UNIVERSITY OF THE WITWATERSRAND

FACULTY OF HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

Title:

Validity of self-reported Peripheral Neuropathy (PN) as a surrogate marker for clinically-determined PN in HIV/AIDS patients initiating ART in Masaka, Uganda, 2004-2008

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April 2022

A research report that is submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree Master of Science in Epidemiology in the Field of Epidemiology and Biostatistics

Supervisor: **Prof Jonathan Levin, Wits University**

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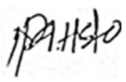
DECLARATION

I, Mpho Nomthimkhulu Pitso, declare that this thesis is my work. It is being submitted for the degree of Masters in Epidemiology (Epidemiology and Biostatistics) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



Mpho Nomthimkhulu Pitso

07 April 2022

DEDICATION

To my mother (Nthofeela Mokhafola) and sister (Malejota Mokhafola);

for the support and sacrifices you made for me to be who and where I am.

To my husband (Thabang Pitso) and Son (Lwazi Pitso);

For the love that you have shown me, and most importantly for believing in me.

To my best friend (Motheba 'Matli Koali)

For the love, support, encouragement, and being by my side in all I do.

ABSTRACT

Title

Validity of self-reported Peripheral Neuropathy (PN) as a surrogate marker for clinically-determined PN in HIV/AIDS patients initiating ART in Uganda, Masaka, 2004-2008

Background

Globally, the prevalence of HIV/AIDS is about 37.9 million with Sub-Saharan Africa being the epicenter of the pandemic with 25.6 million people living with HIV/AIDS as of June 2019 (1). While opportunistic HIV-related infections have declined steadily in recent years, peripheral sensory neuropathies related to HIV and ART continue to be high and recurrent (2). Peripheral neuropathy (PN) is a neurological disorder regularly found in People Living with HIV (PLHIV), individuals with dysproteinemic disorders, and those on chemotherapy (3,4). Brief Peripheral Neuropathy Screen (BPNS), a screening tool used for symptom reporting and clinical assessment of PN, is not widely used in resource-limited settings due to cost constraints (3). For resource-limited settings, it would be beneficial to have a surrogate marker for determining PN in PLHIV. A surrogate marker is a physical measurement that can be used as a substitute or be considered a valid predictor of the true recognized outcome measure (clinical assessment) (5). For validation of a surrogate marker, Ross Prentice came up with two conditions; if both of these are satisfied then the surrogate can be considered to be valid (6). The Prentice criteria firstly indicate that a surrogate marker needs to be correlated with the true endpoint and secondly it should capture the entire effect of treatment upon the true endpoint (6).

Aim

The study aims to investigate whether self-reported PN can be used as a surrogate outcome measure for clinically determined PN in HIV/AIDS patients who are initiating antiretroviral therapy.

Methods

The study is a repeated cross-sectional sub-study nested within the CRYPTOPRO trial that took place in Masaka Uganda in 2004 - 2008. It consisted of 370 participants before the initiation of ART and 191 participants after initiation of ART. Participants were drawn from those enrolled in the CRYPTOPRO

trial, who were still involved in the trial at the beginning of 2006 and had not yet initiated ART. All consenting individuals were assessed for the existence of peripheral neuropathy using both self-report and clinical methods. Descriptive analysis was used to describe socio-demographic variables, sensitivity and specificity tests were performed and logistic regression was used to assess whether factors associated with PN were similar for both self-reported and clinically determined PN. Separate analyses were carried out before the initiation of ART and after the initiation of ART.

Results

Before the initiation of ART, 370 participants were assessed while only 191 were assessed after the initiation of ART. For both before and after ART initiation, approximately 66% of the participants were females, more than 50% of participants were on WHO stage 3, and the majority of the participants were between the ages of 25 and 44. Participants were on ART for approximately 4 months on average. The prevalence of PN was approximately 23% for the self-reported method and approximately 10% for clinically determined PN both before and after initiation of ART. The sensitivity and specificity of the self-reported method of assessing PN were 39.5% and 78.0% before initiation of ART and 73.7% and 83.1% after initiation of ART respectively.

In a logistic regression analysis before initiation of ART, the clinically determined method had isoniazid as the only variable that was statistically associated with PN (AOR =4.25, 95% CI =1.37 - 13.16; P=0.012) while with the self-reported no variable was statistically associated with PN. After the initiation of ART, use of isoniazid was statistically associated with PN (aOR=2.87, 95% CI =1.03-8.01; P=0.044) for the self-reported method, while it was only marginally significant (aOR=3.13; 95% CI =0.87 – 11.29; P=0.081) for the clinically determined method. The number of months on ART was statistically associated with PN (aOR =1.16, 95% CI =1.02 - 1.32; P=0.025) for the clinically determined method but there was no association when using the self-reported method.

Conclusion

Self-reported PN cannot be used as a surrogate marker for clinically determined PN because it does not meet the requirements of the Prentice criteria for a surrogate marker.

ACKNOWLEDGEMENTS

- To Glaxo Smith Kline (GSK) in collaboration with WITS Consortium; for the massive financial contribution and academic support.
- To my Supervisors Prof J. Levin and Dr. Andrew Abaasa; for all the support, research skills, guidance, and time spent constructively criticizing this report.
- To MRC/UVRI and LSHTM Uganda Research Unit, for permitting me to use their data.
- To lecturers at Wits School of Public Health, for the knowledge and skills, they have instilled in me to better understand Public Health.

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LIST OF ACRONYMS

AIDS	Acquired immunodeficiency syndrome
AOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
ARV	Antiretroviral drug
AZT	Zidovudine
BPNS	Brief Peripheral Neuropathy Screen
CI	Confidence Interval
DART	Development of Antiretroviral Therapy in Africa
ddl	Didanosine
d4T	Stavudine
EMA	European Medicines Agency
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PLHIV	People Living with HIV
PN	Peripheral Neuropathy
QST	Quantitative sensory testing
SSW-EMLA	Stimulated Skin Wrinkling Eutectic Mixture of Local Anesthetic
TB	Tuberculosis
WHO	World Health Organization
3TC	Lamivudine
FDA	Food and Drug Administration

CHAPTER 1: INTRODUCTION

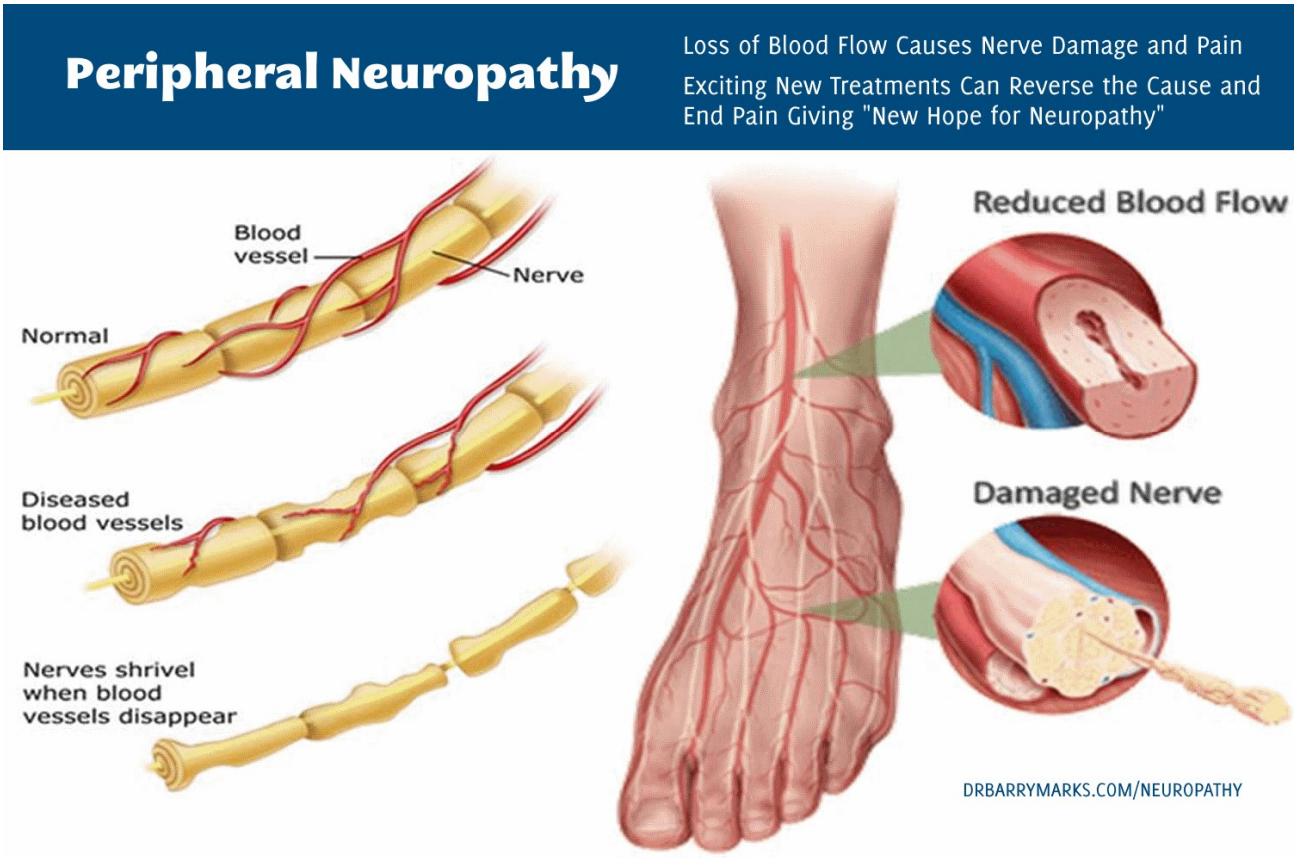
1.1 Background

Globally, the number of individuals infected with HIV/AIDS is about 37.9 million with Sub-Saharan Africa being the epicenter of the pandemic with 25.6 million people living with HIV/AIDS as of June 2019 (1). HIV impairs the nervous and immune systems and patients experience a variety of neurological symptoms directly or indirectly related to the viral infection with progression through various HIV stages (7). Sub-Saharan Africa accounted for 72 percent of the world's deaths associated with AIDS in 2008 (8). In 2018, the latest figures given, an estimated 470,000 people died of AIDS-related illnesses in sub-Saharan Africa (9). After more than three decades of the HIV epidemic, there is still no cure or effective vaccine, but significant advances have been made in the treatment of HIV (10,11).

The availability and rapid expansion of antiretroviral therapy (ART) have turned what was a fatal disease into a chronic, manageable condition that has contributed to substantial declines in the worldwide rates of deaths and new infections associated with HIV/AIDS (12). However, due to the possible increase in life expectancy and the long-term use of ART, other chronic complications like ART-associated Peripheral Neuropathy (PN) have become a concern (13). While opportunistic HIV-related infections have declined steadily in recent years, peripheral sensory neuropathies related to HIV and ART continue to be high and recurrent (2).

Peripheral neuropathy (PN) is a neurological disorder regularly found in people living with HIV (PLHIV), individuals with dysproteinemic disorders, and those on chemotherapy (3,4). PN can also be expressed as damage in the nerves. The symptoms of PN in PLHIV include tingling, burning, pricking, pain, stiffness, and numbness in the feet, particularly the sole and toes; this could also be experienced in wrists, hands, and fingers (3,14). Different studies have found a wide variation in the prevalence of PN in PLHIV in Sub-Saharan Africa, ranging from 1.2% - 69.4% (7). PN is attributed to the direct effects of HIV, as well as to exposure to ART. Figure 1 below shows what a damaged nerve on the feet looks like.

Figure 1 Peripheral Neuropathy Nerve damage



(Source: Mark 1986)(15)

PN associated with HIV is known to exist in at least six patterns, with distal symmetrical polyneuropathy (DSPN) the most commonly occurring type, accounting for more than 90 percent of all neuropathies related to HIV. Other types of PN include mononeuropathy multiplex, inflammatory demyelinating polyneuropathy, autonomic neuropathy, progressive polyradiculopathy, and diffuse infiltrative lymphocytosis syndrome (14). Most of the peripheral neuropathies are sensory predominant, length-dependent, and the severity is clinically mild to moderate without significant functional limitations(4).

Table 1 below shows a summary of HIV-associated patterns of peripheral neuropathy, their clinical symptoms, and their neurological signs.

Table 1: *Peripheral neuropathies associated with HIV*

Diagnosis	HIV stage	Clinical symptoms	Neurological signs
Distal symmetric polyneuropathy	Late	Distal symmetric numbness, burning sensations, and tingling; aching or parasthesias	Absent or depressed ankle reflexes Stocking-glove sensory loss;
Inflammatory demyelinating polyneuropathy	Early>>late	Progressive weakness; paresthesias	Mild sensory loss; Muscle weakness; areflexia
Mononeuritis multiplex	Early (limited) Late (progressive)	Facial weakness; Foot or wrist drop; focal pain	Multifocal cranial and peripheral neuropathies
Progressive polyradiculopathy	Late	Sphincter dysfunction; Lower extremity weakness; paresthesias	Saddle distribution anesthesia; Flaccid paraparesis; depressed ankle and knee reflexes
Autonomic neuropathy	Early>>late	Diarrhea; anhidrosis; palpitations; Orthostatic dizziness; syncope; impotence; urinary dysfunction	Orthostatic hypotension; pupillary abnormalities; sweating dysfunction; resting tachycardia

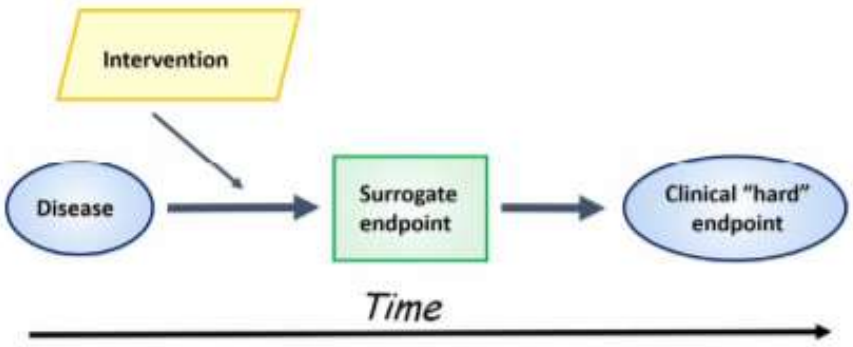
(Source: Wulff et al 2000 (14).)

It is noted that the pattern and frequency of neuropathies are similar, whether concerning HIV disease or ARV therapy, although differences may occur (16). Recognition of PN in patients with highly prevalent disorders may affect the treatment of this disease (4). The incidence of peripheral nerve involvement increases with falling CD4 count, and subclinical evidence of peripheral neuropathy may be found in up to 90% of AIDS patients (3). Due to highly active antiretroviral therapy, the life expectancy of PLHIV is nowadays increasing (3). Peripheral neuropathy (PN) is typical in the resource-limited setting of antiretroviral (ARV) programs and presents major challenges in management and assessment (17). Although antiretroviral therapy (ART) reduces the incidence of opportunistic infections in PLHIV, PN is a side effect of certain ART regimens; PN is therefore associated with both HIV infection and its treatment using ART (18). PN remains a side effect of the old ART drugs Stavudine (d4T) and didanosine (ddI) but not a side effect for modern/recent HIV treatment like DTG (19).

The Brief Peripheral Neuropathy Screen (BPNS) is a screening tool used for symptom reporting and clinical assessment (3). BPNS consists of two examination components, namely the subjective (Self-reported) and objective (physically/clinically determined) components (20). The objective component (physically / clinically determined) is not widely used in resource-limited settings due to cost constraints (3). Because of the cost associated with the clinical determination of PN in resource-limited settings, this study assesses whether the self-reported component of the test can be used as a surrogate marker for the clinically determined component in determining PN. Nervous conduction tests have historically been considered the gold standard for the diagnosis of peripheral neuropathies, but can be painful and expensive (21). In this instance, the objective component will be used as the gold standard for checking the validity of the subjective component.

A surrogate marker, also known as a surrogate endpoint is a physical measurement that can be used as a substitute or be considered a valid predictor of the true recognized outcome measure (clinical assessment) (5). It is an alternative to direct measures of how people survive, feel and function in clinical trials as well as in clinical practice (22). For example, in oncology, the tumor size is used as a surrogate marker for the clinical outcome which is improvement in survival or quality of life (23). Validated surrogate markers are approved by the US Food and Drug Administration (FDA)(23). Figure 2 below illustrates that in the disease process, a surrogate marker is in the causal pathway and the entire effect of the intervention on the true clinical outcome is mediated through its effect on the surrogate.

Figure 2 Surrogate marker in a disease process



Source (Villian et al, 2017)(24)

Surrogate markers are advantageous to use in clinical trials, not only do they save costs but also the time in the assessment procedure itself. They allow the trial to be concluded sooner, which means that a successful treatment could be adopted earlier hence providing an opportunity for early intervention (25). As appealing as they are, surrogate markers need to meet the criteria proposed by Prentice to be considered valid (6). To put one's trust in the use of a surrogate marker, it must be validated (26). To validate surrogates, several authors have identified different statistical methods. The complexity of many of these statistical techniques, however, means that their use in practice is relatively poor (27). For validation of a surrogate marker, Ross Prentice came up with two conditions; if both of these are satisfied then the surrogate can be considered to be valid (6).

The Prentice criteria firstly indicate that a surrogate marker needs to be correlated with the true endpoint and secondly it should capture the entire effect of treatment upon the true endpoint (6). While many had the misunderstanding that the first requirement would be sufficient to validate a surrogate, the second condition needed is less likely to be met and much more difficult to verify (28). Research has proven that a strong statistical correlation does not alone suffice as a criterion for the definition of a surrogate marker (29). It is very difficult to accurately measure the number of beneficial results of a treatment that is recorded by a marker. A direct consequence of this issue is that treatments that have a beneficial effect on markers would also have a proportionate clinical effect, particularly if the effect of treatment on markers is only observed in the short term (30). It is therefore critically important that the second condition is satisfied to conclude that a surrogate is valid.

An effective surrogate marker needs to be easily measured and affected in a similar way to the true outcome by the treatment, be in the causal pathway and have a strong association with the true outcome (31). For resource-limited settings, it would be beneficial to have a surrogate marker for determining PN in PLHIV. Self-reported PN determination is basic and fast to administer as it does not need any special kind of equipment (32). To our knowledge, no studies have been done on self-reported PN as a surrogate marker for clinically determined PN. There was however a study conducted at Johns Hopkins University in 1998 that was conducted to assess the reliability and validity of self-reported PN; In a sample of 83 study subjects, self-reported PN was found to have been valid and reliable (21).

Cherry also indicated in a study of 80 participants he was undertaking at Alfred Hospital in Melbourne Australia, that self-reported PN (presence and severity of numbness) strongly correlated with the

clinically determined PN (32). Although that may be a good sign, it is not enough to conclude that self-reported PN can be a surrogate marker, hence the need to undertake this research. Although there is a lot of interest in the use of surrogate markers, there have been some studies that question their validity (33). The possible failure of surrogate markers implies that it is important to determine explicitly in advance the validity of the relationship between the surrogate and the outcome (27).

1.2 Problem Statement

The limited or absent access to specialized equipment and neurologists in resource-limited settings makes the diagnosis of PN challenging, as a result, PN is under-recognized and under-treated (34). The pain experienced because of peripheral neuropathy can be devastating, it can be mild to severe, affecting one's walking or daily living activities (35). This indicates that PN is disabling and compromises the quality of life (36). Not only is HIV-associated PN a common complication of HIV infection but also a substantial cause of morbidity (37). Since the prevalence of HIV is highest in Sub-Saharan Africa, it is of importance to have an affordable and accessible method for the early detection of PN (38). Determining PN is costly in resource-limited settings (39). Self-reported PN will be assessed to check if it can be a good enough method of determining PN.

1.3 Justification

If self-reported PN meets the criteria of a surrogate marker, resource-limited settings could use self-reported PN where definitive methods are unavailable. This implies that the easier, quicker, and cheaper method of determining PN can be used for the improvement of PN diagnosis (34). Prevention of disability and improvement of quality of life can be obtained through early diagnosis, the earlier the diagnosis, the earlier the treatment. To our knowledge, there is limited information on the assessment of self-reported PN as a surrogate marker for definitive PN.

1.4 Research question aim and objectives

1.4.1 Research Question

Can self-reported PN be used as a surrogate outcome measure for clinically-determined PN in HIV/AIDS patients who are initiating antiretroviral therapy in Masaka, Uganda?

1.4.2 Aim

To investigate whether self-reported PN can be used as a surrogate outcome measure for clinically-determined PN in HIV/AIDS patients who are initiating antiretroviral therapy.

1.4.3 Objectives

1. To describe the socio-demographic characteristics of PLHIV in Masaka, Uganda by presence and absence of PN.
2. To determine the prevalence of PN among PLHIV before and after ART
3. To compare the sensitivity and specificity of self-reported PN as a surrogate marker of the gold standard, clinically determined PN.
4. To see whether self-reported PN meets the Prentice criteria for a surrogate marker in determining PN before ART initiation.
5. To see whether self-reported PN meets the Prentice criteria for a surrogate marker in determining PN after ART initiation.

1.5 Outline of the thesis

The research report consists of the following four chapters.

Chapter 1: Background and Literature review

The chapter gives the background and literature review of peripheral neuropathy and surrogate markers. It provides the problem statement and justification of the research as well as outlining the aim and objectives of the study.

Chapter 2: Methods

Our study is a sub-study, the chapter, therefore, starts by briefly explaining the primary study. It describes the current study and further explains how PN was assessed, it also describes how data will be analysed for each objective.

Chapter 3: Results

In this chapter, the outcomes obtained from the data analysis are presented in tables and charts. Interpretation of the findings is also provided. Results will be presented corresponding to each objective.

Chapter 4: Discussion

This chapter discusses the results obtained in chapter 3. It also compares the results obtained to those from previous studies, a conclusion is made about the study, and the research question is answered.

1.6 Literature Review

1.6.1 PN in HIV infected individuals

HIV disease neuropathy is characterized as a symmetrical, distal, axonal sensory polyneuropathy that affects the feet most often, but may affect the hands as well. Pressure, aching, burning, or tingling of the distal extremities are signs of neuropathy, with the toes and feet more frequently affected than the fingers and hands. It is noted that pain symptoms intensify at night (39). PN is one of the main neurological disorders in PLHIV (40). It is briefly characterized as harm to the fringe nerves, through damage, aggravation, or degeneration of the fringe nerve strands (40). Many neurological effects of HIV infection have a strong association with the incidence of peripheral neuropathy (14).

The most common pathogenic characteristics linked with HIV-PN are distal axonal degeneration, loss of neurons within the influenced dorsal root ganglia, penetration of incendiary cells, and a diminishing of epidermal nerve fiber thickness, the clinical indications change from serious torment, hypoesthesia, and weakness to asymptomatic (20). These conditions contribute to the impedance of a patient's everyday movement, which diminishes the quality of life (36). The social and financial burden of HIV-PN is great, therefore early detection is important (20).

In Sub-Saharan Africa, the prevalence of PN among PLHIV has been reported to range between 1.2% and 69.4 % by different cross-sectional studies (7). Most previous studies used a cross-sectional design. The prevalence of PN in our country of interest (Uganda) was found to be 39% among PLHIV in the Development of Antiretroviral Therapy in Africa (DART) trial. Table 2 below shows the prevalences in other countries.

Table 2: Prevalences of PN in other countries

Country	**Prevalence**
Ethiopia	24.5% (41)
Rwanda	59% (40)
Malawi	21.3% (42)
India	38.5% (43)
Ghana	17.7% (44)

Even though PN is the foremost common neurological complication in PLHIV, its diagnosis and treatment are regularly deferred (14). In resource-limited settings, this is a result of the costs associated with the diagnosis. While PN is not life-threatening it results in significant morbidity (14). Health practitioners caring for such patients require an easy and convenient means of diagnosing PN to provide treatment. Neuropathy is a big concern for symptom management in resource-poor environments, with limited access to pain-controlling drugs (39).

1.6.2 The association between ART and PN

In the mid-1990s, the advent of combined antiretroviral therapy (cART) turned HIV infection from a high-mortality illness into a chronic disease, the life expectancy of newly infected individuals changed, approaching that of the general population (37). PN has been explained as a complication of HIV-disease progression in patients who have not yet initiated ART, but can also be a result of ART-induced immune restoration (45). The associated neuropathic symptoms of Distal Sensory Polyneuropathy (DSP) that emerge after initiation of ART are more likely to occur within the first three to six months of initiation of ART, and this risk is higher if the person has been or is currently receiving tuberculosis treatment (46).

While some studies have found that ART reduces the incidence of opportunistic infections, reduces vulnerability, and also reduces any negative impacts of individual ARVs which results in a lower probability of developing PN (47), other authors point out that the prevalence of PN has not diminished since the advent of ART (48). PN has often been recorded as the most common complaint among PLHIV using ART in resource-limited settings (40). Although ART has significant benefits for survival in HIV disease, it is essential for those living with HIV disease to have symptom management for pain and neuropathy (16).

In a South African study, the frequency and impact of neuropathic signs and symptoms associated with HIV remain high in cohorts that began ART in advanced HIV infection, despite relatively successful ART after 5 years. Over time, both small and large fiber nerve dysfunction accumulates and tends to affect the daily life of a person, emphasizing the burden of HIV-DSP (46).

In the DART trial conducted in Uganda and Zimbabwe, it was found that non-adherence to ART may increase the risk of PN. Also, PN negatively impacts adherence to ART as well as on the quality of life

(3). PN is regularly considered as an adverse reaction to dideoxynucleosides or "d-drugs", especially stavudine (d4T) and didanosine (ddI) which in the early years of the ART roll-out were commonly used in Sub-Saharan African nations (42,49). Research provides evidence of a high prevalence of PN in PLHIV from Sub-Saharan African countries during first-line failure and Protease Inhibitor (PI)-based second-line therapy (49). Protease inhibitors stop protease enzymes from working (50). As a result, protease enzymes are unable to play their function in permitting HIV to proliferate, disrupting the HIV life cycle (50).

Independently of pre-ART weight and age, in addition to the two antiretroviral drugs (stavudine and didanosine), the drug isoniazid which is used in the treatment of TB as well for prophylaxis against TB, also increases the incidence of PN. Although didanosine is no longer prescribed by World Health Organization (WHO) for second-line, it is being utilized in certain patients; other second-line medications may be ideal in higher-risk patients, especially if they were using isoniazid for treatment or as prophylaxis. The high prevalence of HIV and TB co-infection in Sub-Saharan Africa may raise the need for further consideration of PN screening (3).

Loss of sensation and pain are the major signs and symptoms of PN (51). Pain due to ART-PN is more severe than that induced by HIV (52). It has a sudden start and also advances quickly (52). Prompt diagnosis is, therefore, necessary for early treatment. In a study conducted by Van As in Johannesburg, PN-related pain was found to have an association with functional activity limitations; 71% of impairments in that study were sensation loss and pain (51). In another study by Ellis in the US, PN-related pain was associated with impediments of day-to-day activities becoming a major source of disability in PLHIV (53).

1.6.3 Diagnosis of PN

The clinical diagnosis of PN is made based on the patient's history and physical examination. The development of symptoms is usually subacute and progresses over two to four weeks. There is a development of stiffness or discomfort in the toes that causes pain to develop. The pain is generally characterized as stabbing, burning, or shooting, and there is sometimes a feeling of pins-and-needles with contact hypersensitivity. Symptoms remain limited to the feet in the majority of cases. In certain patients with long-term PN, symptoms can develop above the ankles and sometimes affect the hands

(54). Neuropathic pain sometimes diminishes over time and is replaced by residual symptoms of numbness and hypersensitivity to contact. Symmetric involvement is more usual, and generally, there is no associated weakness (54). The most common results of physical exams include diminished or absent jerks. The feeling of light contact and pinprick is altered and irregular temperature and sense of vibration may occur(21)

Several tools have been used in determining PN in PLHIV, the tools include quantitative sensory testing (QST), BPNS, the stimulated skin wrinkling eutectic mixture of local anesthetic (SSW-EMLA) test, and electrophysiological evidence (43). When administered by skilled doctors in high-income countries, these methods have demonstrated high diagnostic utility (34). The BPNS tool tests subjective and objective findings associated with PN and was developed and validated by the National Institutes of Health-funded AIDS Clinical Trials Group (35).

BPNS is a tool used for determining PN in most Sub-Saharan Africa countries; it assesses the signs and symptoms of PN subjectively (self-reported) and objectively (clinically determined) (18). However, this tool has been used less frequently in resource-limited settings due to financial challenges (3). As a result, many cases of PN may not be diagnosed, leading to under-diagnosis which will result in under-treatment of PN (41). The BPNS method is not practical as a screening tool in busy clinics in resource-limited environments (35).

Several studies have been carried out to compare the different methods of measuring PN but there are no previous studies conducted specifically in assessing whether self-reported PN can be a good enough measure of PN or a surrogate marker for clinically determined PN.

Since the Single Question Neuropathy Screen requires virtually no preparation and very little time to be administered, it is possible to introduce it in resource-constrained clinical environments with a high volume of patients and staff turnover. It was found to have outstanding sensitivity and negative predictive value for neuropathy when conducted by health care staff in HIV resource-limited outpatient clinical settings. It could easily be applied across Sub-Saharan Africa because it needs virtually no training and less than a minute to administer. A simple, low-technology and low-cost diagnostic tool that can be administered by non-physician healthcare workers for HIV-associated peripheral neuropathy can improve the treatment and diagnosis of this condition (34).

1.6.4 Surrogate Markers

A surrogate marker is a test used and regarded as a measure of the impact of an explicit outcome (5). It is a first-hand experience of how a patient feels and is relied upon to anticipate the impact of the treatment (5). Even though the use of surrogate markers may be problematic, they can provide significant opportunities for more effective clinical trials and quicker access to emerging health technology that supports patients and healthcare systems when chosen and validated appropriately (55). Table 3 below shows some surrogate markers that have been used in medicine.

Table 3: Some samples of true endpoints and surrogate endpoints in medicine

Research condition	True endpoints	Surrogate endpoints
Hypertension	Cardiovascular events	Arterial pressure
Cancer	Death	Tumor size
Diabetes	Cardiovascular events	Glycaemia
Alzheimer disease	Death/functional evaluation	Brain image exam
Vaccine	Disease protection	Serological response
Osteoporosis	Bone fracture	Bone density
Short	Final height of the individual	Height gain
Glaucoma	Loss of vision	Intraocular pressure
Atherosclerosis	Cerebral infarction	Arterial pressure
	Acute myocardial infarction	Cholesterol dosage

Source (Pedrazzi et al 2020) (56)

Surrogate markers are beneficial both practically and financially (29). The results of surrogate markers generally accumulate more quickly than those of the actual final endpoints, allowing for shorter follow-up times and smaller sample sizes in clinical trials (57). Reducing the duration and sample size of the trial ensures faster access to new therapies for patients, and this means the trials are also less costly, making surrogate markers attractive to producers or research sponsors alike (55).

The benefit of quantification is that we can consider surrogate endpoints that are, in some way, less than ideal but theoretically good enough to still be of use (58). If a surrogate marker satisfies all of the Prentice conditions, one may determine that it is 'validated' sufficiently to guarantee its use in

operation, or similar conditions to fit the particular context in which it is to be used (33). The use of properly validated surrogate endpoints offers an important opportunity to speed up access to emerging technologies that offer substantial benefits for health care systems and patients, and also improve efficiency within the development and research areas (55).

Surrogate markers will allow shorter trials to be conducted and hence lead to a shorter time for drugs to be approved for use (59). Because of the aforementioned benefits, many researchers have a great interest in the use of surrogate markers as substitutes for true outcomes (5). Regulatory agencies, including the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), have a long history of licensing technologies strictly on the grounds of evidence of their effect on surrogate markers (55). In the context of the programs initiated by these agencies, the role of surrogate markers is highly significant in offering fast approval to promising new medication (55). In the United Kingdom, several recommendations were made by the National Institute for Health and Care Excellence (NICE) based on cost-effectiveness analyses that relied mainly on treatment effects obtained from clinical trials evaluating surrogate markers (60).

CHAPTER 2: METHODS

This study is a sub-study of the CRYPTOPRO trial, the data used in the sub-study was collected between 2006 and 2008 but has not previously been analysed. Below is a description of the primary study (CRYPTOPRO trial) and the study being reported in this paper (Sub-study).

2.1 Study design and population

2.1.1 Primary Study- CrptoPro trial

The CRYPTOPRO [ISRCTN 76481529] trial was a double-blind, randomized, placebo-controlled trial designed to determine if primary prophylaxis with fluconazole could reduce morbidity and mortality from invasive cryptococcal disease in HIV infected Ugandans. Participants were recruited from five local HIV/AIDS Organisations in Masaka and Kalangala districts, Uganda: the AIDS Support Organisation (TASO), Uganda Cares Masaka, Kitovu Mobile AIDS Organisation, Kalangala District Health Services, and Masaka Regional Referral Hospital. Recruiting and enrollment took place between September 2004 and February 2008. To be included in the study, participants had to be older than 15 years and have a CD4 count of fewer than 200 cells per μL. Excluded were those who were pregnant/lactating, those with a serum titer of CrAg higher than 1/8, moribund patients, and those with concentrations of liver transaminases greater than three times the upper limit of normal (61).

The CRYPTOPRO trial was carried out in the MRC/UVRI and LSHTM Uganda Research Unit study site in Masaka, South West Uganda. A total of 1519 consenting and eligible HIV-infected participants were enrolled for the study, 760 were allocated fluconazole while 759 were on placebo (61). The trial participants were reviewed after 4 weeks of enrolment and thereafter referred for ART to an ART service provider, then followed up every 8 weeks. The time to initiation of ART depended on the service provider having supplies of ARVs available and the patient being able to identify a treatment supporter. Preference was given to those whose immune systems were severely compromised (62).

2.1.2 The PN sub-study

The PN sub-study was a repeated cross-sectional study nested within the CRYPTOPRO trial. Only participants who enrolled from July 2006 onwards were eligible (this was 766 / 1519 participants 50%). Only a sub-sample of those enrolled were selected as the PN study was one of a number of sub-studies and participants were only selected for one sub-study. A random sample of CRYPTOPRO participants who joined the trial from July 2006 onwards were recruited into the PN sub-study. The participants were similar to those not recruited in terms of sex, age, CD4 count and WHO stage at baseline. All consenting individuals were assessed by a study clinician for the existence of peripheral neuropathy using both self-report and clinical methods as described below. Standardized systematic sensation mapping was carried out on all enrolled participants and the distribution of the following symptoms: paraesthesias, aching/ pain (intermittent or electric, burning or tingling or tightness), hyperaesthesias, allodynia, and signs: pain (pin-prick), temperature, vibration, position, and deep tendon reflexes were noted.

The sensation mapping was repeated and the changes and any new developments in the different sensory modalities were noted. The date, duration, and type of ART regimen started were also recorded. If there was a change in the ART regime, that and the change in the clinical features of the patients were noted. WHO staging at enrollment was recorded. Other parameters that were recorded include age, sex, full blood count, and CD 4 count. CD 4 count and full blood counts were repeated at 4 months and every subsequent visit. Other laboratory tests conducted included random blood sugar (RBS), urea, creatinine, liver function tests. Any drugs the participant had taken in the last 2 weeks were noted in a bid to exclude drugs that cause peripheral neuropathy (i.e. pyridoxine, dapsone, ethambutol, isoniazid, hydralazine, metronidazole, cisplatin, vincristine, and suramin).

There were no fixed times concerning starting ART as the commencement of ART was at the discretion of the ART service providers rather than the CRYPTOPRO investigators. The patients therefore started ART at different times after recruitment into the CRYPTOPRO trial and the sub-study. Note that while the PN sub-study was carried out during the duration of the CRYPTOPRO study, the data has never been analysed.

2.2 Participant assessment for PN

All participants underwent an evaluation to determine self-reported PN and clinically determined PN once before ART and multiple times after the initiation of ART, for progress or new development of neuropathy as described below.

Self-reported method- Patients were asked questions about the presence and severity of their signs and symptoms (pain, pins, and needles, numbness) of PN for their left and right feet and legs, a severity scale of 1-10 was used, 1 being mild and 10 being severe. A single highest score was used from the scale to have subjective grades where grade 1 = 01-03, grade 2 = 04-06, grade 3 = 07-10 and grade 0 = where there were no signs and symptoms. An individual would be regarded as having PN if they had grades 1 - 3.

Clinically determined method – Physical examination was done using a fork to see the patient's recognition of vibration or buzzing when placed on their wrist and when placed on the joint of one great toe, counting the seconds for which the vibration lasted. Vibration seconds were graded, with grade 0 = greater than 10 seconds, grade 1 = 06-10 seconds, grade 2 = less than 5 seconds, grade 3 = no vibration feeling, grade 8 = no evaluation or assessment. Secondly, deep tendon reflexes were evaluated; with the subject seated the examiner used one hand to press upward on the ball of the foot, dorsiflexing the subject's ankle to 90 degrees. Using a reflex hammer the examiner then struck the Achilles tendon. The tendon reflex was felt by the examiner's hand as plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck. Ankle reflex grading was also created as follows, grade 0 = absent, grade 1 = hypoactive, grade 2 = normal tendon reflex, grade 3 = hyperactive, grade 4= clonus, grade 8 = no evaluation or assessment. An individual would be regarded as having PN if they had grade 1 – 3 in the self-reported method and vibration grade of 1-3 or ankle reflex of grade 1.

The questionnaire also included questions regarding their medical and drug history, besides the assessment of PN, the study investigator recorded the following: age, sex, weight, height, CD4+ cell count, WHO stage, ART regimen, use of other drugs, and alcohol intake.

2.3 Analysis

Objective 1: To describe the socio-demographic characteristics of PLHIV in Masaka, Uganda by presence and absence of PN

The categorical variables: sex, WHO stage, and ART regime were described using frequency percentages and charts while the continuous variables; age, days on ART, and units of alcohol intake were described using both the mean (standard deviation) and median (interquartile range). A unit of alcohol is equal to either one beer, a glass of wine, or a tot of spirits.

Objective 2: To determine the prevalence of PN among PLHIV before and after ART.

Two binary variables namely self-reported PN and clinically determined PN were used for the determination of prevalence. The prevalence of PN was determined separately for the two periods (enrolment into the sub-study and after initiating ART) and for the two methods of determining PN (self-reported and clinically determined)

Objective 3: To compare the sensitivity and specificity of self-reported PN as a surrogate marker of the gold standard, clinically determined PN.

Sensitivity and specificity for self-reported PN were determined using clinically determined PN as the gold standard separately for the two periods (enrolment into the sub-study and after initiating ART). A two by two (Diagnosis and Disease (PN)) table was created for the calculation of sensitivity and specificity.

Objective 4: To see whether Self-reported PN meets the Prentice criteria for a surrogate marker in determining PN before ART initiation.

The data that was provided was already cleaned, checks for missing data, and consistency had already been performed. Calculation of neuropathy score was performed, and the PN binary variables for both before and after ART were generated.

The important was to see whether the prediction models are similar for the two outcomes (self-reported and clinical PN). Including all variables in the model would result in multicollinearity which could blur the final model. The potential explanatory categorical (sex, WHO Stage, and isoniazid) and continuous

variables (age and alcohol intake) were available for selection into the model. A univariate analysis was done with all the potential explanatory variables to determine their association with PN. The model was built with potential explanatory variables, including only those which are significant at the 10% level to ensure that all important confounders are retained in the model.

To find a model for clinically determined PN, our outcome variable was the binary PN that was clinically determined; Fitted with explanatory continuous and dichotomous variables as they are and categorical variables recoded to specify indicators for each level of the variable. Confounders (Sex and age) were controlled for by being kept in the model even if they did not reach the 10% level of significance. A multivariate logistic regression model was fitted to estimate the association between PN and its risk factors. The model was fitted with clinically determined PN and the same model was refitted with self-reported PN as an outcome. To evaluate the 2nd Prentice criterion, the same variables were included in both models (Self-reported and Clinically determined), as long as the term was significant in one of the models it was included in both to compare the effect sizes.

A comparison was made to check whether variables that are found to have an association with PN for self-reported PN are the same as those found to have an association with PN for clinically determined PN, effect sizes were compared if the variables were significant for either clinically determined PN or self-reported PN.

Objective 5: To see whether self-reported PN meets the Prentice criteria for a surrogate marker in determining PN after ART initiation.

The above-described analyses in objective 4 were carried out on data obtained before ART to address objective 4 and after ART to address objective 5. The ART regimen variable was added to the model for objective 5 analysis as it was not relevant for objective 4 analysis.

2.4 Limitations

Recall bias – since participants were asked about their signs and symptoms, some may have recalled inaccurately. Post ART visits took place at different times after starting ART, since ART initiation took place at different times after enrolment into both the CRYPTOPRO trial and the PN sub-study, the prevalence of PN may differ depending on the duration on which one had been on ART. Study doctors would have been especially looking out for PN in the sub-study and were, therefore, more likely to find it.

2.5 Data and Ethical considerations

Approval for the use of the data was obtained from the MRC/UVRI and LSHTM Uganda Research Unit. Data confidentiality was maintained, anonymous identifiers were used instead of patient names. STATA 15 software was used for data analysis, the database file was password protected. Since this was a sub-study from the primary study, the two data sets were merged. New PN variables were created from the diagnosis results, another new variable age group was extracted from the continuous variable age. Participants gave written informed consent for the CRYPTOPRO trial which had approval from the Ethics Committee of the Uganda Virus Research Institute, the Ugandan Council for Science and Technology, and the Liverpool School of Tropical Medicine Research Ethics committee (63).

An ethical clearance certificate was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC), identifiers were used instead of participant names, the data set, and formal approval of data usage from MRC/UVRI and LSHTM Uganda Research Unit were also received. Confidentiality was always maintained, data was password protected with access by the researcher and supervisor only. The data will be kept for approximately 2.5 years until the publication of the research.

CHAPTER 3: RESULTS

The chapter presents and interprets the data analysis results obtained from our statistical analysis specified in Chapter 2. The structure of the chapter follows the five objectives of the study in order.

3.1 Description of socio-demographic characteristics

3.1.1 Before the initiation of ART

Table 4 below presents the socio-demographic characteristics of the participants before the initiation of ART. The demographics are presented for the self-reported and clinically determined methods of assessing PN.

Table 4 Distribution of socio-demographic characteristics before ART

Demographic Characteristics	Frequency	Proportion
Sex-		
Male	129	34.9%
Female	241	65.1%
WHO Stage –		
Stage 1	13	3.5%
Stage 2	83	22.4%
Stage 3	237	64.1%
Stage 4	37	10.0%
Age Group		
16-24	26	7.0%
25-34	144	38.9%
35-44	132	35.7%
45-54	53	14.3%
55-64	10	2.7%
65-74	5	1.4%
Isoniazid Yes	17	4.6%
No	352	95.4%
Alcohol		
None	270	74.6%
One unit	19	5.2%
Two unis	23	6.4%
Three or more units	50	13.8%

There were 370 participants in the study with an evaluation at baseline before they initiated ART. There were more female participants (65.1%) than male participants (34.9%). A very small proportion (3.5%) of participants were on the first WHO stage. More than half (64.1%) of the participants were at the third WHO stage. Approximately 75% of the participants did not drink alcohol and about 20% drank two or more units of alcohol.

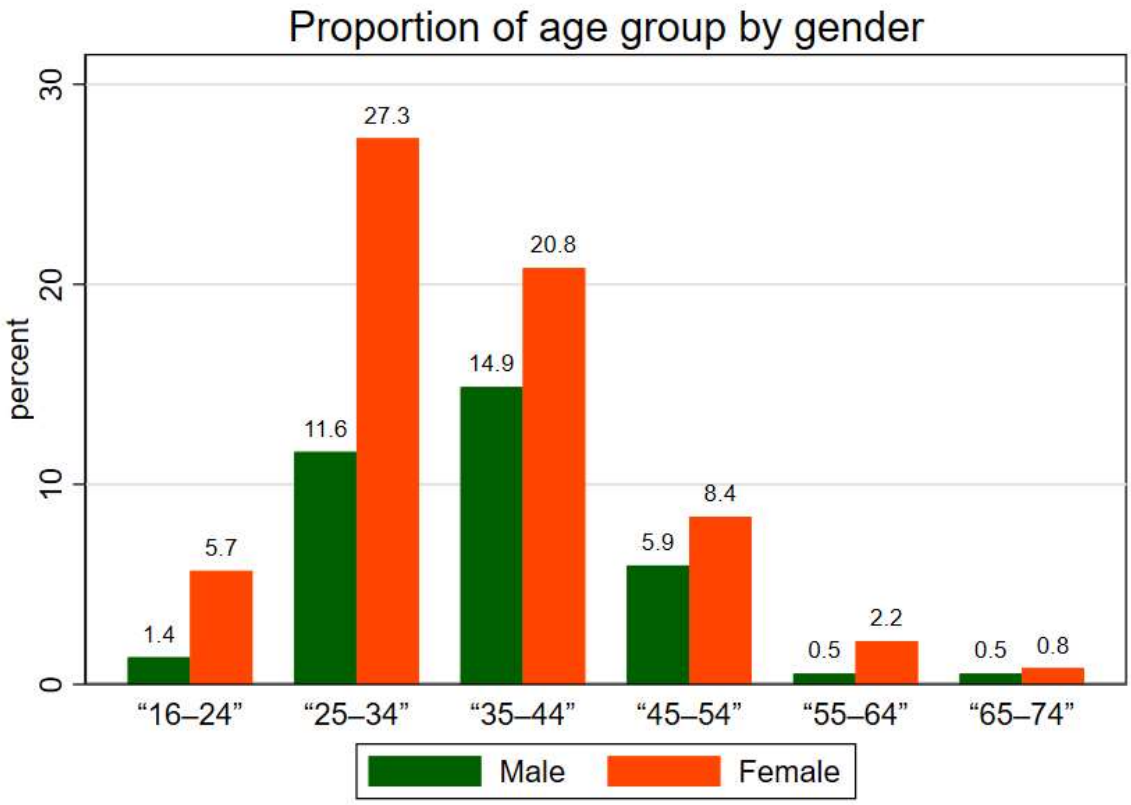
Table 5 Description of categorical demographics before ART

Demographic Characteristics	Self-Reported PN		Clinically-determined PN	
	PN n (%)	No PN n (%)	PN n (%)	No PN n (%)
Sex-				
Male	38 (29.5)	91 (70.5)	15 (11.6)	114 (88.4)
Female	50 (20.7)	191 (79.3)	23 (9.5)	218 (90.5)
WHO Stage –				
Stage 1	2 (15.4)	11 (84.6)	3 (23.1)	10 (76.9)
Stage 2	19 (22.9)	64 (77.1)	8 (9.6)	75 (90.4)
Stage 3	56 (23.6)	181 (76.4)	22 (9.3)	215 (90.7)
Stage 4	11 (29.7)	26 (70.3)	5 (13.5)	32 (86.5)
Age Group				
16-24	7 (26.9)	19 (73.1)	1 (3.8)	25 (96.2)
25-34	30 (20.8)	114 (79.2)	12 (8.3)	132 (91.7)
35-44	32 (24.2)	100 (75.8)	16 (12.1)	116 (87.9)
45-54	15 (28.3)	38 (71.7)	8 (15.1)	45 (84.9)
55-64	3 (30.0)	7 (70.0)	0 (0.0)	10 (100.0)
65-74	1 (20.0)	4 (80.0)	1 (20.0)	4 (80.0)
Isoniazid				
Yes	6 (35.3)	11 (64.7)	5 (29.4)	12 (70.6)
No	81 (23.0)	271 (77.0)	33 (9.4)	319 (90.6)
Alcohol				
None	65 (24.1)	205 (75.9)	29 (10.7)	241 (89.3)
One unit	3 (15.9)	16 (84.2)	0 (0.0)	19 (100.0)
Two unis	7 (30.4)	16 (69.6)	2 (8.7)	21 (91.3)
Three or more units	10 (20.0)	40 (80.0)	7 (14.0)	43 (86.0)
Total	88	282	38	332

Using self-report, 88 participants had PN, while only 38 (less than half the number) had PN when clinically assessed. In both assessments of PN, the prevalence of PN was higher among males than among females. For self-reported PN assessment, the prevalence of PN was higher in WHO stage 4 with 29.7%, while for clinically determined PN assessment, PN was more prevalent in the first WHO

stage with 23.1%, but this was based on only 13 participants who were at WHO stage 1. The prevalence of PN was high among those who drank two units of alcohol for self-reported assessment and for clinically determined assessment the prevalence was high among those who drank three or more units.

Figure 3 Distribution of study population by age and gender



Looking at figure 3 above, it is observed that the majority of the participants in the study before initiation of ART were females between the ages of 25 and 44. More than a quarter were males between ages 25 to 44. Less than 5% of the participants were over the age of 54 and less than 10% were below the age of 25. In all the categories of age group, the proportion of females is greater than that of males.

Table 6 Description of continuous demographics before ART

						Quantiles		
Variable	n	Mean	S.D	Min	Max	25%	Mdn	75%
Age	370	36.4	9.2	16	69	30	35	41

Table 6 above shows the average age of participants was 36, with the youngest participant being 16 years of age and the oldest being 69 years old. The median age was 35 years and 75% of the participants were under 41 years of age.

3.1.2 After the initiation of ART

Table 7 Distribution of socio-demographic characteristics after ART

Demographic Characteristics	Frequency	Proportion
Sex-		
Male	62	32.5%
Female	129	67.5%
WHO Stage –		
Stage 1	10	5.24%
Stage 2	51	26.7%
Stage 3	110	57.6%
Stage 4	20	10.5%
Age Group		
16-24	11	5.8%
25-34	82	42.9%
35-44	64	33.5%
45-54	27	14.1%
55-64	1	3.7%
Isoniazid		
Yes	18	9.6%
No	170	90.4%
Stavudine (D4T)		
Yes	85	45.0%
No	104	55.0%
Didanosine (Ddl)		
Yes	0	0.0%
No	189	100.0%
Lamivudine (3TC)		
Yes	185	96.9%
No	6	3.1%
Zidovudine (AZT)		
Yes	99	51.8%
No	92	48.2%
Alcohol		
None	168	88.0%
One unit	4	2.1%
Two unis	6	3.1%
Three or more units	13	6.8%

Table 7 above shows the distribution of socio-demographic characteristics after ART. Only 191 participants had PN assessed after initiation of ART, participants initiated ART at different times. Of the 191 participants, 67. 5% were females and 32.5% were males. . None of the participants had taken the ART drug ddl, while 3TC was the most commonly used ART drug, being taken by 96.9% of the participants. Ten percent of participants were taking isoniazid. About 88% of the participants did not drink alcohol and approximately 10% drank two or more units of alcohol.

Table 8 Description of categorical demographics after ART

Demographic Characteristics	Self-Reported PN		Clinically-determined PN	
	PN n (%)	No PN n (%)	PN n (%)	No PN n (%)
Sex-				
Male	19 (30.6)	43 (69.4)	8 (12.9)	54 (87.1)
Female	24 (18.6)	105 (81.4)	11 (8.5)	118 (91.5)
WHO Stage –				
Stage 1	0 (0.0)	10 (100.0)	0 (0.0)	10 (100.0)
Stage 2	16 (31.4)	35 (68.6)	8 (15.7)	43 (84.3)
Stage 3	22 (20.0)	88 (80.0)	9 (8.2)	101 (91.8)
Stage 4	5 (25.0)	15 (75.0)	2 (10.0)	18 (90.0)
Age Group				
16-24	2 (18.2)	9 (81.8)	1 (9.1)	10 (90.9)
25-34	16 (19.5)	66 (80.5)	5 (6.1)	77 (93.9)
35-44	14 (21.9)	50 (78.1)	8 (12.5)	56 (87.5)
45-54	9 (33.3)	18 (66.7)	4 (14.8)	23 (85.2)
55-64	2 (28.6)	5 (71.4)	1 (14.3)	6 (85.7)
D4T Yes	21 (24.7)	64 (75.3)	10 (11.8)	75 (88.2)
No	22 (21.2)	82 (78.8)	9 (8.7)	95 (91.3)
Ddl Yes	0	0	0	0
No	43 (22.8)	146 (77.2)	19 (10.1)	170 (89.9)
3TC Yes	42 (22.7)	143 (77.3)	18 (9.7)	167 (90.3)
No	1 (16.7)	5 (83.3)	1 (16.7)	5 (83.3)
AZT Yes	21 (21.2)	78 (78.8)	8 (8.1)	91 (91.9)
No	22 (23.9)	70 (76.1)	11 (12.0)	81 (88.0)
Isoniazid Yes	8 (44.4)	10 (55.6)	4 (22.2)	14 (77.8)
No	35 (20.6)	135 (79.4)	15 (8.8)	155 (91. 2)
Alcohol				
None	40 (23.8)	128 (76.1)	19 (11.3)	149 (88.7)
One unit	1 (25.0)	3 (75.0)	0 (0.0)	4 (100.0)
Two unis	2 (33.3)	4 (66.7)	0 (0.0)	6 (100.0)
Three or more units	0 (0.0)	13 (100.0)	0 (0.0)	13 (100.0)
Total	43	148	19	172

It is observed in Table 8 above that using self-report, 43 (22.5%)participants had PN, while only 19 (9.9%) (less than half the number) had PN when clinically assessed. The prevalence of PN was higher among males for both self-reported and clinically determined PN assessment with 30.6% and 12.9% respectively. PN was not detected in WHO stage 1 of either PN assessment method. The majority of the participants were at WHO stage 3, the prevalence of PN was however found to be greater at WHO stage 2 for both self-reported PN assessment and clinically determined PN assessment with 31.4% and 15.7% respectively. The prevalence of PN among those taking isoniazid was 44.4% for self-reported assessment and 22.2% for clinically determined PN assessment. The prevalence of PN was high among those who drank two units of alcohol for self-reported assessment and the prevalence was zero for those who drank alcohol when the clinically determined assessment was used.

Table 9 Description of continuous demographics after ART

						Quantiles		
Variable	n	Mean	S.D	Min	Max	25%	Mdn	75%
Age	191	36.3	8.9	16	62	30	35	41
Months on ART	191	3.9	3.1	0.9	22.9	1.5	3.2	4.7

The description of continuous demographics after ART is stipulated in Table 9 above. The average age of participants was 36, with the youngest participant being 16 years of age and the oldest being 62 years old. The median age was 35 years and 75% of the participants were under 41 years of age. A higher prevalence of PN was observed in those older than 45 years for both assessments of PN. On average, participants drank 0.7 units of alcohol. Over 75% of the participants did not drink but only one participant drank up to a maximum of 40 units of alcohol. The participants were on ART for approximately 4 months on average, the minimum months on ART was approximately 1 month, and a maximum of 23 months. Three-quarters of the population had been on ART for 4 months and 3 weeks.

3.2 Prevalence of PN among PLHIV before and after ART.

Table 10 Prevalence of PN before ART

Before ART	Self-reported PN		Clinically determined PN	
PN	Frequency	(%)	Frequency	(%)
Yes	88	23.8	38	10.3
No	282	76.2	332	89.7
Total	370	100	370	100

Before the initiation of ART, PN was assessed using the self-reported and clinically determined methods. Table 10 above indicates that with the self-reported assessment, PN was detected in 23.8% of participants while for clinically determined, only 10.3% had PN. The self-reported method detected more than double what the clinically determined method of assessment detected.

Table 11 Prevalence of PN after ART

After ART	Self-reported PN		Clinically determined PN	
PN	Frequency	(%)	Frequency	(%)
Yes	43	22.5	19	9.9
No	148	77.5	172	90.1
Total	191	100	191	100

After the initiation of ART, PN was assessed using the self-reported and clinically determined methods. With the self-reported assessment, PN was detected in 22.5% of participants while for clinically determined, less than 10% had PN. The self-reported method has detected more than double what the clinically determined method of assessment had detected. More than 75% of participants did not have PN regardless of the PN assessment method used.

3.3 Sensitivity and specificity of self-reported PN

Table 12 Sensitivity and Specificity test before initiation of ART

Agreement between Clinically determined and self-reported PN			
	PN		
Test	Yes	No	Total
Positive	15	73	88
Negative	23	259	282
Total	**38**	**332**	**370**
Sensitivity	39.5 %	(95% Confidence Interval)	(24% ; 57%)
Specificity	78.0 %	(95% Confidence Interval)	(73% ; 82%)
Positive Predictive value	17.1 %	(95% Confidence Interval)	(10% ; 27%)
Negative predictive value	91.8 %	(95% Confidence Interval)	(88% ; 95%)
Accuracy (Overall)	74.1 %	(95% Confidence Interval)	

In the assessment of PN, the self-reported screening method was tested for validity with the clinically determined method as the gold standard. The probability that the self-reported assessment will correctly detect a positive PN for participants who were assessed to have PN by the clinically determined assessment method of PN is 39.5% (Sensitivity). The sensitivity rate is very low, it indicates that the use of the self-reported assessment method of PN may detect false negatives for 60.5% of participants who have PN.

Looking at Table 12 above, the specificity of the self-reported assessment of PN is 78.0%. This implies that the ability of the self-reported assessment method to detect a negative PN for participants who do not have PN is 78.0%. It may return false positives for 22% of the participants who do not have PN.

A total of 88 participants were assessed to have PN by the self-reported method, but only 15 of these participants had the disease according to the clinically determined method. The positive predictive value provided in Table 12 above indicates that among those who were assessed to have PN by the self-reported method, the probability of actually having PN was 17.1%.

A total of 282 participants were assessed not to have PN by the self-reported method, but only 259 of these participants did not have PN according to the clinically determined method. The negative predictive value provided in Table 12 above indicates that among those who were assessed not to have PN by the self-reported method, the probability of actually not having PN was 91.8%.

Table 13 Sensitivity and Specificity test after initiation of ART

Correlation between Clinically determined and self-reported PN			
	PN		
Test	Yes	No	Total
Positive	14	29	43
Negative	5	143	172
Total	**19**	**172**	**191**
Sensitivity	73.7 %	(95% Confidence Interval)	(49% ; 91%)
Specificity	83.1 %	(95% Confidence Interval)	(77% ; 88%)
Positive Predictive value	32.6 %	(95% Confidence Interval)	(19% ; 49%)
Negative predictive value	96.6 %	(95% Confidence Interval)	(92% ; 99%)
Accuracy (Overall)	82.2 %	(95% Confidence Interval)	

In the assessment of PN after ART initiation, the self-reported screening method was tested for validity with the clinically determined method as the gold standard. The probability that the self-reported assessment will correctly detect a positive PN for participants who were assessed to have PN by the clinically determined assessment method of PN is 73.7% (Sensitivity). With that sensitivity rate, the use of the self-reported assessment method of PN may detect false negatives for 26.3% of participants who have PN.

Looking at Table 13 above, the specificity of the self-reported assessment of PN is 83.1%. This implies that the ability of the self-reported assessment method to detect a negative PN for participants who do not have PN is 83.1%. It may return false positives for 16.9% of the participants who do not have PN.

A total of 43 participants were assessed to have PN by the self-reported method, but only 14 of these participants had the disease according to the clinically determined method. The positive predictive value provided in Table 13 above indicates that among those who were assessed to have PN by the self-reported method, the probability of actually having PN was 32.6%.

A total of 172 participants were assessed not to have PN by the self-reported method, but only 143 of these participants did not have PN according to the clinically determined method. The negative

predictive value provided in the Table 13 above indicates that among those who were assessed not to have PN by the self-reported method, the probability of actually not having PN was 96.6%.

3.4 To see whether Self-reported PN meets the Prentice criteria for a surrogate marker in determining PN before ART initiation

3.4.1 Factors associated with PN before initiation of ART.

The table below presents the results of logistic regression analysis to determine the factors associated with PN for both self-reported and clinically determined PN before initiation of ART.

Table 14 Logistic regression analysis determining factors associated with PN before ART

Factors	**Self-Reported**				**Clinically determined**			
	Univariate analysis		Multivariate		Univariate analysis		Multivariate	
	Unadjusted OR (CI 95%)	***P-value***	***Adjusted AOR (CI 95%)***	***P-value***	***Unadjusted OR (CI 95%)***	***P-value***	***Adjusted AOR (CI 95%)***	***P-value***
Age	1.01 (0.98-1.04)	0.330	1.01 (0.99-1.04)	0.348	1.01 (0.98-1.05)	0.353	1.02 (0.98-1.06)	0.268
Sex- *Male* *Female*	 Reference 0.63 (0.38-1.02)	 0.062	 Reference 0.68 (0.41-1.12)	 0.129	 Reference 0.80 (0.40-1.60)	 0.530	 Reference 0.91 (0.45-1.85)	 0.801
WHO Stage *Stage 1* *Stage 2* *Stage 3* *Stage 4*	 Reference 1.63 (0.33-8.02) 1.70 (0.37-7.91) 2.33 (0.44-12.3)	 0.546 0.498 0.320			 Reference 0.36 (0.08-1.56) 0.34 (0.09-1.33) 0.52 (0.11-2.57)	 0.171 0.122 0.424		
Isoniazid No Yes	 Reference 1.82 (0.65-5.09)	 0.250	 1.73 (0.61-4.92)	 0.301	 Reference 4.03 (1.34-12.14)	 0.013	 Reference 4.25 (1.37-13.16)	 0.012
Alcohol	0.99 (0.94-1.05)	0.840			0.99 (0.91-1.07)	0.715		

3.4.1.1 Self-reported PN

Table 14 above shows the logistic regression analysis determining factors associated with PN before ART. the univariable analysis of self-reported PN, no variable was significantly associated with PN, although sex was marginally significant (OR=0.63, 95% CI =0.38 – 1.02; P=0.062). This indicates that females were less likely to be diagnosed with PN compared to Males. In the multivariable logistic regression model, no variable was statistically significantly associated with PN.

3.4.1.2 Clinically determined PN

In a univariate analysis, isoniazid was the only variable that was found to be statistically associated with PN (OR = 4.03, 95% CI =1.34 – 12.14; P=0.013). This indicated that those taking isoniazid were four times more likely to be diagnosed with PN compared to those who were not taking isoniazid. For the multivariate analysis, isoniazid remained significant while age and sex had no statistical association with PN.

The Univariate analysis results for self-reported PN differ from those of clinically determined PN. For self-reported PN, only sex is marginally significant while for clinically determined PN isoniazid is the only statistically significant variable. For clinical PN, the effect size for isoniazid is given by an OR of 4.03 compared to an OR of 1.82 for self-reported PN – so the estimated effect sizes are very different. For multivariate analysis, the results still differ. All variables are not statistically significant for self-reported while isoniazid remains the only statistically significant variable for clinically determined PN. For clinical PN, the effect size for isoniazid is given by an aOR of 4.25 compared to an aOR of 1.73 for self-reported PN indicating that the estimated effect sizes are very different. Prentice criteria does not hold since the effect sizes for all variables except age differ when compared using self-reported PN and clinical PN.

3.5 To see whether Self-reported PN meets the Prentice criteria for a surrogate marker in determining PN after ART initiation.

3.5.1 Factors associated with PN after initiation of ART.

The table below presents the results of logistic regression analysis to determine the factors associated with PN for both self-reported and clinically determined PN after initiation of ART.

Table 15 Logistic regression analysis determining factors associated with PN after ART

Factors	**Self-Reported**				**Clinically determined**			
	Univariate analysis		Multivariate		Univariate analysis		Multivariate	
	Unadjusted OR (CI 95%)	***P-value***	***Adjusted AOR (CI 95%)***	***P-value***	***Unadjusted OR (CI 95%)***	***P-value***	***Adjusted AOR (CI 95%)***	***P-value***
Age	1.02 (0.98-1.06)	0.280	1.02 (0.98-1.06)	0.393	1.04 (0.99-1.10)	0.105	1.04 (0.99-1.10)	0.123
Sex- *Male* *Female*	 Reference 0.52 (0.26-1.04)	 0.064	 Reference 0.64 (0.31-1.33)	 0.228	 Reference 0.63 (0.24-1.65)	 0.347	 Reference 0.87 (0.31-2.43)	 0.792
WHO Stage *Stage 1* *Stage 2* *Stage 3* *Stage 4*	 Reference 1.4 (0.42-4.42) 0.75 (0.25-2.29) Omitted	 0.597 0.613			 Reference 1.67 (0.32-8.67) 0.80 (0.16-4.02) Omitted	 0.539 0.788		
ART Drugs *D4T* *Ddl* *3TC* *AZT*	 0.82 (0.41-1.62) Omitted 0.68 (0.08-5.99) 1.17 (0.59-2.30)	 0.563 0.729 0.655			 0.71 (0.27-1.84) Omitted 1.86 (0.21-16.8) 1.54 (0.59-4.03)	 0.481 0.582 0.374		
Isoniazid	3.09 (1.13-8.40)	0.027	2.87 (1.03-8.01)	0.044	2.95 (0.86-10.11)	0.085	3.13 (0.87-11.29)	0.081
Alcohol	0.70 (0.42-1.15)	0.160			Omitted			
ART Months	1.09 (0.99-1.21)	0.085	1.09 (0.98-1.22)	0.104	1.15 (1.02-1.30)	0.023	1.16 (1.02-1.32)	0.025

3.5.1.1 Self-reported PN

Table 15 above shows the logistic regression analysis determining factors associated with PN after ART. For the univariable analysis of self-reported PN, only the use of isoniazid was statistically associated with PN (OR = 3.09, 95% CI =1.13 – 8.40; P=0.027), while sex was marginally significant with (OR = 0.52, 95% CI =0.26 – 1.04; P=0.064). Those taking isoniazid were three times more likely to be diagnosed with PN compared to those who were not taking isoniazid and females were less likely

to be diagnosed with PN compared to males. In a multivariable logistic regression model only use of isoniazid was statistically associated with PN (OR = 2.87, 95% CI =1.03 – 8.01; P=0.044).

3.5.1.2 Clinically determined PN

In univariable analysis, only months on ART variable was statistically significant with (OR = 1.15, 95% CI =1.02 – 1.30; P=0.023), while the use of isoniazid was marginally significant with (OR = 2.95, 95% CI =0.86 – 10.11; P=0.085). The marginal significance of the use of isoniazid shows that those on TB treatment were 2.95 times more likely to be diagnosed with PN compared to those who were not on the TB treatment. With an increase in the number of months on ART, the likelihood of being diagnosed with PN was 15% more. For the multivariable analysis, months on ART remained statistically associated with PN (OR = 1.16, 95% CI =1.02 – 1.32; P=0.025) and isoniazid also remained marginally significant with (OR = 3.13, 95% CI =0.87 – 11.29; P=0.081) while age and sex were not statistically associated with PN.

The Univariate analysis results for self-reported PN differ from those of clinically determined PN. For self-reported PN, sex and months on ART are marginally significant while isoniazid is statistically associated with PN. For clinically determined PN, months on ART is statistically significant while isoniazid is marginally significant. The clinical PN effect size for isoniazid is given by an OR of 2.95 compared to an OR of 3.09 for self-reported PN – so the estimated effect sizes are similar as they are approximately equal to 3. The effect size for months on ART was 1.15 and 1.09 for clinically determined PN and Self-reported PN respectively, they are also similar.

For multivariate analysis, the results still differ. For Self-reported assessment of PN, the odds of developing PN is 2.78 times among those using Isoniazid compare to those not using it. Other variables fitted in the model did not have an association with PN; With clinically determined PN, those who were on ART for one more month were 16% more likely to develop PN while those using Isoniazid were 3.13 times more likely to develop PN compared to those not using it. Age and sex were not statistically associated with PN but are possible confounders. For clinical PN, the effect size for isoniazid is given by an aOR of 3.13 compared to an aOR of 2.87 for self-reported PN indicating that the estimated effect sizes are similar. Even though the effect sizes are similar after ART, the Prentice criteria does not hold because for it to hold it must hold in all circumstances, which is not the case

since it did not hold at baseline (pre-ART), the fact that isoniazid is only marginally significant for clinically determined PN but is significant for self-reported PN also denotes a significant difference.

CHAPTER 4: DISCUSSION

In this chapter, an overview of the study findings presented in the previous chapter is provided. The results are also compared to previously conducted similar studies. To investigate whether self-reported PN can be used as a surrogate outcome measure for clinically-determined PN, self-reported PN needs to be easily measured, it has to have a strong association with clinical PN and it has to be affected in a similar way to clinical PN. While several peripheral neuropathy screening instruments have been tested in various clinical settings, none has been assessed for use with PLHIV (21).

Before Initiation of ART

Self-reported PN is easily measured as it does not require any special equipment for it to be measured, but it may attract information bias because its results depend solely on what the participant indicates following the questionnaire. According to a previous study in Kenya, it was evident that it can be administered quickly as it took just a few minutes and was incorporated within time constraints of follow-up visits in a busy clinic without any undesirable consequences (35).

To determine its accuracy in estimating PN before ART initiation, it was observed that the self-reported method reported more participants 88 (23.5%) with PN compared to the clinically determined method which reported 38 (10.3%) participants with PN. The prevalence of PN determined using the self-reported method was more than double the prevalence of PN determined using the clinically determined method. With the clinically determined method being the gold standard, we can conclude that the self-reported method of determination overstates the number of participants with PN. Similar results were obtained in a study in Rwanda, where a high prevalence of PN in women was observed using self-reported method compared to using the clinically determined method, the study suggested that there was a possibility that the self-reported method overstated the prevalence of PN (64). Using both self-reported and clinically determined methods, the prevalence of PN was higher in males and in participants who were taking isoniazid. The magnitude of the proportion is however different for the two assessment methods. The prevalence of PN was higher in those who were in WHO stage 4 when determined through the self-reported method, but higher in those who were in WHO stage 1 when determined through the clinically determined method. The prevalence was also observed to be higher

in the age group 55-64 when using the self-reported method, while PN prevalence was higher in the age group 65-74 when using the clinically determined method.

In establishing the validity of the self-reported method, the sensitivity and specificity of the self-reported method were 39.4% and 78.0% respectively. The sensitivity is very low and will result in a lot of positive PN being missed. Using the self-reported method of assessing PN, 60.5% of those who have PN will be wrongly classified as not having PN and 22.0% of those who do not have PN will be wrongly classified as having PN. The probability of actually having PN among those who tested positive for PN using the self-reported method is 17.1% and the probability of not having PN among those who tested negative is 91.8%. In a study in Kenya, about 46% of participants who indicated having symptoms of PN were found not to have PN on physical examination, and 33% of those who did not have any PN symptoms had PN on physical examination (35). This indicates that we cannot solely depend on reported PN symptoms for assessment as some people may be asymptomatic. The lower specificity of the self-reported PN method is due to the absence of the physical test, which is primarily contained in the clinically determined method.

For the univariate analysis of the clinically determined PN method, all factors besides being on TB treatment were not significant, suggesting a statistical association does not exist between them and PN. Being on TB treatment continued to be significant in the multivariate analysis, those on TB treatment were four times more likely to develop PN. For the self-reported method of PN, all factors were not significant for multivariate analysis, showing no association with PN. Only sex was marginally significant for univariate analysis but had no statistical association with multivariate analysis.

Clinically determined and self-reported methods of PN do not yield the same factors that are associated with PN, all variables are not statistically significant for self-reported while isoniazid remains the only statistically significant variable for clinically determined PN. For clinical PN, the effect size for isoniazid is given by an aOR of 4.03 compared to an aOR of 1.82 for self-reported PN – so the estimated effect sizes are very different, this indicates that self-reported PN does not capture the entire effect of the association with clinically determined PN.

The chi-square however indicated that there is an association between the two assessment methods. Fleming once said, “a correlate does not a surrogate make” (28), he simply wanted to clarify that

correlation alone does not qualify a surrogate marker. Since the self-reported PN method does not meet all Prentice criteria for the surrogate marker, it cannot be considered as a surrogate marker. In multiple cardiovascular diseases, surrogate markers have proved to be unreliable predictors of true endpoints, an example is the antiarrhythmic medications' inability to improve survival rates by lowering Ventricular Premature Beats (VPB) rates (59).

After initiation of ART

Similar results were observed after initiation of ART, the self-reported method reported 24 (12.6%) more participants with PN compared to the clinically determined method. Self-reported still detected more than double the number of cases that were detected by the clinically determined method. Both assessment methods of PN reported more PN in males than in females, more PN in WHO stage 2 compared to other stages, and more PN in participants aged 45 to 54 years although the proportions varied between the two assessment methods.

The self-reported method had a sensitivity and specificity rate of 73.7% and 83.1% respectively. A little more than a quarter of participants with PN is missed and a little more than a quarter of participants without PN may be misclassified as having PN. The probability of actually having PN among those whom the self-reported method detected PN is 32.6% and the probability of not having PN among those whom PN was not detected is 96.6%. The sensitivity, specificity, and negative predictive value of self-reported after the initiation of ART are good. One would for this reseason believe self-reported can be a surrogate marker for clinically determined PN, however self-reported PN needs to satisfy all criteria set by Ross Prentice to be considered as a surrogate marker.

In a univariate analysis of the clinically determined PN method, being on TB treatment was marginally significant and the number of months on ART was significant. The results remained the same for multivariate analysis. For univariate analysis of the self-reported method, sex was marginally significant, and being on TB treatment was significant. Being female was protective while having TB increased the risk of PN. When the multivariate analysis was done, only being on TB treatment was statistically associated with PN with 2.9 times the likelihood to develop PN.

Clinically determined and self-reported methods of PN both yielded that being on TB treatment is associated with PN, it increased the risk of PN with similar effect sizes for both assessments. Self-reported PN yielded that sex is associated with PN but clinically determined PN did not have the same result. This indicates that self-reported PN does not capture the entire effect of the association with clinically determined PN. In a study about the reliability of subjective peripheral neuropathy screening, McArthur indicated that subjective peripheral neuropathy screening cannot be used alone for a definitive diagnosis of peripheral neuropathy (21).

The self-reported PN predicts the clinically determined outcome better after the initiation of ART compared to before the initiation of ART. A similar study however stated that after initiation of ART, a combination of these two assessments would accurately assess the incidence of PN (35). Looking at what has been discussed above, it is evident that the self-reported PN method does not satisfy some of the criteria set by Prentice for a surrogate marker for both before and after initiation of ART. Twaddell advises that without evidence of validity, they should not be put into use as surrogates (65). A similar study found self-reported PN to be a reliable assessment method for the determination of PN (21), the difference in findings could have been constituted by different validation methods that have been used.

There are several possible reasons why surrogates may fail, firstly, the surrogate marker may not be on the disease process's causal pathway. Secondly, one pathway can be mediated by the surrogate, but not all pathways may be mediated by the surrogate. Thirdly, the surrogate may not be on the intervention's effect pathway. And lastly, under some poorly understood circumstances, a given pathway can be significant, but not in others (66). A few studies assessed the reliability of self-report PN but not surrogacy. Self-reported PN was found to be reliable in most studies, but not in all. However, that does not qualify it to be a surrogate marker. An example is a previous study in Zambia that had high sensitivity (95.7%), specificity (80%), PPV (88.2%), and NPV (92.3%) for self-reported PN (67).

Limitations

The study used both assessments of PN on the same people, an individual was assessed for PN using the self-reported and the clinically determined method by the same assessor, providing more accuracy on individual results. Several limitations however have to be considered. The self-reporting may attract reporting bias, therefore under or overestimating the reported presence of PN. Some risk factors could attract social desirability bias as participants tend to underreport those behaviors that are not desirable and over-report those that are desirable, this leads to skewed results. Secondary data was analyzed, the limitation is that the data is not analysed by the person who collected it. As a result, they are likely to be unaware of study-specific details or data collecting flaws that could affect the interpretation of specific variables in the dataset.

Due to the study being a cross-sectional study, our ability to make inferences about the causality was limited. The limitation on selection was that there were a number of sub-studies running concurrently, leading to a smaller number of participants into the study. This resulted in a small number of participants with clinically determined PN. The characteristics of those who enrolled in the sub-study were not different from those who did not enroll; the participants were similar to those not recruited in terms of sex, age, CD4 count and WHO stage at baseline. Information was collected on several factors in the main study, data access approval was however provided for the PN sub-study data only with fewer factors.

Since the sub-study only started in 2006, only about half the CRYPTOPRO participants were eligible. There were a number of sub-studies and each could only have a limited number of participants as each participant could only partake in one. This resulted in a relatively small number of participants in the PN study, which was an issue given the low proportion with clinical PN. Due to the limitation of ART stock in Uganda, participants took different ART regimens, the effect of these drugs on PN differed. The number of participants with clinically diagnosed PN after starting ART was very small (N=19); It has an impact on the reliability of the results since it causes more variability, which can contribute to bias as a result of sparse data.

Conclusion and recommendation

Self-reported PN cannot be used as a surrogate marker for clinically determined PN because it does not meet the Prentice criteria requirements of a surrogate marker, particularly in the case of PN before the initiation of ART. Although there is a significant statistical relationship between self-reported PN and clinically determined PN, the sensitivity of self-reported PN was very low before the initiation of ART indicating unreliability. Self-reported PN also does not capture the entire effect of the association with clinically determined PN as the factors associated with PN varied for the two assessments. Both assessment methods are valuable for determining PN.

Surrogate markers can be good replacements for true endpoints in certain situations when validated but not in situations where their reliability and validity are unknown (66). After assessing the disease's mechanisms of action, researchers can carefully select those that fit the criteria of being a surrogate marker. Follow-up research with true endpoints is recommended before a surrogate marker is accurate.

Had the self-reported method satisfied the Prentice criteria of a surrogate marker, it would have helped PLHIV in resource-limited environments to avoid severe morbidity and improve their life by accurately and rapidly diagnosing PN. I however recommend the use of self-reported PN, more especially after initiation of ART, not as a surrogate marker but as a preliminary assessment while waiting to access the clinically determined diagnosis. This will assist those who are found to be PN positive to start with unharmful PN treatment methods such as managing symptoms and the use of nutritional supplements.

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APPENDICES

Appendix 1: Plagiarism declaration report

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Mpho Nomthimkhulu Pitso (Student number: 337718) am a student registered for the degree of MSC (Epidemiology & Biostatistics) in the academic year 2022

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 07 April 2022

Appendix 2: Questionaire

CRYPTOCOCCAL TRIAL – Neuropathy study

Name NAME

SP number / SPNO Trial No TRNUM

Clinical Assessment

Date of assessment

Date of enrolment

Is the participant taking or taken in the last 2 months any of the following medications?

	Yes = 1 no = 2	If yes,	Dose currently taking	Length of time at this dose
D4T	D4T			
DdI	DDI			
3TC	3TC			
AZT	AZT			
Isoniazid	ISO			
Ethambutol	ETH			
Metronidazole	MTZ			
Dapsone	DAP			

Chemotherapy CHEM if yes specify _____

How much alcohol does the participant take per week? Units UNITS
(1 bottle of beer = 2 units, 1 tot of spirit = 1 unit, 1 glass of wine = 1 unit)

Does the participant have any existing medical conditions (apart from HIV) e.g. diabetes, renal failure, liver failure, thryroid problems, COPD, carcinoma, porphyria, vitamin defiencencies, malabsorbtion, myeloma, polycythaemia?

Version1.18.07.06 Form C.PN1 page 1

Trial Number ☐☐☐☐☐ Date ☐☐ ☐☐ ☐☐☐☐

Subjective Evaluation

Instructions
a) Ask the subject to rate the severity of each symptom listed in Q2 (a-c) on a scale of 01 (mild) to 10 (most severe) for right and left feet and legs.

b) Enter the score for each symptom in the column marked presence/ severity
- 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"
- The use of –1 is not acceptable as an answer to any question

1. Was a subjective elicited peripheral neuropathy evaluation completed? (1=yes, 2=no) ☐ EVAL
if yes, go to question 2.

If no, indicate reason. 1= subject declined, specify why _____ ☐ NOEVAL
9=other reason, specify _____

2. Symptoms (use table below to grade)

	Right		Left	
2.1. Pain, aching, or burning in feet, legs	☐☐	PAINR	☐☐	PAINL
2.2 "Pins and needles" in feet, legs	☐☐	PINR	☐☐	PINL
2.3 Numbness (lack of feeling) in feet, legs	☐☐	NUMR	☐☐	NUML

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

3. Subjective peripheral neuropathy grade
Use the single highest severity score from 01-10 in question 2 (a-c) above to obtain a subjective peripheral neuropathy grade.
If all severity scores are "00" or "11" the subjective peripheral neuropathy grade will equal "0"

Presence / severity score of
01-03 = grade1
04-06 = grade 2
07-10 = grade 3
11 or 00 = grade 0

Subjective peripheral neuropathy grade ☐☐ SPNG

Trial Number ☐☐☐☐☐ Date ☐☐ ☐☐ ☐☐☐☐

Examination

1. Vibration

Strike the end of a 128Hz tuning fork hard enough so that the sides touch.
Place the vibrating tuning fork on the subject's wrist so that they can recognise the vibration or "buzzing" of the fork.
Again strike the fork hard enough so that the sides touch
Place the fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops.
Repeat for the other great toe.

1.a. Was an evaluation of perception of vibration completed? (yes=1, no=2) ☐ VIBE

If no, Why _____

Now continue to Q2

	Right	Left
If yes, What was the perception for the DIP great toe	☐ VIBR	☐ VIBL

Vibration perception grading
0 = Vibration felt for >10 seconds (normal)
1 = Vibration felt for 6-10 seconds (mild loss)
2 = Vibration felt for 5 seconds or less (moderate loss)
3 = No feeling of vibration (severe loss)
8 = unable to evaluation or did not assess

2. Deep tendon reflexes

With the subject seated the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subject's ankle to 90 degrees.
Using a reflex hammer the examiner then strikes the Achilles tendon.
The tendon reflex is felt by the examiners hand as a planter flexion of the foot, appearing after a slight delay from the time the Achilles tendon was struck.
If necessary use reinforcement, but having subject clench fist first.

2.a. Was an evaluation of deep tendon reflexes completed? (yes=1, no=2) ☐ REFE

If no, why _____

	Right	Left
If yes, what was the ankle reflex response?	☐ REFR	☐ REFL

Ankle reflex grading
0=absent
1=hypoactive
2=Normal deep tendon reflex
3=Hyperactive
4=Clonus
8 = unable to evaluation or did not assess

Trial Number ☐☐☐☐☐ Date ☐☐ ☐☐ ☐☐☐☐

If the subject has the following continue with assessment:

1) Subjective peripheral neuropathy grade of 1-3
AND one of
2) Vibration grade of 1-3 at DIP of great toe **OR** ankle reflex response of 1

Then proceed to further neuropathy assessment ↓ and affix substudy sticker to front of file

If no evidence of neuropathy, stop here.

Detailed Neuropathy Assessment

Tendon reflexes (please grade as above)

	R	L
Knee	☐	☐
Ankle	☐	☐
Planter	☐	☐

(upgoing, downgoing or absent)

Sensation

Light touch and pinprick (use neuropen, as per instructions). Document pattern of reduced sensation (red for pinprick and blue for light touch)

Proprioception

Hold joint at either side (not on top) and document if the participant can feel the position of the joint

	R	L
Great toe DIP	☐	☐
Ankle	☐	☐
Knee	☐	☐

Trial Number ☐☐☐☐☐ Date ☐☐ ☐☐ ☐☐☐☐

Urine and blood glucose assessment

Please dipstick the urine using Cypress Diagnostics Urine 10 dipsticks

	Neg	+/-	+	++	+++
What is the glucose result?	☐	☐	☐	☐	☐

Are there any other urinary abnormalities? (yes =1/ no =2.) ☐
If yes, specify _____

What is the blood glucose on the rapid test? ☐☐

If these are abnormal, proceed to serum glucose assessment (1 x grey top bottle) →

Laboratory assessment

ALT	☐☐☐.☐	IU/l
AST	☐☐☐.☐	IU/l
ALP	☐☐☐.☐	IU/l
Total Bilirubin	☐☐☐.☐	µmol/l

Is the liver function normal? (yes =1/ no =2.) ☐ LFT Date taken ☐☐ ☐☐ ☐☐☐☐

Urea	☐☐☐.☐	mmol/l
Creatinine	☐☐☐.☐	µmol/l

Is the renal function normal? (yes =1/ no =2.) ☐ RFT Date taken ☐☐ ☐☐ ☐☐☐☐

Glucose ☐☐☐.☐ mmol/l

Is there evidence of Diabetes? (yes =1/ no =2.) ☐ DM Date taken ☐☐ ☐☐ ☐☐☐☐

What is the CD4 count? ☐☐☐☐ CD4 Date taken ☐☐ ☐☐ ☐☐☐☐

HB ☐☐.☐ g/dl

HCT ☐☐.☐ % Date taken ☐☐ ☐☐ ☐☐☐☐

MCV ☐☐☐ fl.

Are there RBC abnormalities (suggesting polycythaemia or B12 def?) (yes =1/ no =2.) ☐

Appendix 3: Ethical Clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Ms M Pitso
School of Public Health
Medical Shool
University

E-mail: 337718@students.wits.ac.za

CC: Supervisor: Professor J Levin <Jonathan.Levin@wits.ac.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/09/11

REF: *R14/49*

PROTOCOL NO: **M200128** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Validity of self-reported peripheral neuropathy as a surrogate marker for clinically-determined peripheral neuropathy in HIV/AIDS patients initiating ART in Masaka, Uganda, 2004-2008*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Ms M Pitso

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200128

NAME: (Principal Investigator)	Ms M Pitso
DEPARTMENT:	School of Public Health Medical Shool University
PROJECT TITLE:	Validity of self-reported peripheral neuropathy as a surrogate marker for clinically-determined peripheral neuropathy in HIV/AIDS patients initiating ART in Masaka, Uganda, 2004-2008
DATE CONSIDERED:	2020/01/31
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor J Levin
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/09/11

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **January** and will therefore reports and re-certification will be due early in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

12/09/2020
Date

Appendix 4: Approval of title

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

06 January 2021
Person No: 337718
PAG

Mrs MN Pitso

Dear Mrs Mpho Pitso

Master of Science in Epidemiology: Approval of Title

We have pleasure in advising that your proposal entitled *Validity of Self-reported Peripheral Neuropathy (PN) as a surrogate marker for clinically-determined PN in HIV/AIDS patients initiating ART in Uganda, Masaka, 2004-2008* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 5: Data use agreement

MRC/UVRI and LSHTM Uganda Research Unit

Medical Research Council | Uganda Virus Research Institute | London School of Hygiene & Tropical Medicine

SHARING OF DATA

We propose that the data described below will be shared with the centre and the individuals specified and that research for the purpose also specified in detail below can be conducted on these data.

We guarantee that:

1. These data will not be passed on in whole or in part to a third party without permission from the Director of the MRC / UVRI and LSHTM Uganda Research Unit.
2. Publications of any sort, or public presentations, based on these data will be prepared in collaboration with the MRC/UVRI and LSHTM Project team, and the authorship list will be approved by the Head of Programme of the Unit and the Director of the Unit.
3. The data will not be used for any other purpose other than that for which approval was given.
4. The data will be used only once the written approval of the Director of the Unit has been obtained.
5. Any data stored on laptop computers will be encrypted.

Name: Prof Jonathan Levin

Signature:

Date: 10th February 2020

Specified Centre: School of Public Health, University of the Witwatersrand

Description of the data: Data from a sub-study from the CRYPTOPRO trial. The CRYPTOPRO trial was carried out in Masaka, Uganda from September 2004 to April 2008, in order to investigate aimed to examine the efficacy and safety of fluconazole as primary prophylaxis against cryptococcal disease before initiation and in the first few months of antiretroviral therapy. A sub-study on Peripheral Neuropathy (PN) was carried out within the CRYPTOPRO trial, with evaluations before initiation of ART and after initiation of ART. The data requested are the data from the CRYPTOPRO trial together with the baseline data for participants in the PN sub-study, including trial arm.

Purpose: For M.Sc. student Ms Mpho Pitso to carry out a secondary data analysis for her M.Sc. (Epidemiology and Biostatistics) project investigating whether self-reported PN can be used as a surrogate outcome measure for clinically determined PN in HIV/AIDS patients who initiated antiretroviral therapy in Masaka, Uganda.

Approved by MRC/UVRI and LSHTM Uganda Research Unit

Project Leader: Professor David Lalloo .....

Programme Head: .....

Director: .....

Appendix 6: Turn it in Report

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This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

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File size:	669.78K
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Word count:	13,915
Character count:	75,803
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Validity of self-reported Peripheral Neuropathy (PN) as a surrogate marker for clinically-determined PN in HIV/AIDS patients initiating ART in Masaka, Uganda, 2004-2008

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