomized controlled trial. AIDS Res. Hum. Retroviruses 24, 15–23. doi:10.1089/aid.2007.0023

Mutimura, E., Stewart, A., Crowther, N.J., Yarasheski, K.E., Cade, W.T., 2008b. The effects of exercise training on quality of life in HAART-treated HIV-positive Rwandan subjects with body fat redistribution. Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil. 17, 377–385. doi:10.1007/s11136-008-9319-4

Mutimura, E., Stewart, A., Rheeder, P., Crowther, N.J., 2007. Metabolic function and the prevalence of lipodystrophy in a population of HIV-infected African subjects receiving highly active antiretroviral therapy. J. Acquir. Immune Defic. Syndr. 1999 46, 451–455.

Mweemba, P., Zeller, R., Ludwick, R., Gosnell, D., 2009. Quality of Life of Zambians Living with HIV & AIDS. Med. J. Zambia 36, 143–150.

Myezwa, H., Stewart, A., Musenge, E., Nesara, P., 2009. Assessment of HIV-positive in-patients using the International Classification of Functioning, Disability and Health (ICF) at Chris Hani Baragwanath Hospital, Johannesburg. Afr. J. AIDS Res. 8, 93–105. doi:10.2989/AJAR.2009.8.1.10.723

Naidoo, P., Peltzer, K., Louw, J., Matseke, G., McHunu, G., Tutshana, B., 2013. Predictors of tuberculosis (TB) and antiretroviral (ARV) medication non-adherence in public primary care patients in South Africa: a cross sectional study. BMC Public Health 13, 396. doi:10.1186/1471-2458-13-396

Nicholas, P.K., Kemppainen, J.K., Canaval, G.E., Corless, I.B., Sefcik, E.F., Nokes, K.M., Bain, C.A., Kirksey, K.M., Sanzero Eller, L., Dole, P.J., Hamilton, M.J., Coleman, C.L., Holzemer, W.L., Reynolds, N.R., Portillo, C.J., Bunch, E.H., Wantland, D.J., Voss, J., Phillips, R., Tsai, Y.-F., Rivero Mendez, M., Lindgren, T.G., Davis, S.M., Gallagher, D.M., 2007a. Symptom management and self-care for peripheral neuropathy in HIV and AIDS. AIDS Care 19, 179–189. doi:10.1080/09540120600971083

Nicholas, P.K., Mauceri, L., Slate Ciampa, A., Corless, I.B., Raymond, N., Barry, D.J., Viamonte Ros, A., 2007b. Distal Sensory Polyneuropathy in the Context of HIV and AIDS. J. Assoc. Nurses AIDS Care 18, 32–40. doi:10.1016/j.jana.2007.05.003

Nixon, S., O'Brien, K., Glazier, R., Tynan, A., 2002. Aerobic exercise interventions for adults living with HIV and AIDS, in: The Cochrane Collaboration (Ed.), The Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, Chichester, UK.

Nixon, S., O'Brien, K., Glazier, R.H., Tynan, A.M., 2005. Aerobic exercise interventions for adults living with HIV and AIDS. Cochrane Database Syst. Rev. CD001796. doi:10.1002/14651858.CD001796.pub2

Njoki, E., Frantz, J., Mpofu, R., 2007. Health-promotion needs of youth with a spinal cord injury in South Africa. Disabil. Rehabil. 29, 465–472. doi:10.1080/09638280600841224

O'Brien, K., Nixon, S., Tynan, A.-M., Glazier, R., 2010. Aerobic exercise interventions for adults living with HIV and AIDS. Cochrane Database Syst. Rev. Online CD001796. doi:10.1002/14651858.CD001796.pub3

O'Brien, K., Tynan, A.-M., Nixon, S., Glazier, R.H., 2008. Effects of progressive resistive exercise in adults living with HIV and AIDS: systematic review and meta-analysis of randomized trials. AIDS Care 20, 631–653. doi:10.1080/09540120701661708

O'Sullivan, K., Murray, E., Sainsbury, D., 2009. The effect of warm-up, static stretching and dynamic stretching on hamstring flexibility in previously injured subjects. BMC Musculoskelet. Disord. 10, 37. doi:10.1186/1471-2474-10-37

Ogbuji, Q.C., Oke, A.E., 2010. Quality of life among persons living with HIV infection in Ibadan, Nigeria. Afr. J. Med. Med. Sci. 39, 127–135.

Oguntibeju, O.O., 2012. Quality of life of people living with HIV and AIDS and antiretroviral therapy. HIVAIDS Auckl. NZ 4, 117–124. doi:10.2147/HIV.S32321

Onokerhoraye, A.G., Maticka-Tyndale, E., HP4RY Team, 2012. HIV prevention for rural youth in Nigeria: background overview. Afr. J. Reprod. Health 16, 25–38.

Oshinaike, O., Akinbami, A., Ojo, O., Ogbera, A., Okubadejo, N., Ojini, F., Danesi, M., 2012. Influence of Age and Neurotoxic HAART Use on Frequency of HIV Sensory Neuropathy. AIDS Res. Treat. 2012. doi:10.1155/2012/961510

Oskay, D., Meriç, A., Kirdi, N., Firat, T., Ayhan, C., Leblebicioğlu, G., 2010. Neurodynamic mobilization in the conservative treatment of cubital tunnel syndrome: long-term follow-up of 7 cases. J. Manipulative Physiol. Ther. 33, 156–163. doi:10.1016/j.jmpt.2009.12.001

Padua, L., Schenone, A., Aprile, I., Benedetti, L., Caliandro, P., Tonali, P., Orazio, E.N., Italian NEUROPA Study Group, 2005. Quality of life and disability

assessment in neuropathy: a multicentre study. J. Peripher. Nerv. Syst. JPNS 10, 3–10. doi:10.1111/j.1085-9489.2005.10103.x

Pahuja, M., Grobler, A., Glesby, M.J., Karim, F., Parker, G., Gumede, S., Naidoo, K., 2012. Effects of a reduced dose of stavudine on the incidence and severity of peripheral neuropathy in HIV-infected adults in South Africa. Antivir. Ther. 17, 737–743. doi:10.3851/IMP2087

Parlak, A., Aytekin, A., Develi, S., Ekinci, S., 2014. Piriformis syndrome: a case with non-discogenic sciatalgia. Turk. Neurosurg. 24, 117–119. doi:10.5137/1019-5149.JTN.7904-13.0

Parry, O., Mieike, J., Latif, A.S., Ray, S., Levy, L.F., Siziya, S., 1997. Peripheral neuropathy in individuals with HIV infection in Zimbabwe. Acta Neurol. Scand. 96, 218–222. doi:10.1111/j.1600-0404.1997.tb00272.x

Pefura-Yone, E.W., Soh, E., Kengne, A.P., Balkissou, A.D., Kuaban, C., 2013. Non-adherence to antiretroviral therapy in Yaounde: prevalence, determinants and the concordance of two screening criteria. J. Infect. Public Health 6, 307–315. doi:10.1016/j.jiph.2013.02.003

Perez, C., Galvez, R., Huelbes, S., Insausti, J., Bouhassira, D., Diaz, S., Rejas, J., 2007. Validity and reliability of the Spanish version of the DN4 (Douleur Neuropathique 4 questions) questionnaire for differential diagnosis of pain syndromes associated to a neuropathic or somatic component. Health Qual. Life Outcomes 5, 66. doi:10.1186/1477-7525-5-66

Perna, F.M., LaPerriere, A., Klimas, N., Ironson, G., Perry, A., Pavone, J., Goldstein, A., Majors, P., Makemson, D., Talutto, C., Schneiderman, N., Fletcher, M.A., Meijer, O.G., Koppes, L., 1999. Cardiopulmonary and CD4 cell changes in response to exercise training in early symptomatic HIV infection. Med. Sci. Sports Exerc. 31, 973–979.

Petroczi, A., Hawkins, K., Jones, G., Naughton, D.P., 2010. HIV Patient Characteristics that Affect Adherence to Exercise Programmes: An Observational Study~!2009-10-07~!2010-02-04~!2010-06-25~! Open AIDS J. 4, 148–155. doi:10.2174/1874613601004010148

Phaladze, N.A., Human, S., Dlamini, S.B., Hulela, E.B., Hadebe, I.M., Sukati, N.A., Makoae, L.N., Seboni, N.M., Moleko, M., Holzemer, W.L., 2005. Quality of life and the concept of “living well” with HIV and AIDS in sub-Saharan Africa. J. Nurs. Scholarsh. Off. Publ. Sigma Theta Tau Int. Honor Soc. Nurs. Sigma Theta Tau 37, 120–126.

Phillips, K.D., Skelton, W.D., Hand, G.A., 2004. Effect of Acupuncture Administered in a Group Setting on Pain and Subjective Peripheral Neuropathy in Persons with Human Immunodeficiency Virus Disease. J. Altern. Complement. Med. 10, 449–455. doi:10.1089/1075553041323678

Phillips, T.J.C., Cherry, C.L., Cox, S., Marshall, S.J., Rice, A.S.C., 2010. Pharmacological treatment of painful HIV-associated sensory neuropathy: a

systematic review and meta-analysis of randomised controlled trials. PloS One 5, e14433. doi:10.1371/journal.pone.0014433

Pucci, G., Reis, R.S., Rech, C.R., Hallal, P.C., 2012. Quality of life and physical activity among adults: population-based study in Brazilian adults. Qual. Life Res. 21, 1537–1543. doi:10.1007/s11136-011-0083-5

Ramírez-Crescencio, M.A., Velásquez-Pérez, L., Ramírez-Crescencio, M.A., Velásquez-Pérez, L., 2013. Epidemiology and trend of neurological diseases associated to HIV and AIDS. Experience of Mexican patients 1995-2009. Clin. Neurol. Neurosurg. 115, 1322–1325. doi:10.1016/j.clineuro.2012.12.018

Rao, D., Chen, W.T., Pearson, C.R., Simoni, J.M., Fredriksen-Goldsen, K., Nelson, K., Zhao, H., Zhang, F., 2012. Social support mediates the relationship between HIV stigma and depression/quality of life among people living with HIV in Beijing, China. Int. J. STD AIDS 23, 481–484. doi:10.1258/ijsa.2009.009428

RBC, 2011. National guidelines for comprehensive care of people living with HIV. Rwanda Biomedical Centre, KIGALI RWANDA.

RBC,, 2013. Progressive increase and accessibility ARVs to PLHIV in Rwanda (RBC, 2013). Rwanda Biomedical Centre, KIGALI RWANDA.

RDHS, 2010. Rwanda Demographic Health Survey. Rwanda National Institute of Statistics, KIGALI RWANDA.

Recent developments in the HIV neuropathies : Current Opinion in Neurology [WWW Document], n.d. URL http://journals.lww.com/co-neurology/Fulltext/2003/06000/Recent_developments_in_the_HIV_neuropathies.22.aspx (accessed 2.4.14).

Renaud-Théry, F., Nguimfack, B.D., Vitoria, M., Lee, E., Graaff, P., Samb, B., Perriëns, J., 2007. Use of antiretroviral therapy in resource-limited countries in 2006: distribution and uptake of first- and second-line regimens. AIDS Lond. Engl. 21 Suppl 4, S89–95. doi:10.1097/01.aids.0000279711.54922.f0

Robinson-Papp, J., Gelman, B.B., Grant, I., Singer, E., Gensler, G., Morgello, S., National NeuroAIDS Tissue Consortium, 2012. Substance abuse increases the risk of neuropathy in an HIV-infected cohort. Muscle Nerve 45, 471–476. doi:10.1002/mus.23231

Robinson-Papp, J., Morgello, S., Vaida, F., Fitzsimons, C., Simpson, D.M., Elliott, K.J., Al-Lozi, M., Gelman, B.B., Clifford, D., Marra, C.M., McCutchan, J.A., Atkinson, J.H., Dworkin, R.H., Grant, I., Ellis, R., 2010. Association of self-reported painful symptoms with clinical and neurophysiologic signs in HIV-associated sensory neuropathy. PAIN 151, 732–736. doi:10.1016/j.pain.2010.08.045

Rubini, E.C., Costa, A.L.L., Gomes, P.P.S.C., 2007. The Effects of Stretching on Strength Performance. Sports Med. 37, 213–224. doi:10.2165/00007256-200737030-00003

Rueda, S., Raboud, J., Rourke, S.B., Bekele, T., Bayoumi, A., Lavis, J., Cairney, J., Mustard, C., 2012. Influence of employment and job security on physical and mental health in adults living with HIV: cross-sectional analysis. Open Med. Peer-Rev. Indep. Open-Access J. 6, e118–126.

Ruhland, J.L., Shields, R.K., 1997. The effects of a home exercise program on impairment and health-related quality of life in persons with chronic peripheral neuropathies. Phys. Ther. 77, 1026–1039.

Rusine, J., Asiimwe-Kateera, B., van de Wijgert, J., Boer, K.R., Mukantwali, E., Karita, E., Gasengayire, A., Jurriaans, S., de Jong, M., Ondoa, P., 2013. Low primary and secondary HIV drug-resistance after 12 months of antiretroviral therapy in human immune-deficiency virus type 1 (HIV-1)-infected individuals from Kigali, Rwanda. PloS One 8, e64345. doi:10.1371/journal.pone.0064345

Ryder, M.I., Nittayananta, W., Coogan, M., Greenspan, D., Greenspan, J.S., 2012. Periodontal disease in HIV and AIDS. Periodontol. 2000 60, 78–97. doi:10.1111/j.1600-0757.2012.00445.x

Sacktor, N., 2002. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. J. Neurovirol. 8 Suppl 2, 115–121. doi:10.1080/13550280290101094

Salmon, P., 2001. Effects of physical exercise on anxiety, depression, and sensitivity to stress: A unifying theory. Clin. Psychol. Rev. 21, 33–61. doi:10.1016/S0272-7358(99)00032-X

Sandoval, R., Roddey, T., Giordano, T.P., Mitchell, K., Kelley, C., 2013. Pain, Sleep Disturbances, and Functional Limitations in People Living with HIV and AIDS-Associated Distal Sensory Peripheral Neuropathy. J. Int. Assoc. Provid. AIDS Care. doi:10.1177/2325957413494237

Sandoval, R., Runft, B., Roddey, T., 2010. Pilot study: does lower extremity night splinting assist in the management of painful peripheral neuropathy in the HIV and AIDS population? J. Int. Assoc. Physicians AIDS Care Chic. Ill 2002 9, 368–381. doi:10.1177/1545109710373828

Scanlon, M.L., Vreeman, R.C., 2013. Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings. HIVAIDS Auckl. NZ 5, 1–17. doi:10.2147/HIV.S28912

Scarsella, A., Coodley, G., Shalit, P., Anderson, R., Fisher, R.L., Liao, Q., Ross, L.L., Hernandez, J.E., 2002. Stavudine-associated peripheral neuropathy in zidovudine-naïve patients: effect of stavudine exposure and antiretroviral experience. Adv. Ther. 19, 1–8.

Schep, N.W.L., van Lieshout, E.M.M., Patka, P., Vogels, L.M.M., 2009. Long-term functional and quality of live assessment following post-traumatic distraction osteogenesis of the lower limb. Strateg. Trauma Limb Reconstr. Online 4, 107–112. doi:10.1007/s11751-009-0070-3

Schifitto, G., McDermott, M.P., McArthur, J.C., Marder, K., Sacktor, N., Epstein, L., Kieburtz, K., Dana Consortium on the Therapy of HIV Dementia and Related Cognitive Disorders, 2002. Incidence of and risk factors for HIV-associated distal sensory polyneuropathy. Neurology 58, 1764–1768.

Schifitto, G., McDermott, M.P., McArthur, J.C., Marder, K., Sacktor, N., McClernon, D.R., Conant, K., Cohen, B., Epstein, L.G., Kieburtz, K., NEAD Consortium, 2005. Markers of immune activation and viral load in HIV-associated sensory neuropathy. Neurology 64, 842–848. doi:10.1212/01.WNL.0000152981.32057.BB

Schroder, S., Beckmann, K., Franconi, G., Meyer-Hamme, G., Friedemann, T., Greten, H.J., Rostock, M., Efferth, T., 2013. Can Medical Herbs Stimulate Regeneration or Neuroprotection and Treat Neuropathic Pain in Chemotherapy-Induced Peripheral Neuropathy? Evid.-Based Complement. Altern. Med. ECAM 2013. doi:10.1155/2013/423713

Schuch, F.B., Pinto, S.S., Bagatini, N.C., Zaffari, P., Alberton, C.L., Cadore, E.L., Silva, R.F., Kruel, L.F.M., 2013. Water-based exercise and quality of life in women: the role of depressive symptoms. Women Health. doi:10.1080/03630242.2013.870634

Schuelter-Trevisol, F., H. Wolff, F., R. Alencastro, P., Grigoletti, S., L. Ikeda, M., B. M. Brandao, A., T. Barcellos, N., C. Fuchs, S., 2012. Physical Activity: Do Patients Infected with HIV Practice? How Much? A Systematic Review. Curr. HIV Res. 10, 487–497. doi:10.2174/157016212802429794

Sherr, L., Lampe, F., Norwood, S., Leake-Date, H., Fisher, M., Edwards, S., Arthur, G., Anderson, J., Zetler, S., Johnson, M., Harding, R., 2007. Successive switching of antiretroviral therapy is associated with high psychological and physical burden. Int. J. STD AIDS 18, 700–704. doi:10.1258/095646207782193821

Shurie, J.S., Deribew, A., 2010. Assessment of the prevalence of distal symmetrical polyneuropathy and its risk factors among HAART-treated and untreated HIV infected individuals. Ethiop. Med. J. 48, 85–93.

Sigal, R.J., Kenny, G.P., Wasserman, D.H., Castaneda-Sceppa, C., 2004. Physical Activity/Exercise and Type 2 Diabetes. Diabetes Care 27, 2518–2539. doi:10.2337/diacare.27.10.2518

Silberberg, D., Katabira, E., 2006. Neurological Disorders, in: Jamison, D.T., Feachem, R.G., Makgoba, M.W., Bos, E.R., Baingana, F.K., Hofman, K.J., Rogo, K.O. (Eds.), Disease and Mortality in Sub-Saharan Africa. World Bank, Washington (DC).

Simpson, D.M., Haidich, A.-B., Schifitto, G., Yiannoutsos, C.T., Geraci, A.P., McArthur, J.C., Katzenstein, D.A., ACTG 291 study team, 2002. Severity of HIV-associated neuropathy is associated with plasma HIV-1 RNA levels. AIDS Lond. Engl. 16, 407–412.

Simpson, D.M., Kitch, D., Evans, S.R., McArthur, J.C., Asmuth, D.M., Cohen, B., Goodkin, K., Gerschenson, M., So, Y., Marra, C.M., Diaz-Arrastia, R., Shriver, S., Millar, L., Clifford, D.B., 2006. HIV neuropathy natural history cohort study Assessment measures and risk factors. Neurology 66, 1679–1687. doi:10.1212/01.wnl.0000218303.48113.5d

Skevington, S.M., 2002. Advancing cross-cultural research on quality of life: observations drawn from the WHOQOL development. World Health Organisation Quality of Life Assessment. Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil. 11, 135–144.

Skevington, S.M., 2012. Is quality of life poorer for older adults with HIV and AIDS? International evidence using the WHOQOL-HIV. AIDS Care 24, 1219–1225. doi:10.1080/09540121.2012.661838

Skevington, S.M., Lotfy, M., O'Connell, K.A., WHOQOL Group, 2004. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil. 13, 299–310.

Skopelitis, E.E., Kokotis, P.I., Kontos, A.N., Panayiotakopoulos, G.D., Konstantinou, K., Kordossis, T., Karandreas, N., 2006. Distal sensory polyneuropathy in HIV-positive patients in the HAART era: an entity underestimated by clinical examination. Int. J. STD AIDS 17, 467–472. doi:10.1258/095646206777689062

Smidt, N., de Vet, H.C.W., Bouter, L.M., Dekker, J., Arendzen, J.H., de Bie, R.A., Bierma-Zeinstra, S.M.A., Helders, P.J.M., Keus, S.H.J., Kwakkel, G., Lenssen, T., Oostendorp, R.A.B., Ostelo, R.W.J.G., Reijman, M., Terwee, C.B., Theunissen, C., Thomas, S., van Baar, M.E., van 't Hul, A., van Peppen, R.P.S., Verhagen, A., van der Windt, D.A.W.M., Exercise Therapy Group, 2005. Effectiveness of exercise therapy: a best-evidence summary of systematic reviews. Aust. J. Physiother. 51, 71–85.

Smyth, K., Affandi, J., McArthur, J., Bowtell-Harris, C., Mijch, A., Watson, K., Costello, K., Woolley, I., Price, P., Wesselingh, S., Cherry, C., 2007. Prevalence of and risk factors for HIV-associated neuropathy in Melbourne, Australia 1993–2006. HIV Med. 8, 367–373. doi:10.1111/j.1468-1293.2007.00478.x

Sobolewski, E.J., Ryan, E.D., Thompson, B.J., 2013. Influence of maximum range of motion and stiffness on the viscoelastic stretch response. Muscle Nerve 48, 571–577. doi:10.1002/mus.23791

Sonya and Anderson, 2006. Physical Therapy for Patients with HIVAIDS. Cardiopulmonary Physical Therapy Journal 17, 103 – 109.

Souza, P.M.L. de, Jacob-Filho, W., Santarém, J.M., Zomignan, A.A., Burattini, M.N., 2011. Effect of progressive resistance exercise on strength evolution of elderly patients living with HIV compared to healthy controls. Clinics 66, 261–266. doi:10.1590/S1807-59322011000200014

SOWELL, R.L., SEALS, B.F., MONEYHAM, L., DEMI, A., COHEN, L., BRAKE, S., 1997. Quality of life in HIV-infected women in the south-eastern United States. AIDS Care 9, 501–512. doi:10.1080/713613191

Stanziano, D.C., Roos, B.A., Perry, A.C., Lai, S., Signorile, J.F., 2009. The effects of an active-assisted stretching program on functional performance in elderly persons: a pilot study. Clin. Interv. Aging 4, 115–120.

Subbaraman, R., Chaguturu, S.K., Mayer, K.H., Flanigan, T.P., Kumarasamy, N., 2007. Adverse effects of highly active antiretroviral therapy in developing countries. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 45, 1093–1101. doi:10.1086/521150

Subramanian, T., Gupte, M.D., Dorairaj, V.S., Periannan, V., Mathai, A.K., 2009. Psycho-social impact and quality of life of people living with HIV and AIDS in South India. AIDS Care 21, 473–481. doi:10.1080/09540120802283469

Suna, J.M., Mudge, A., Stewart, I., Marquart, L., O'Rourke, P., Scott, A., 2014. The effect of a supervised exercise training programme on sleep quality in recently discharged heart failure patients. Eur. J. Cardiovasc. Nurs. J. Work. Group Cardiovasc. Nurs. Eur. Soc. Cardiol. doi:10.1177/1474515114522563

Tapsfield, J., Mathews, T., Lungu, M., van Oosterhout, J.J., 2011. Underreporting of side effects of standard first-line ART in the routine setting in Blantyre, Malawi. Malawi Med. J. J. Med. Assoc. Malawi 23, 115–117.

Taylor, N.F., Dodd, K.J., Shields, N., Bruder, A., 2007. Therapeutic exercise in physiotherapy practice is beneficial: a summary of systematic reviews 2002-2005. Aust. J. Physiother. 53, 7–16.

Tehranzadeh, J., Ter-Oganesyan, R.R., Steinbach, L.S., 2004. Musculoskeletal disorders associated with HIV infection and AIDS. Part II: Non-infectious musculoskeletal conditions. Skeletal Radiol. 33, 311–320. doi:10.1007/s00256-004-0765-y

Tesfaye, S., Chaturvedi, N., Eaton, S.E.M., Ward, J.D., Manes, C., Ionescu-Tirgoviste, C., Witte, D.R., Fuller, J.H., 2005. Vascular Risk Factors and Diabetic Neuropathy. N. Engl. J. Med. 352, 341–350. doi:10.1056/NEJMoa032782

The Effect of HIV and AIDS on Society [WWW Document], n.d. Something. URL http://www.dosomething.org/actnow/tipsandtools/the-effect-hivaids-society (accessed 1.25.14).

Theroux, N., Phipps, M., Zimmerman, L., Relf, M.V., 2013. Neurological complications associated with HIV and AIDS: clinical implications for nursing. J. Neurosci. Nurs. J. Am. Assoc. Neurosci. Nurses 45, 5–13. doi:10.1097/JNN.0b013e318275b1b2

Thomas, B.E., Chandra, S., Selvi, K.J.A., Suriyanarayanan, D., Swaminathan, S., 2009. Gender differences in sexual behaviour among people living with HIV in Chennai, India. Indian J. Med. Res. 129, 690–694.

Titlic, M., Jukic, I., Tonkic, A., Josipovic-Jelic, Z., Boschi, V., Mihalj, M., Punda, A., 2008. Lamotrigine in the treatment of pain syndromes and neuropathic pain. Bratisl. Lekárske Listy 109, 421–424.

Tofthagen, C., Visovsky, C., Berry, D.L., 2012. Strength and balance training for adults with peripheral neuropathy and high risk of fall: current evidence and implications for future research. Oncol. Nurs. Forum 39, E416–424. doi:10.1188/12.ONF.E416-E424

Tonley, J.C., Yun, S.M., Kochevar, R.J., Dye, J.A., Farrokhi, S., Powers, C.M., 2010. Treatment of an individual with piriformis syndrome focusing on hip muscle strengthening and movement reeducation: a case report. J. Orthop. Sports Phys. Ther. 40, 103–111. doi:10.2519/jospt.2010.3108

Topcu, S.Y., Findik, U.Y., 2012. Effect of Relaxation Exercises on Controlling Postoperative Pain. Pain Manag. Nurs. 13, 11–17. doi:10.1016/j.pmn.2010.07.006

Torpy JM, Kincaid JL, Glass RM, 2010. PEripheral neuropathy. JAMA 303, 1556–1556. doi:10.1001/jama.303.15.1556

UNAIDS, 2011. UNAIDS World's Aids day report.

UNAIDS, 2012. UNAIDS Report on the global AIDS epidemic, 2012. WHO, Geneva.

UNAIDS, 2013. UNAIDS report on the global HIV and AIDS epidemic 2013 (HIV and AIDS epidemic global annual report). WHO, Geneva.

Uwimana, J., Struthers, P., 2007. Met and unmet palliative care needs of people living with HIV and AIDS in Rwanda. SAHARA J J. Soc. Asp. HIVAIDS Res. Alliance 4, 575–585.

Uzochukwu, B.S.C., Onwujekwe, O.E., Onoka, A.C., Okoli, C., Uguru, N.P., Chukwuogo, O.I., 2009. Determinants of non-adherence to subsidized anti-retroviral treatment in southeast Nigeria. Health Policy Plan. 24, 189–196. doi:10.1093/heapol/czp006

Van As, M., Myezwa, H., Stewart, A., Maleka, D., Musenge, E., 2009. The International Classification of Function Disability and Health (ICF) in adults

visiting the HIV outpatient clinic at a regional hospital in Johannesburg, South Africa. AIDS Care 21, 50–58. doi:10.1080/09540120802068829

Van Oosterhout, J.J., Mallewa, J., Kaunda, S., Chagoma, N., Njalale, Y., Kampira, E., Mukaka, M., Heyderman, R.S., 2012. Stavudine toxicity in adult longer-term ART patients in Blantyre, Malawi. PloS One 7, e42029. doi:10.1371/journal.pone.0042029

Venkataramana, A.B., Skolasky, R.L., Creighton, J.A., McArthur, J.C., 2005. Diagnostic utility of the subjective peripheral neuropathy screen in HIV-infected persons with peripheral sensory polyneuropathy. AIDS Read. 15, 341–344, 348–349, 354.

Verma, A., 2001. Epidemiology and clinical features of HIV-1 associated neuropathies. J. Peripher. Nerv. Syst. 6, 8–13. doi:10.1046/j.1529-8027.2001.006001008.x

Vidrine, D.J., Amick, B.C., 3rd, Gritz, E.R., Arduino, R.C., 2003. Functional status and overall quality of life in a multiethnic HIV-positive population. AIDS Patient Care STDs 17, 187–197. doi:10.1089/108729103321619791

Vigneshwaran, E., Padmanabhareddy, Y., Devanna, N., Alvarez-Uria, G., 2013. Gender Differences in Health Related Quality of Life of People Living with HIV and AIDS in the Era of Highly Active Antiretroviral Therapy. North Am. J. Med. Sci. 5, 102–107. doi:10.4103/1947-2714.107526

Vinik, A., Emir, B., Cheung, R., Whalen, E., 2013. Relationship between pain relief and improvements in patient function/quality of life in patients with painful diabetic peripheral neuropathy or postherpetic neuralgia treated with pregabalin. Clin. Ther. 35, 612–623. doi:10.1016/j.clinthera.2013.03.008

Vinik, A.I., Casellini, C.M., 2013. Guidelines in the management of diabetic nerve pain: clinical utility of pregabalin. Diabetes Metab. Syndr. Obes. Targets Ther. 6, 57–78. doi:10.2147/DMSO.S24825

Viswanathan, H., Anderson, R., Iii, J.T., 2005. Nature and correlates of SF-12 physical and mental quality of life components among low-income HIV adults using an HIV service center. Qual. Life Res. 14, 935–944. doi:10.1007/s11136-004-3507-7

Wabiri, N., Taffa, N., 2013. Socio-economic inequality and HIV in South Africa. BMC Public Health 13, 1037. doi:10.1186/1471-2458-13-1037

Wadley, A.L., Cherry, C.L., Price, P., Kamerman, P.R., 2011. HIV neuropathy risk factors and symptom characterization in stavudine-exposed South Africans. J. Pain Symptom Manage. 41, 700–706. doi:10.1016/j.jpainsymman.2010.07.006

Wagner, G.J., Ghosh-Dastidar, B., Garnett, J., Kityo, C., Mugyenyi, P., 2012. Impact of HIV antiretroviral therapy on depression and mental health among

clients with HIV in Uganda. Psychosom. Med. 74, 883–890. doi:10.1097/PSY.0b013e31826629db

Walensky, R.P., Wood, R., Ciaranello, A.L., Paltiel, A.D., Lorenzana, S.B., Anglaret, X., Stoler, A.W., Freedberg, K.A., for the CEPAC-International Investigators, 2010. Scaling Up the 2010 World Health Organization HIV Treatment Guidelines in Resource-Limited Settings: A Model-Based Analysis. PLoS Med. 7, e1000382. doi:10.1371/journal.pmed.1000382

Wang, H., Zhou, J., He, G., Luo, Y., Li, X., Yang, A., Fennie, K., Williams, A.B., 2009. Consistent ART Adherence Is Associated with Improved Quality of Life, CD4 Counts, and Reduced Hospital Costs in Central China. AIDS Res. Hum. Retroviruses 25, 757–763. doi:10.1089/aid.2008.0173

Ward, S.A., 2005. Diabetes, exercise, and foot care: minimizing risks in patients who have neuropathy. Phys. Sportsmed. 33, 33–38. doi:10.3810/psm.2005.08.169

Wen, Y., Shi, Y., Jiang, C., Detels, R., Wu, D., 2013. HIV and AIDS patients' medical and psychosocial needs in the era of HAART: a cross-sectional study among HIV and AIDS patients receiving HAART in Yunnan, China. AIDS Care 25, 915–925. doi:10.1080/09540121.2012.729804

White, C.M., Pritchard, J., Turner-Stokes, L., 2004. Exercise for people with peripheral neuropathy. Cochrane Database Syst. Rev. CD003904. doi:10.1002/14651858.CD003904.pub2

WHO | Antiretroviral therapy for HIV infection in adults and adolescents [WWW Document], n.d. WHO. URL http://www.who.int/hiv/pub/guidelines/adult/en/ (accessed 1.19.14).

WHO | Gender inequalities and HIV [WWW Document], n.d. WHO. URL http://www.who.int/gender/hiv_aids/en/ (accessed 1.24.14).

Wig, N., Lekshmi, R., Pal, H., Ahuja, V., Mittal, C., Agarwal, S., 2006a. The impact of HIV and AIDS on the quality of life: A cross sectional study in north India. Indian J. Med. Sci. 60, 3. doi:10.4103/0019-5359.19670

Wig, N., Lekshmi, R., Pal, H., Ahuja, V., Mittal, C.M., Agarwal, S.K., 2006b. The impact of HIV and AIDS on the quality of life: a cross sectional study in north India. Indian J. Med. Sci. 60, 3–12.

Woldemedhin, B., Wabe, N.T., 2012. The Reason for Regimen Change Among HIV and AIDS Patients Initiated on First Line Highly Active Antiretroviral Therapy in Southern Ethiopia. North Am. J. Med. Sci. 4, 19–23. doi:10.4103/1947-2714.92898

Wolfort, S.F., Dellon, A.L., 2012. Peripheral neuropathy in HIV patients: treatment by decompression of peripheral nerves. Microsurgery 32, 31–34. doi:10.1002/micr.20938

Wong, R., Sagar, S., 2006. Acupuncture treatment for chemotherapy-induced peripheral neuropathy--a case series. Acupunct. Med. J. Br. Med. Acupunct. Soc. 24, 87–91.

Worthington, C., Krentz, H.B., 2005. Socio-economic factors and health-related quality of life in adults living with HIV. Int. J. STD AIDS 16, 608–614. doi:10.1258/0956462054944408

Wulff, E.A., Wang, A.K., Simpson, D.D.M., 2000. HIV-Associated Peripheral Neuropathy. Drugs 59, 1251–1260. doi:10.2165/00003495-200059060-00005

Xiao, J.J., Tang, C., Shim, S., 2009. Acting for Happiness: Financial Behavior and Life Satisfaction of College Students. Soc. Indic. Res. 92, 53–68. doi:10.1007/s11205-008-9288-6

Miura, Y., Kishida, S., 2013. [Neurological complications with HIV infection]. Brain Nerve Shinkei Kenkyu No Shinpo 65, 275–281.

Yen, C.-F., Tsai, J.-J., Lu, P.-L., Chen, Y.-H., Chen, T.-C., Chen, P.-P., Chen, T.-P., 2004. Quality of life and its correlates in HIV and AIDS male outpatients receiving highly active antiretroviral therapy in Taiwan. Psychiatry Clin. Neurosci. 58, 501–506. doi:10.1111/j.1440-1819.2004.01292.x

Zakas, A., Grammatikopoulou, M.G., Zakas, N., Zahariadis, P., Vamvakoudis, E., 2006. The effect of active warm-up and stretching on the flexibility of adolescent soccer players. J. Sports Med. Phys. Fitness 46, 57–61.

Zanetti, C., Manzano, G.M., Gabbai, A.A., 2004. The frequency of peripheral neuropathy in a group of HIV positive patients in Brazil. Arq. Neuropsiquiatr. 62, 253–256. doi:10.1590/S0004-282X2004000200012

Zonta, M.B., Almeida, S.M. de, Carvalho, M.T.M. de, Werneck, L.C., 2003. Functional assesment of patients with AIDS disease. Braz. J. Infect. Dis. 7, 301–306. doi:10.1590/S1413-86702003000500004

APPENDICES

Appendix 1: Outcome measures

Outcome measures for screening of Peripheral Neuropathy, related functional limitation and quality of life, among PLWHA on ART in Rwanda

Section A: Checklist

Date of screening ----------

ID No given. ……. .....Code.....
Demographic characteristics and general health status of the patient

Instruction: Circle the option corresponding to the answer given by the participant or as indicated in the participant's medical file; unless otherwise indicated

a) **Gender**: Female 1) Male 2)

b) **Fill in the D.O.B** ----------

c) Highest level of education
1. None
2. Primary education
3. Secondary school education (S1 – 3)
4. Secondary school education (S4 – 6)
5. Tertiary education (University, Institution of higher learning

d) Occupation
1. Public (government) service
2. Peasant (farmer, or livestock)
3. Self – employed (business)
4. Private organisation (NGO, bank, insurance, etc)
5. Unemployed (do not have a job for the last 3 months)
6. Any other (please specify)

e) Marital status
1 Single
2 Married
3 Divorced
4 Separated
5 Widow / widower
6 Cohabitating (live together with a temporally male/female partner
7 Any other (please specify)

f) **Place of residence**
1. Urban 2. Rural

g) When the patient's HIV was diagnosed:
1) 1 – 6 months ago
2) 6 – 12 months ago
3) 1 – 3 years ago
4) 4 – 6 years ago
5) 7 – 9 years ago
6) 10 – 15 years ago
7) More than 15 years ago

h) Current CD cell count (/mm3)

1) ≤ 200
2) 201-350
3) 351-500
4) > 500
5) None

i) Have you started on ARVs? 1) yes 2) No

j) If yes, circle the current ARV regimens' combination

1) Triviro – 30 (D4T+ 3TC+ NVP)
2) Duovir – N (AZT + 3TC+ NVP)
3) TDF + 3TC + NVP
4) TDF + 3TC + EFV
5) TDF + 3TC + Kaletra
6) D4T + 3TC + EFV
7) ABC + 3TC + EFV
8) ABC + ddI
9) D4T + AZT + Kaletra
10) AZT + 3TC+ Stocrin
11) 3TC + NVP

k) For how long the patient has been on ARVs treatment?

1) 1 – 6 months
2) 6 – 12 months
3) 1 – 3 years
4) 4 – 6 years
5) 7 – 9 years
6) 10 – 15 years
7) More than 15 years

l) How many regimen changes have you had so far?

0) None
1) One
2) Two
3) More than two

m) If any change, which regimen did you start with?

1) Triviro – 30 (D4T+ 3TC+ NVP)
2) Duovir – N (AZT + 3TC+ NVP)
3) TDF + 3TC + NVP
4) TDF + 3TC + EFV
5) TDF + 3TC + Kaletra
6) D4T + 3TC + EFV
7) ABC + 3TC + EFV
8) ABC + ddI
9) D4T + AZT + Kaletra
10) AZT + 3TC+ Stocrin
11) 3TC + NVP

<u>For exclusion Criteria</u>

k) Please indicate if the patient has been known to have the following condition(s): (Circle all that apply) (ask the patient in case the information is not available in the file)

1) Diabetes mellitus
2) Spinal cord disorders
3) Alcoholism
4) TB and is taking anti – TB
5) Any other (please specify).....
6) None

l) Please indicate if the patient presents the following symptoms :(Tick all that apply)

1) Pain: (muscle pain) Hand and arms □ Feet and Legs □
2) Paraesthesia/tingling Hand and arms □ Feet and Legs □
3) Numbness: Hand and arms □ Feet and Legs □
4) None

m) If the patient presents any of the above symptoms, when did the symptoms start? (If remember/ recorded)

1) Before start ARVs □
2) After starting ARVs □

n) If after start ARVs, after how long on ARVs did the symptoms commence (if remember or recorded)

1) 1 – 6 months
2) 6 – 12 months
3) 1 – 3 years
4) 4 – 6 years
5) 7 – 9 years
6) 10 – 15 years
7) More than 15 years

Section B: Neuropathic diagnosis (DN4)

To estimate the probability of neuropathic pain, please answer yes or no for each item of the following four questions.

INTERVIEW OF THE PATIENT

QUESTION 1:
Does the pain have one or more of the following characteristics? YES NO

Burning . . . . . ❑ ❑
Painful cold . . . . . ❑ ❑
Electric shocks . . . . . ❑ ❑

QUESTION 2:
Is the pain associated with one or more of the following symptoms in the same area?
YES NO

Tingling . . . . . ❑ ❑
Pins and needles . . . . . ❑ ❑
Numbness. . …..... . . . . . ❑ ❑
Itching . . . . . ❑ ❑

EXAMINATION OF THE PATIENT

QUESTION 3:
Is the pain located in an area where the physical examination may reveal one or more of the following characteristics? YES NO

Hypoesthesia to touch . . . . ❑ ❑
Hypoesthesia to pinprick . . . . . ❑ ❑

QUESTION 4:
In the painful area, can the pain be caused or increased by: YES NO

Brushing? . . . . . ❑ ❑
YES = 1 point
NO = 0 points Patient's Score: /10

Neuropathic pain is diagnosed if the total score ≥ 4/10

Section C: Recording Subjective Elicited Symptoms (completed by the researcher/ trained research assistant)

Instructions

Ask the participant 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" in feet, legs ……		
c. Numbness (lack of feeling) in feet, legs ……		

Instructions for grading subjective elicited symptoms

Use the single highest severity score from question 1. above to obtain a subjective sensory neuropathy score. If all severity scores are '00' or '11', the subjective sensory neuropathy score will equal '0'

Presence/Severity Score of:
01 – 03 = Grade of 1
04 – 06 = Grade of 2
07 – 10 = Grade of 3
11 or 00 = Grade of 0

	R	L
2. Subjective sensory neuropathy grade ……		

3. 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" in feet, legs ……..		
c. Numbness (lack of feeling) in feet, legs ……		

Instructions for evaluating perception of vibration

Compress the ends of a 128 Hz tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the participant to tell you when the "buzzing" stops. Repeat for the other great toe.

4. Vibration Perception

	R	L
a. Great toe DIP joint perception of vibration in seconds		

	R	L
b. Vibration perception score Vibration Perception		

0 = felt > 10 seconds
1 = felt 6-10 seconds
2 = felt < 5 seconds
3 = not felt
8 = unable/did not evaluate

Instructions for evaluating deep tendon reflexes

With the subject comfortably kneeling on a chair (with a cushion/pillow on) with foot free, the examiner uses a reflex hammer and strikes the Achilles tendon. The tendon reflex is seen as a plantar flexion 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
3 = Hyperactive
4 = Clonus
8 = unable/did not assess

	R	L
5. Ankle reflexes ……..		

Section D: Lower Extremity Functional Scale (LEFS-Modified)

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your lower limb problem (s). **Please provide an answer for each activity.** Today, do you or would you have any difficulty with:

(Circle one number on each line that corresponds to your appropriate answer)

Activity	Unable to perform activity	Quite a bit of difficulty	Moderate difficulty	A little a bit difficulty	No difficulty
1.Any of your usual work, (e.g work that earns you income, or any other work you do) housework, or school activities	0	1	2	3	4
2.Your usual hobbies, recreational or sporting activities, eg attending weddings, church or visiting friends	0	1	2	3	4
3. Getting into or out of the bath/taking bath.	0	1	2	3	4
4.Walking between rooms (such as walking from your room to toilet, bath room, kitchen, etc)	0	1	2	3	4
5. Putting on any kind shoes or socks you want, including slippers or open shoes, if applied.	0	1	2	3	4
6.Squatting (e.g squatting on pit latrine/doing any squatting activity)	0	1	2	3	4
7.Lifting an object, like a bag of groceries or a small container like 5 litres container full of water, basket of potatoes, etc, from floor	0	1	2	3	4
8.Performing light activities around your home(such as prepare a meal, cleaning a house, making bed, or any other light activity at home)	0	1	2	3	4
9.Performing heavy activities around your home (digging, lifting a heavy bag of potatoes, 20 litres Jerican of water, shifting big items, etc	0	1	2	3	4
10. Getting into or out of a car/taxi.	0	1	2	3	4
11.Walking across from your home to neighbours or walk like 100m across	0	1	2	3	4
12.Walking a Km, such as going to market, church or any other place where you walk	0	1	2	3	4
13.Going up or down 10 stairs (about 1 flight of stairs) or walking up a steep and irregular ground	0	1	2	3	4
14.Standing for 1 hour,	0	1	2	3	4
15.Sitting for 1 hour, like when in church, tax, or meetings	0	1	2	3	4
16.Fast walking on even ground	0	1	2	3	4
17.Fast walking/running on uneven ground	0	1	2	3	4
18.Making sharp turns while walking/running very fast	0	1	2	3	4
19.Standing up fast from squatting as needed	0	1	2	3	4
20.Turning in bed	0	1	2	3	4

Section E: ASSESSMENT OF QOL: WHOQOL-HIV BREF QUESTIONNAIRE

After reading each question, assess your feelings, and circle the number on the scale for each question that gives the best answer that corresponds to your feelings

		Very poor	Poor	Neither poor nor good	Good	Very good
1(G1)	How would you rate your QOL?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisf
2(G4)	How satisfied are you with your life?	1	2	3	4	5

The following questions ask about how much you have experienced certain things in the last two weeks.

		Not at all	A little	moderate amount	Very much	An extren amount
3(F1.4)	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4(F11.3)	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5(F4.1)	How much do you enjoy life?	1	2	3	4	5
6(F24.2)	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	moderate	Very much	Extreme
7(F5.3)	How well are you able to concentrate?	1	2	3	4	5
8(F16.1)	How safe do you feel in your daily life?	1	2	3	4	5
9(F22.1)	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last 2 weeks

		Not at all	A little	Moderately amount	Mostly	Complete
10(F2.1)	Do you have enough energy for everyday life?	1	2	3	4	5
11(F7.1)	Are you able to accept your bodily appearance?	1	2	3	4	5
12(F18.1)	Have enough money to meet your needs?	1	2	3	4	5
13(F20.1)	How available to you is information that you need in your day-to –day life?	1	2	3	4	5

14(F21.1)	To what extent do you have opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very goo
15(F9.1)	How were you able to get around?	1	2	3	4	5

The following questions ask you to say how good or satisfied you have felt about various aspects of your life over the last two weeks.

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisf
16(F3.3)	How satisfied are you with your sleep?	1	2	3	4	5
17(F10.3)	How satisfied are you with your ability to perform your daily activities?	1	2	3	4	5
18(F12.4)	How satisfied are you with your capacity for work?	1	2	3	4	5
19(F6.3)	How satisfied are you with yourself?	1	2	3	4	5
20(13.3)	How satisfied are you with your personal relationships?	1	2	3	4	5
21(F15.3)	How satisfied are you with your sex life?	1	2	3	4	5
22(F14.4)	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23(F17.3)	How satisfied with the conditions of your living place?	1	2	3	4	5
24(F19.3)	How satisfied are you with your access to health services?	1	2	3	4	5
25(F23.3)	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last two weeks.

		Never	Seldom	Quite often	Very often	Always
26(F8.1)	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Appendix 2: Physiotherapeutic exercise[1] protocol for the intervention on PN among PLHIV on ART in Rwanda

For lower extremities

Design of the programme: An exercise interventional programme.

Table of detailed exercises programme

S/N	Order of exercise	Type of exercise	Duration	Exercise technique and instructions
1.	Warm up exercises	Moderate aerobic exercises	10 minutes	Walking slowly at start for the first 5 minutes and then progress brisk walking. Patient are instructed to walk according their capacity and in pain free limits
2.	Mobility and flexibility	Self - stretching	15 minutes	In long sitting, cross sitting and lying positions: stretching of the toes, ankle and knee muscles. Each stretch is held 15 seconds, followed by relaxation of 10 seconds; then repeat twice the procedure for the same muscle, and change to another muscle group and do the same: should breath normally and stretch into pain free limits
3.	Muscle conditioning	Isometric exercises	15 minutes	For muscles of the foot, leg and thigh. Starting with foot; Hold and count up to 5: at “time second pace” (participants will be taught to do that counting): relax for 10 seconds: repeat the procedure twice for the same group of muscles and then change to other groups of muscles: participants are instructed not to hold the breath during performance of exercises; and counting helps them not to hold breath.
4.	Stability	Balance exercises	10 minutes	Moving from sit to stand with partial support, then without support, bilateral squat with support and then progress to without support, body weight transfer to one limb as much as he/she can while standing with support from wall/wall bar, progresses to lift one leg to a step while keeping the opposite leg down, with support, progress by reducing the support and eventually stands with a step un

[1] Physiotherapy prescribed and supervised therapeutic exercise protocol

				supported. Progression continues until the participant may stand on one leg un supported. participants are always instructed to exercise to their capacity limits
5.	Cool down	Stretching and relaxation exercises	10 minutes	Long sitting, side and prone lying positions, then stretches the muscles of the toes, foot, ankle and knee slowly hold for 10 seconds while breathing in and out deeply. Relax for 15 seconds and repeats twice and then change to another muscle group

N.B: Progression in any of the exercises above may start after the first and second sessions of the program and will be according to participant's improvement performance

Appendix 3: Research ethics clearance certificate from the University of Witwatersrand

Appendix 4: Research protocol approval by the national commission in charge of HIV and AIDS in Rwanda,

Appendix 5: Research ethics clearance from IRB at Kigali Health Institute in Rwanda

(Indicated on the next pages; the appendices 3, 4 & 5)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Tumusiime

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080812**
PROJECT	Prevalence of Peripheral Neuropathy and Effects of Physiotherapeutic Exercises Integrated into the Management of Peripheral Neuropathy among Individuals Living with HIV on Antiretroviral Therapy in...
INVESTIGATORS	Mr DK Tumusiime
DEPARTMENT	Department of Physiotherapy
DATE CONSIDERED	08.08.29
DECISION OF THE COMMITTEE* from the relevant authorities in Rwanda	Approved subject to submitting written permission

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

DATE 08.09.16 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof A Stewart

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

PRESIDENCE DE LA REPUBLIQUE DU RWANDA
COMMISSION NATIONALE DE LUTTE CONTRE LE SIDA

Kigali, le 29 JUL 2009

B.P 7162 KIGALI

N. Réf : 0137/CNLS/2009/S.E
V. Réf : .....

Mr. David K. TUMUSIIME
Principal Investigator
KHI- Kigali

Objet : Approbation de votre Projet de recherche

Monsieur,

Suite à votre demande d'approbation du projet de recherche intitulé : «**Prevalence of Peripheral Neuropathy and Effects of Physiotherapeutic Exercises Integrated into the Management of Peripheral Neuropathy among people living with HIV on Antiretroviral Therapy in Rwanda**» adressée à la CNLS, j'ai le plaisir de vous informer qu'après lecture et analyse de votre protocole par le Comité de pilotage des recherches du domaine du VIH/SIDA, votre projet a été approuvé.

A cet effet, la CNLS vous accorde l'approbation de votre projet et vous remercie pour l'intérêt que vous portez à la recherche dans le domaine du VIH/SIDA.

Par ailleurs, il vous est demandé de bien vouloir partager avec le Comité de recherche dans le domaine du VIH/SIDA, les résultats de votre recherche.

Veuillez agréer Monsieur, l'expression de ma franche collaboration.

Dr Anita ASIIMWE
Secrétaire Exécutif

CPI :
- Ministre de la Santé
- Président du Comité national d'Ethique

KIGALI HEALTH INSTITUTE

B.P. 3286 Kigali, RWANDA
Tel: +(250) 572172; +250 571788
Fax: +(250) 571787
Website: http://www.khi.ac.rw
E-mail: info@khi.ac.rw

05th January 2009

Institutional Review Board

Mr David K. Tumusiime
Principal Investigator

Dear Mr Tumusiime,

RE: YOUR APPLICATION FOR THE ETHICS CLEARANCE

Reference is made to your application for ethics clearance for the study entitled **"Prevalence of Peripheral Neuropathy and effects of Physiotherapeutic Exercises Integrated into the Management of Peripheral Neuropathy among Individuals living with HIV on Antiretroviral Therapy in Rwanda"**.

You will be pleased to learn that the Ethics clearance has been offered after receiving your revised proposal which did incorporate all the components proposed by the reviewers.

You shall be required to submit the progress report and any other major changes made in the proposal during the implementation stage. At the end of the survey the Institutional Review Board shall also require to be given a final report of the study.

I wish you a successful survey.

Kigali Health Institute
K.H.I
Faculty of Community Health Development

Dr KJ NJUNWA
Chairperson, KHI Institutional Review Board

CC:

- Vice Rector, Academics and Research, KHI
- Rector, KHI
- Members of IRB
- Chairperson, National Ethics Committee