DETERMINANTS OF SENSORY NEUROPATHY AMONG HIV/AIDS PATIENTS ATTENDING COMPREHENSIVE CARE CLINIC AT WEBUYE COUNTY HOSPITAL, KENYA

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Thesis submitted in partial fulfilment for the requirement of the degree of Masters of Medicine (M.MED) in Family Medicine of Moi University.

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other university. No part of this thesis may be reproduced without prior written permission of the author and/or Moi University.

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Declaration by the Supervisors

This thesis is submitted with our approval as the University supervisors.

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DEDICATION

To my late grandmother, Juliah Njeri Kinuthia.

Your inspiration keeps me going.

Abstract

Background: Sensory neuropathy is a frequent complication of HIV infection. It is widely under-recognised and undertreated in resource constrained settings. It is estimated that the prevalence of HIV associated sensory neuropathy (HIV-SN) globally ranges from 30% to 60% or more in antiretroviral therapy (ART) treated cohorts. Up to 90 % of affected patients experience potentially debilitating neuropathic pain and reduced quality of life.

Objective: To assess the prevalence and determinants associated with HIV-SN in patients attending Webuye County Hospital comprehensive care clinic (CCC).

Methods: A total of 340 HIV positive adult patients were randomly selected for this cross sectional study. A pre-tested structured questionnaire was used to collect data. Patients with HIV-SN were identified using the Brief Peripheral Neuropathy Screening (BPNS) tool. HIV-SN was defined as the presence of neuropathic symptoms and at least an abnormal perception of vibration or abnormal ankle reflexes or both. Demographic, clinical, and laboratory factors determined from literature review were considered as possible determinants for HIV-SN. Analysis was done using R software for statistical analysis. Association between categorical variables and HIV-SN was assessed using Pearson's Chi Square test. Association between HIV-SN and normally distributed continuous variables was assessed using two sample t-test.

Results: The mean age was 42.5 ± 11.0 years. The male to female ratio was 1:2. The median current viral load was 0.0 copies/ml, the median baseline CD4 Count was 203 cells/mm^3 and the median duration of HIV from diagnosis was 6 years. The prevalence of HIV-SN was 30.0% (95% CI: 25.2% to 35.2%). Age, OR: 1.04 (95% CI: 1.01, 1.06) was associated with HIV-SN, that is older participants were more likely to be diagnosed with HIV-SN. Participants who had higher baseline CD4 count (CD4>350 cells/mm^3) had 49% reduced odds of HIV-SN, OR: 0.51 (95% CI: 0.28, 0.99) while those with hypertension had more than threefold likelihood of having HIV-SN OR: 3.26 (95% CI: 1.40, 7.57).

Conclusions: There is high prevalence of HIV-SN. Age and baseline CD4 count were associated with HIV-SN. Hypertension, a less studied factor (comorbidity) was strongly associated with HIV-SN.

Recommendations: Since increasing age was associated with HIV-SN, we recommend routine screening of adult patients for HIV-SN during clinic visits. Further study to evaluate the role of hypertension in HIV-SN.

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ACRONYMS AND ABBREVIATIONS LIST

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
ART	Antiretroviral Therapy
WHO	World Health Organization
HIV-SN	HIV associated Sensory Neuropathy
DSP	Distal Sensory Polyneuropathy
HAART	Highly Active Antiretroviral Therapy
ACTG	AIDS Clinical Trials Group
BPNS	Brief Peripheral Neuropathy Screening
DIP	Distal Interphalangial Joint
IDP	Inflammatory Demyelinating Polyneuropathy
CD4	Cluster of Differentiation 4
d4T	stavudine
PLWHA	People Living with HIV/AIDs
USA	United States of America
IREC	Institutional Research and Ethics Committee
PN	Peripheral Neuropathy

CCC	Comprehensive Care Clinic
SD	Standard Deviation
TB	Tuberculosis
AMPATH	Academic Model Providing Access To Healthcare
ATN	Antiretroviral Toxic Neuropathy
NASCOP	National AIDS and Sexually Transmitted Infections Control Program
IASP	International Association for the Study of Pain

DEFINITION OF KEY TERMS

HIV-SN: it is a small fibre, length-dependent, distal sensory polyneuropathy involving both myelinated and unmyelinated fibres that is frequently painful and which is one of the most common AIDS-associated neurologic disorders (Ferrari et al., 2006).

BPNS tool: It is an AIDS Clinical Trials Group validated tool for identifying patients with HIV-SN. This tool is based on a directed symptoms questionnaire and limited clinical examination (Cherry, Wesselingh, Lal, & McArthur, 2005).

Determinant: An element, factor, event, characteristic or other definable entity that influences or changes an outcome or health condition (Segen, 2002).

Alcohol drinking problem: Defined using CAGE criteria. Two "yes" responses to the following four questions (Saitz, 2005).

1. Have you ever felt you needed to **C**ut down on your drinking?
2. Have people **A**nnoyed you by criticizing your drinking?
3. Have you ever felt **G**uilty about drinking?
4. Have you ever felt you needed a drink first thing in the morning (**E**ye-opener) to steady your nerves or to get rid of a hangover?

CHAPTER ONE: INTRODUCTION

1.1 Background

Globally, an estimated 36.7 million people were living with HIV in 2015. This is an increase from previous years as more people are receiving the life-saving antiretroviral therapy. Trends in new adult infections differ among regions. The epidemic continues to disproportionately affect sub-Saharan Africa, home to 70% of all new HIV infections (UNAIDS, 2015). An estimated 1.6 million people are living with HIV in Kenya (National AIDS and STI Control Programme [NASCOP], 2015).

HIV associated sensory neuropathy (HIV-SN) is the most frequent and problematic neurological complication associated with HIV infection and advanced AIDS. There are at least six patterns of HIV associated peripheral neuropathy; distal sensory polyneuropathy (DSP), inflammatory demyelinating polyneuropathy (IDP), progressive polyradiculopathy (PP), rapidly progressive flaccid paraparesis, mononeuritis multiplex (MM), and autonomic neuropathy (Wulff, Wang, & Simpson, 2000).

Distal sensory peripheral neuropathy which is the most common of all HIV-SN exists as two major types: primary HIV-associated distal sensory polyneuropathy (HIV-DSP), and antiretroviral toxic neuropathy (ATN), ATN being the most frequent antiretroviral therapy related toxicity in sub-Saharan Africa (UNAIDS, 2008). HIV-DSP and ATN together involve approximately 30-67% of patients with advanced HIV disease (Kamerman, Wadley, & Cherry, 2012). Several pathophysiologic mechanisms likely exist. HIV-SN can be a consequence of the infection itself like in the case of HIV associated Distal Sensory Polyneuropathy (DSP), or as a result of treatment related ATN. DSP and ATN are clinically indistinguishable and differentiation between the two categories is primarily based on the timing of onset in relation to ART initiation. HIV-SN is a global term covering both DSP and ATN (Kamerman et al., 2012).

The symptoms of HIV-SN typically are pain, pins and needles and numbness. Symptoms are bilateral, symmetrical and have a “glove and stocking” distribution. When present, pain is often described as cramping, hot, burning, tight or itching and is frequently experienced as moderate to severe in intensity (Shaikh, Bentley, & Kamerman, 2013).

Globally, studies have shown that the prevalence of HIV-SN ranges from 30% to 60% or more in ARV treated cohorts. Up to 90 % of affected patients experience potentially debilitating neuropathic pain (International Association for the Study of Pain [IASP], 2014). Clinical examination plus electrophysiology has found that DSP affects 36% of HIV-infected patients being treated with highly active antiretroviral therapy, although it may remain subclinical in about two-thirds of cases (Robinson-Papp et al., 2010). Studies in Africa have shown the prevalence of HIV-SN to be between 30 to 67% (Kamerman et al., 2012; Luma et al., 2012).

Several suspected determinants of HIV-SN have been studied in several developing countries. CD4 count and antiretroviral drugs regimen were associated with development of HIV-SN as shown in studies in developed nations (Lichtenstein et al., 2005). History of TB treatment and alcohol drinking problem were also shown to be determinants of HIV-SN in the African studies(Oshinaike et al., 2012; Maritz et al., 2010.

1.2 Problem statement

The burden of HIV-SN pain is a problem of enormous global importance (UNAIDS, 2015; IASP, 2014). It is under recognised and under treated especially in resource limited setting. It frequently complicates some HIV treatments (McArthur, Brew & Nath, 2005).

With high rates of HIV-SN now reported globally, and up to 90% of affected patients experiencing potentially debilitating neuropathic pain, it represents a large and potentially worsening source of global HIV-related morbidity. The presence of HIV-SN-related neuropathic pain is a factor associated with greater unemployment, higher rates of depression and greater dependency in daily life activities (IASP, 2014). HIV-SN presents a number of challenges to the clinician and patient. Diagnostic difficulties arise from a wide differential and the inability to clinically distinguish etiological processes – a delay in diagnosis, which is frequently missed, and may lead to a subsequent intractable course (Gonzalez-Duarte, Robinson-Papp, & Simpson, 2008).

Therapeutic choices are limited and poorly effective for neuropathic pain which is under-treated (Maritz et al., 2010; Robinson-Papp et al., 2009). The strong placebo response in HIV-SN treatment trials has complicated attempts to identify treatments that are superior to placebo at relieving the painful symptoms of the neuropathy (IASP, 2014). Lack early diagnosis and preventative strategies may result in the necessity to interrupt and substitute ART to alleviate HIV-SN (Westreich et al., 2009).

Many patients from Webuye County Hospital CCC seek treatment in the clinic and outpatient department multiple times before their appointment dates due to sensory neuropathy and related complications. Symptomatic relief therapy is usually not

satisfactory. This study was conducted to find out the prevalence of HIV-SN and the various factors associated with it in HIV/AIDS patients attending Webuye County Hospital CCC and disseminate this information to the caregivers.

1.3 Research question

1. What is the prevalence, and what are the determinants of HIV-SN in HIV/AIDs patients attending Webuye County Hospital CCC?

1.4 Objectives

1.4.1 Broad

To assess the prevalence and determinants of HIV-SN in patients attending Webuye County Hospital Comprehensive Care Clinic.

1.4.2 Specific

1. To describe the prevalence HIV-SN in HIV/AIDS patients attending Webuye County Hospital CCC.
2. To determine the factors associated with HIV-SN in patients attending the Webuye CCC.

1.5 Justification of the study

Kenya, being a developing nation in Sub Saharan Africa is experiencing high HIV prevalence. Kenya's HIV burden is described as generalized with an average HIV prevalence of 5.6% among the general population of ages 15-64 years, and an even higher prevalence among some populations and geographical regions (NASCOP, 2015; UNAIDS, 2015). HIV-SN in Kenya is estimated to range between 36% and 53% (Mehta et al., 2010; Cettomai et al., 2010).

Results from research done previously elsewhere may differ from current situation owing to changes in HAART initiation criteria, occasioning earlier initiations of Antiretroviral Therapy e.g. all HIV positive patients are to be started on HAART regardless of their CD4 Count of WHO clinical stage (NASCOP, 2016). The first line regimen has also changed to exclude stavudine.

Literature review did not yield studies on HIV-SN in Bungoma County. It is expected that the study will establish the proportion of HIV/AIDS patients suffering from HIV-SN in Webuye County Hospital and the various risk factor associated with HIV-SN. It is hoped that this information will help health care givers better understand HIV SN. This will in turn help them give better care to patients with HIV-SN, by early detection and intervention for symptomatic relief and prevention of deterioration by addressing modifiable factors that the study seek to assess.

CHAPTER TWO: LITERATURE REVIEW

2.1 Overview

HIV-SN is common in HIV infection and several pathophysiologic mechanisms have been postulated. HIV may act directly by infecting dorsal root ganglion neurons. These neurons may also be injured by locally infiltrating activated macrophages that secrete neurotoxic cytokines or other metabolites (IASP, 2014). There is a preferential loss of small, unmyelinated nerve fibres in HIV-SN and evidence of neuronal and axonal degeneration, both within the dorsal root ganglia and along the peripherally directed axons. It has been showed that HIV-1 envelope protein gp120 could induce indirect neuronal injury through the Schwann cells (Arasho, Jacob, & Zenebe, 2010).

HIV-SN encompasses the two commonest types of HIV related peripheral neuropathy, these are; distal sensory polyneuropathy (DSP) and ARV toxic neuropathy. These two conditions are phenotypically identical, although the timing of symptom onset may help to differentiate the aetiology (Wulff, Wang, & Simpson, 2000).

HIV-SN is a typical small-fibre sensory neuropathy. Common symptoms are often accompanied by neuropathic signs such as reduced or absent ankle reflexes, diminished vibration sense, and altered sensitivity to light tactile or thermal stimuli (Wulff et al., 2000; Pettersen et al., 2006).

The widely used AIDS Clinical Trials Group validated Brief Peripheral Neuropathy Screening (BPNS) tool is employed in identifying HIV-SN. This tool is based on a directed symptom questionnaire and limited clinical examination (Cherry et al., 2005). HIV-SN is defined as the presence of neuropathic symptoms and at least an abnormal

perception of vibrations of a 128Hz tuning fork on the great toe or abnormal ankle reflexes or both. Numbness has a sensitivity of 86% and a specificity of 81% for the clinical diagnosis of HIV-SN. Asking about numbness has greater sensitivity for the diagnosis of HIV-SN than asking about pain. Reduced or absent ankle Achilles tendon reflex has a sensitivity of 84% and a specificity of 98% for HIV-SN (Cherry et al., 2005; Gonzalez-Duarte et al., 2008).

BPNS tool has been validated against objective measures including both thermal threshold testing and epidermal nerve-fibre density (Oshinaike et al., 2012).

2.2 HIV-SN Globally

It is estimated that the prevalence of HIV-SN globally ranges from 30% to 60%. Up to 90 % of affected patients experience potentially debilitating neuropathic pain (IASP, 2014; Pettersen et al., 2006). Clinical examination plus electrophysiology has found that DSP affects 36% of HIV-infected patients being treated with highly active antiretroviral therapy, although it may remain subclinical in about two-thirds of cases (Lichtenstein et al., 2005).

Several studies have been carried out to identify risk factors for the development of HIV-SN. Risk factors identified include: age, severe prior immune-suppression and treatment with stavudine (d4T) based ART or combinations with zalcitabine (ddC) and didanosine (ddI). The risk of HIV-SN is higher for patients with advanced HIV infection. CD4 count as a marker of immune suppression has been found to be an important determinant of peripheral neuropathy (Lichtenstein et al., 2005).

Early studies emphasized CD4 and viral load as risk factors, but with successful therapy these associations, specifically viral load, have become less important. There is evidence that successful HIV treatment as reflected by higher CD4 cell count is associated with a

lower risk of neuropathy than found in those whose CD4 responses are poorer. Current CD4 count of 200 cells per µl or less, reflecting advanced disease is a risk for HIV-SN. Nadir CD4, in treatment-naive cohort represented by the baseline CD4, also was associated with greater risk of peripheral neuropathy (Morgello et al., 2004; Lichtenstein et al., 2005).

In a study done in Melbourne Australia in 2006 the prevalence of HIV- SN was 42%. Patients' age and stavudine exposure were found to be a risk factor for HIV-SN (Smyth et al., 2006). A study done in New York in the USA by Manhattan HIV Brain Bank, of the 187 patients studied, 99 (53%) had DSP. There was positive association between DSP and substance use disorders. Other risk factors identified were co-morbid conditions with underlying predisposition to cause peripheral neuropathy (e.g., diabetes mellitus, malnutrition, and isoniazid exposure), ethnicity, and increasing height (Morgello et al., 2004).

Ellis et al., (2010) conducted a study between 2003 and 2007 in Six US academic medical centres to provide updated estimates of the prevalence and clinical impact of HIV-SN in the combination antiretroviral therapy (CART) era. One thousand five hundred thirty-nine HIV-infected individuals were enrolled in the CNS (Central Nervous System) HIV Anti-Retroviral Therapy Effects Research (CHATER) study. They found HIV-SN in 881 participants (57.2%). Of these, 38.0% reported neuropathic pain. Neuropathic pain was significantly associated with disability in daily activities, unemployment, and reduced quality of life. Risk factors for HIV-SN after adjustment were advancing age, lower CD4 nadir, current CART use, and past "D-drug" use (specific dideoxynucleoside analogue antiretrovirals). In a study by Pettersen et al., (2006) in Canada, among the 221 patients assessed, 101 displayed HIV-SN, including 64 with distal sensory neuropathy and 37 with antiretroviral toxic neuropathy. HIV-SN

patients exhibited significantly greater mean age, peak plasma viral loads, and exposure to neurotoxic dideoxynucleosides and protease inhibitors.

Affandi et al., (2008) found a neuropathy prevalence of 34% among HIV patients in Jakarta exposed to d4T. The independent associations with neuropathy in this cohort were increasing patient's age, increasing patient's height, and TNF genotype, factors that could readily be measured prior to d4T prescription. Dubey, Raghuvanshi, Sharma, and Saxena (2013) in Central India studied HIV neuropathy in pre-HAART patients, out of 75 patients studied, 40% had clinical HIV-SN and nerve conduction study (NCS) confirmed its presence in all of them. In the patients who had neuropathy, the mean body mass index (BMI) was 17.18 kg/m 2 ($P < 0.0001$), and mean CD4 T-cell count was 497/µl; whereas, in patients not having neuropathy the same values were 20.22 kg/m 2 , and 678/µl, respectively. The conclusion was that HIV-SN is more common among pre-HAART patients with low level of BMI and CD4 T-cell count. Hence, it was found that neuropathy can possibly be prevented by improving immune as well as nutritional status of HIV infected patients and, BPNS, being a simple diagnostic tool should therefore be routinely applied to screen for the neuropathy, to minimize the negative impact it has on the quality of life in patients with HIV infection.

2.3 HIV-SN in Africa

Studies in Africa have shown the prevalence of HIV-SN to be between 30 to 67% with 87% of symptomatic patients having symptoms before HAART initiation. Antiretroviral toxic neuropathy is the most frequent antiretroviral therapy related toxicity in sub-Saharan Africa (UNAIDS, 2008; Pettersen, 2006). In a study done in South Africa by Maritz et al., (2010), a total 598 HIV-infected adults were studied and 49% of the study population were diagnosed with HIV-SN. HIV-SN was independently associated with

ART use, age and prior TB. Stavudine use was significantly associated with HIV-SN. Wadley et al (2011) recruited 404 Black HIV-positive Africans from the Virology Clinic in Johannesburg and assessed HIV-SN using the AIDS Clinical Trials Group BPNS. Of those exposed to stavudine, 57% had HIV-SN. Pain was the most common symptom and was experienced by 74% of those who had HIV-SN. Increasing age and height were independently associated with risk of HIV-SN. However nadir and current CD4 T-cell counts and sex were not associated with HIV-SN.

According to a study done in Douala General Hospital in Cameroon by Luma et al., (2012) out of 295 patients studied, 21% had HIV-SN. History of alcohol drinking problem, low CD4 count, and history of anti-tuberculosis treatment were strongly associated with HIV-SN. In another study done in Lagos Nigeria by Oshinaike et al., (2012) the prevalence of sensory neuropathy was 39.0%. The independent associations with SN were increasing age (P = 0.03) and current exposure to stavudine (P = 0.00). Gender, height, use of HAART, duration of HAART treatment, and lower CD4 count were not associated with an increased SN risk.

In a cohort of 600 patients examined in a study by Maiga et al., (2014) in Bamako Mali, 20% had neurological pain according to DN4 (*Douleur Neuropathique 4*, a questionnaire used in diagnosing neuropathic pain).

2.4 HIV SN in East Africa

In a study by Tumusiime, Venter, Musenge and Stewart (2014) in Rwanda, PN prevalence was 59%. The three factors that were significantly associated with PN were: older age, primary education level and urban setting after adjusting for other factors. None of the health status characteristics namely; the level of CD4 cell count, duration of HIV infection and duration on ART, was independently associated with peripheral

neuropathy. Biraguma and Rhoda (2012) found the prevalence of neuropathy among PLWHA attending the outpatients' clinic at Rutongo Hospital in the Rulindo district of Rwanda to be 40.5%. In addition, patients with neuropathy had lower quality of life scores in the physical and psychological domains than those without neuropathy symptoms. A study in Kampala Uganda found the rate of HIV-SN at 47%, and recommended further studies to determine the natural history and treatment outcomes of this HIV complication (Nakasujja et al., 2004).

2.5 HIV SN in Kenya

A pilot study done in Kisumu Kenya by Cettomai et al., (2009) to assess screening tool for identifying HIV-SN found 53% of the participants had neuropathy, with 20% having moderate to severe neuropathy. However this prevalence estimates for HIV-SN should be interpreted with caution due to small sample size (30), and use of convenience sampling. All participants with moderate/severe neuropathy had previously used stavudine (d4T) and 2 (33%) were taking d4T at study enrolment. In a study looking at implementation of a validated peripheral neuropathy screening tool in patients receiving antiretroviral therapy in Mombasa, of the 102 patients who were screened, 36% had peripheral neuropathy (Mehta et al., 2010). Literature review did not yield studies in the former Western province of Kenya.

CHAPTER THREE: MATERIALS AND METHODOLOGY

3.1 Study site: Webuye County Hospital

Webuye County Hospital is a level 4 facility with a 217 bed capacity. It is located in Webuye West Sub County, Bungoma County, in Kenya. It is approximately 40 kilometres from the political capital of Bungoma County, Bungoma town. It comprises of general medical and surgical departments, obstetrics and gynaecology, paediatrics and outpatient departments. It also incorporates the CCC that is run by AMPATH. It has a catchment population of 60,894 persons.

3.2 Design: Cross-Sectional Study

3.3 Study population:

All adult HIV positive patients on follow up at Webuye County Hospital CCC who met the inclusion criteria were eligible. Webuye County Hospital CCC attends to an average of 100 adults on the designated adult care days. The CCC had 3020 adult client who were on HAART as of June 2014. This number constituted of 27% males and 73% females. The predominant social economic activity of the study population is small scale farming, practised by 90% of the CCC clients.

3.4 Inclusion/exclusion criteria

3.4.1 Inclusion criteria

- Adults aged 18 years and above.
- HIV positive.

3.4.2 Exclusion criteria

- Unstable patients who needed emergency care.

3.5 Sample size

Fisher's Method for calculating sample size was used.

$$n = \frac{Z^2 * p(1-p)}{e^2}$$

n = required sample size.

Z = confidence level at 95% (standard value of 1.96).

p = estimated HIV-SN rate in projected area - 49% (Maritz J et al., 2010).

e = margin of error at 5% (0.05).

N = size of target population (Webuye County Hospital CCC) – 3020.

$$n = \frac{1.96^2 \times 0.49\ (0.51)}{0.05^2}$$

$$= 384$$

Since the sampling frame is less than 10,000 (3020) we adjusted the sample size using the formula below.

$$n = n / (1 + n/N)$$

$$= 384 / (1 + 384/3020)$$

=340

The minimum sample size required for the study was 340 HIV positive adults.

3.6 Sampling method

In this study a systematic random sampling technique was employed in recruiting study subjects. Data was collected two days a week for 12 weeks which was the duration available for data collection. This extended from January to March 2015. The total number of days for collecting data was therefore 24 days (12*2). To get the number of participants to be seen per day (N) we divided the sample size (340) by 24 days and this gave us approximately 15 persons per day(N=15). Dividing the total number of people seen in a day in CCC (100) by N (100/15) gave us a sampling interval, K, of approximately 7(K=7); this means every 7^{th} client at the registration desk was recruited. The study population was considered as a homogeneous population, thus the systematic random selection was done by randomly choosing the first person between 1 and 7, then taking every 7^{th} client thereafter. Participants were asked whether they had participated in the study during a previous visit, if so, they were excluded. The procedure was repeated every day of data collection for the period of study.

3.7 Data collection instrument and procedures

The data was collected by the principal investigator assisted by three trained HIV/AIDS case managers as research assistants, (Clinical officers who were trained and certified by the principal investigator and the biostatistician) using an interviewer-administered and pre-tested structured questionnaires. Socio-demographic data was obtained from patient through a questionnaire. Medical information (including baseline CD4 count, current viral loads and WHO clinical stage) and co-morbidities were extracted from record files and collaborated with history. Anthropometric measures were obtained directly through patient examination. The data was entered into the structured questionnaire (see appendix -3).

The AIDS Clinical Trials Group validated BPNS tool was employed to identify patients with HIV-SN. The tool was administered by the principal investigator and three clinical officers trained on using the tool. This tool is based on a directed symptom questionnaire and limited clinical examination. HIV-SN was defined as the presence of neuropathic symptoms and at least an abnormal perception of vibrations of a tuning fork on the great toe or abnormal ankle reflexes or both.

Each consenting patient underwent a brief peripheral neuropathy screening (BPNS). This consisted of brief questions regarding symptoms of HIV-SN. Each symptom when present was subjectively graded bilaterally from 0 (absent) to 10 (severe).

Lower extremity examination was then done to evaluate participant's perception of vibrations for over 10 seconds using a 128Hz tuning fork. The vibrating tuning fork was first places on the participant's wrist to make sure he/she appreciated the "buzzing" sensation. Then the vibrating tuning fork was then placed on the distal interphalangial

joint of the big toe and the duration of vibration perception recorded in seconds for the right and left big toes.

Ankle reflexes were tested using a reflex hammer. With the participant seated, the examiner used one hand to press upward on the ball of the foot, dorsiflexing participant's ankle to 90 degrees. Using the reflex hammer, the examiner struck the Achilles tendon. The tendon reflex was felt by the examiner's hand as a plantar flexion of the foot. Reinforcement by having the subject clench his/her fist was used before classifying the reflex as absent.

Both findings were graded as follows: vibrations (grade 0: maximum perception for >10s, grade 1: 6 -10s, grade 2: <5s, grade 3: no perception) ankle reflexes (grade 0: absent, grade 1: hypoactive, grade 2: normal, grade 3: hyperactive, grade 4: clonus) (Cherry et al., 2005).

3.8 Data management and statistical analysis

The completed questionnaires were checked for completeness, coded and entered in a Microsoft access database. It was later exported to R software for statistical analysis and computing (R Core Team, 2015) for statistical analysis. Categorical variables were summarized as frequencies and the corresponding percentages. Continuous variables that assumed the Gaussian distribution were summarized as mean and the corresponding standard deviation. Continuous variables that violated the Gaussian assumptions were summarized as median and the corresponding inter quartile ranges (IQR). Gaussian assumptions were assessed empirically and graphically using Shapiro Wilk test for normality and the normal probability plots respectively. The prevalence of HIV-SN was presented as percentage and the corresponding 95% confidence limits (95% CI).

Association between categorical variables and HIV-SN was assessed using Pearson's Chi Square test. Association between HIV-SN and normally distributed continuous variables was assessed using two sample t-test while the association between sensory neuropathy and the continuous variables that violated the Gaussian assumptions was assessed using two-sample Wilcoxon rank sum test.

Factors that were associated with HIV-SN were included in a multiple logistic regression model to model the adjusted effect on the outcome. Odds ratios (OR) was reported and the corresponding 95% confidence limits (95% CI).

Body mass index was determined as ratio of weight in kilograms to the square of height in meters. This variable was categorized using clinically acceptable limits: <18.5 kg/m2, 18.5 – 24.9, kg/m2, 25.0 – 30.0 kg/m2, and >30.0 kg/m2. Similarly, CD4 was categorized as <200, 200-350, and >350 cells per cubic mm. Viral load was categorized as <10000 copies/ml and ≥10000 copies/ml.

Results were presented using graphs and tables.

3.9 Study limitations

1. Due to resource limitations, we were unable to include other objective measures of neuropathy in our gold standard, such as nerve conduction studies, computerized Quantitative Sensory Testing (QST), or intra-epidermal nerve fiber densities.

3.11 Ethical considerations

Approval: Approval was sought and granted from Moi University's IREC (***Approval Number 0001130***), Webuye County Hospital administration and AMPATH Research Program Office before the study commenced.

Consent: Informed consent was obtained from the participants, the consent document was administered by the principal investigator and his research assistants (clinical officers) trained by the principal investigator and biostatistician.

Risks: There were no risks to the participants of this study. Investigators ensured there was no discomfort during the time of interview, physical examination and HIV-SN BPNS tool administration.

Benefits: There was no reward for participation in this study. Patients who were positive for HIV-SN were started on management.

Confidentiality: Participants' information was kept confidential and was not used for any other purpose other than the study. All interviews were conducted in secluded rooms with one individual subject at a time and the filled questionnaires were kept in safe custody by the principal investigator in order to ensure that confidentiality was maintained throughout the study. No names were used and the electronic data were protected by use of passwords.

CHAPTER FOUR: RESULTS

A total of 340 participants were included in the study. The mean age was 42.5 ± 11.0 years. One third of the participants were male giving a male to female ratio of 1:2.

The median weight, and median height were 63.0 (IQR: 57.0, 71.0) kilograms and 166.0 (IQR: 160.0, 172.0) centimeters respectively. This gave a median body mass index (BMI) of 22.8 (IQR: 20.3, 26.1) kg/m^2. Female participants had a significantly higher BMI compared to the male counterparts, 23.2 (IQR: 20.4, 26.9) vs. 21.5 (IQR: 19.9, 24.4), p=0.005 respectively.

Table 1: Demographic and Anthropometric characteristics

Variable	**n (%) or Mean ± SD or Median (IQR)**
Age (Years)	42.5 ± 11.0
Male	111 (32.6%)
Female	229(67.4%)
Weight	63.0 (57.0, 71.0)
Height	166.0 (160.0, 172.0)
BMI	22.8 (20.3, 26.1)

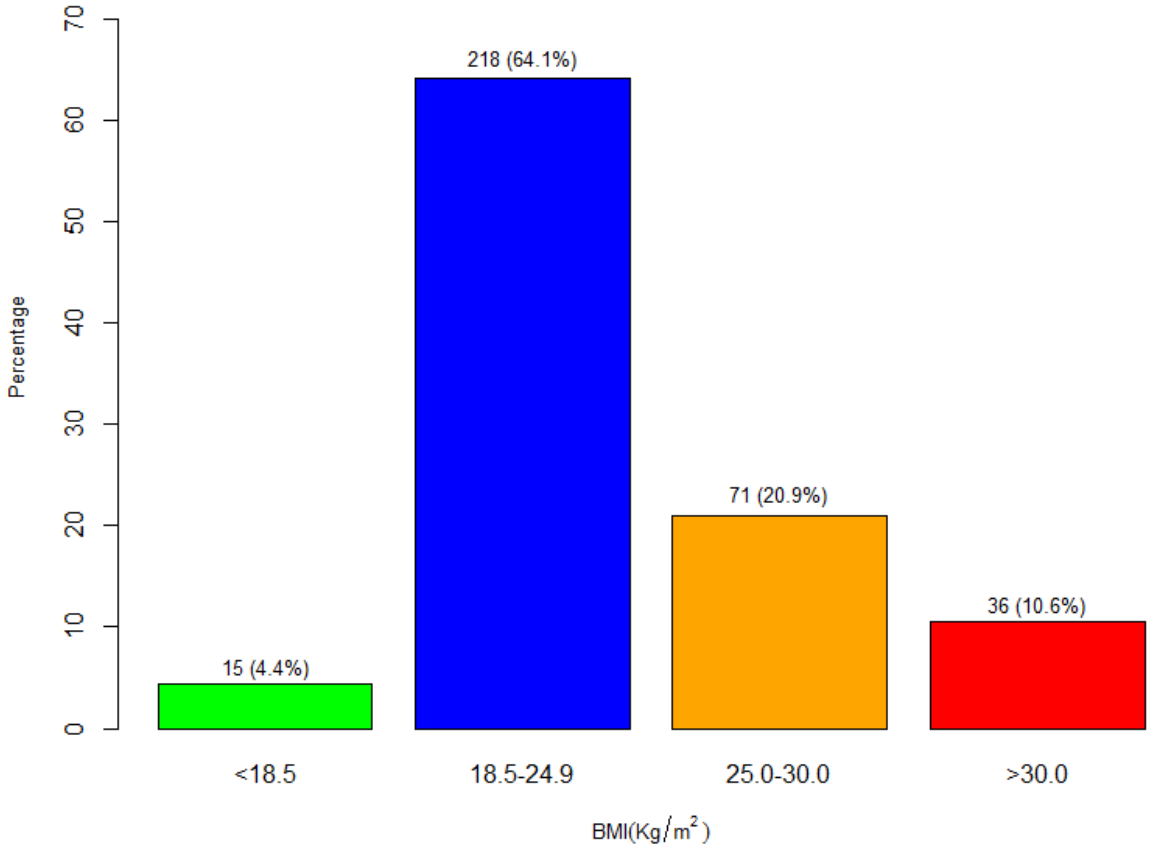

Figure 1: Distribution by BMI Groups

Up to 64.1% of the participants had normal (18.5 – 24.9 kg/m^2) BMI and 31.5% were either overweight (25.0-30.0 kg/m^2) or obese (>30.0 kg/m^2).

Table 2a: Clinical characteristics; categorical variables

Variable	**n (%)**
N=171	
Current viral load (copies/ml) >10000	4 (2.3%)
Highest viral load (copies/ml) >10000	11 (6.4%)
N=340	
Baseline CD4 (cells/mm^3): <200	137 (40.3%)
200-350	97 (28.5%)
>350	106 (31.2%)
Initial WHO stage: Stage 1	119 (35.1%)
Stage 2	89 (26.1%)
Stage 3	124 (36.3%)
Stage 4	8 (2.4%)
Current WHO stage: Stage 1	105 (31.0%)
Stage 2	87 (25.6%)
Stage 3	139 (40.7%)
Stage 4	9 (2.7%)

Table 3b: Clinical characteristics; continuous variables

Variable	**Median (IQR)**
Duration of HIV(years from diagnosis)	6.0 (3.0, 8.0)
Current viral load (copies/ml)	0.0 (0.0, 11.2)
Highest viral load (copies/ml)	61.0 (0.0, 1055.0)
Baseline CD4 count – at diagnosis (cells per cubic mm)	230.0 (109.2, 400.2)

Overall, the participants had been living with HIV for a median duration of 6.0 (IQR: 3.0, 8.0) years. The median baseline CD4 count was 230.0 cells per cubic mm. Based on the current WHO clinical stage, 31.0% were in clinical stage 1, 25.6% were clinical stage 2, 40.7% were in clinical stage 3 and 2.7% was in clinical stage 4.

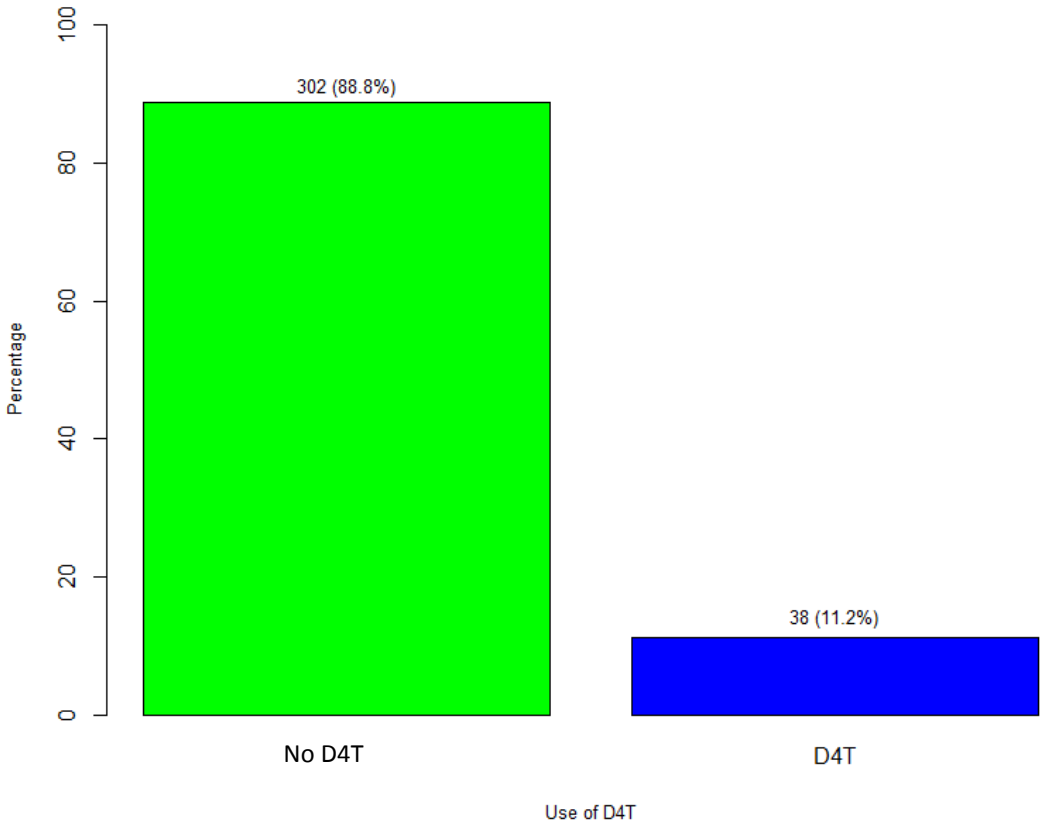

Figure 2: Use of d4T

Eleven percent of the participants had been on a combination containing d4T in the past while the rest had not used d4T ever.

Comorbidities

There were 69 (20.3%) participants who had been on TB treatment and the median duration after treatment was 5.7 ± 2.9 years.

There were 28 (8.2%) participants who reported history of alcohol drinking problem based on CAGE criteria. Among those who reported alcohol drinking problem, the median duration was 6.0 (IQR: 2.8. 10.0) years.

The other comorbidities assessed were hypertension, diabetes, and renal disease. This was through checking records and collaborating the information with history from the participants. There were 29 (8.6%) participants with hypertension and the median duration of hypertension from diagnosis was 2.0 (IQR: 1.0, 4.2) years. Six (1.8%) reported history of diabetes with a median duration of 3.5 (3.0, 6.8) years. None of the participants had renal disease.

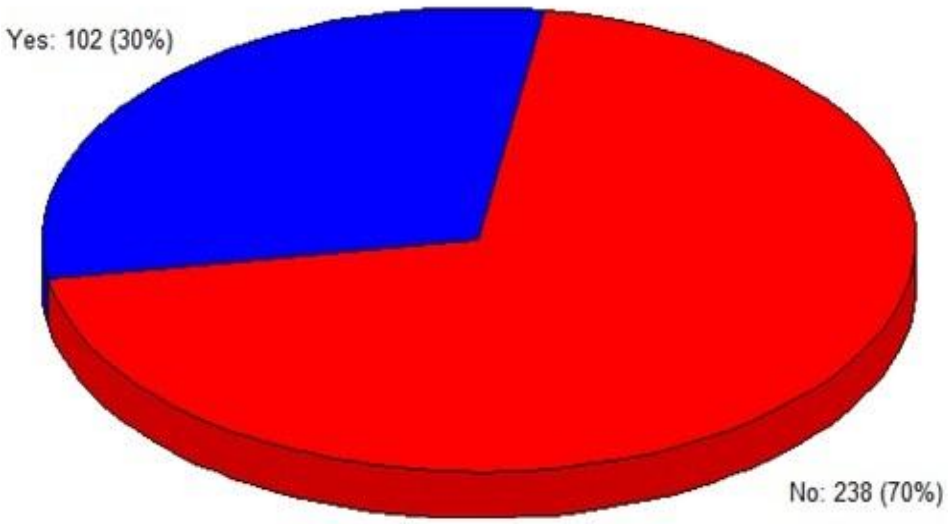

Figure 3:- Prevalence of HIV-SN

The prevalence of HIV-SN was 30.0% (95% CI: 25.2% to 35.2%). The median duration of neuropathic symptoms among those who were diagnosed with HIV- SN was 2.0 (IQR: 1.0, 3.0) years.

Table 3: Factors associated with HIV-SN: Bivariate analysis

Variable		**No HIV-SN (n=238)**	**HIV-SN (n=102)**	
		n (%) or Mean ± SD or Median (IQR)	**n (%) or Mean ± SD or Median (IQR)**	**P**
Age (Years)		41.3 ± 11.3	45.4 ± 9.6	**0.001**
Gender	Female	157 (68.6%)	72 (31.4%)	0.500
	Male	81 (73.0%)	30 (27.0%)	
BMI (kg/m^2)		22.4 (20.2, 25.2)	22.9 (20.1, 26.9)	0.521
Current viral load (copies/ml)		0.0 (0.0, 0.0)	0.0 (0.0, 118.0)	**<0.0001**
Highest viral load (copies/ml)		0.0 (0.0, 103.5)	712.0 (50.0, 1877.0)	**<0.0001**
Baseline CD4 count (cells per cubic mm)		245.0 (140.5, 435.8)	185.0 (78.4, 300.0)	**0.0004**
Current WHO	Stage 1	73 (69.5%)	32 (30.5%)	**0.013[f]**
	Stage 2	71 (81.6%)	16 (18.4%)	
	Stage 3	89 (64.0%)	50 (36.0%)	
	Stage 4	4 (44.4%)	5 (55.6%)	
D4T use		24 (63.2%)	14 (36.8%)	0.430
Duration on HAART		4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	0.655
TB treatment	Past	39 (56.5%)	30 (43.5%)	**0.020[f]**
	Current	5 (71.4%)	2 (28.6%)	
Alcohol drinking problem		18 (64.3%)	10 (35.7%)	0.521
Hypertension		12 (41.4%)	17 (58.6%)	**0.001**
Diabetes		1 (16.7%)	5 (83.3%)	**0.010[f]**

[f] – Fisher's exact P-value was reported because the expected cell frequency of the created 2x2 table was <5, a violation of Chi Square assumptions.

Factors associated with HIV-SN were assessed. It was established that older age was associated with the presence of HIV-SN. Viral load, baseline CD4 count, and WHO clinical stage were all associated with the presence of HIV-SN. Use of anti-TB treatment was associated with the presence of HIV-SN, p=0.020. Hypertension and diabetes were significantly associated with diagnosis of HIV-SN.

The variables that were significant in the bivariate analysis (Table 3) were included in a multiple logistic regression model to assess the adjusted effect. The results were as shown in Table 4.

Table 4: Factors associated with HIV-SN: Multiple Logistic regression

Variable		**UOR (95% CI)**	**AOR (95% CI)**
Age		1.04 (1.01, 1.06)	**1.04 (1.01, 1.06)**
Gender		0.81 (0.49, 1.35)	1.44 (0.81, 2.56)
Duration of HIV from diagnosis (years)		1.07 (0.99, 1.16)	1.03 (0.95, 1.12)
Current viral load (copies/ml)		1.02 (0.39, 0.99)	1.06 (0.89, 1.19)
Baseline CD4 count (cells/mm^3)	200-350 vs. <200	0.63 (0.35, 1.12)	0.76 (0.42, 1.39)
	>350 vs. <200	0.46 (0.25, 0.82)	**0.51 (0.28, 0.99)**
Initial WHO stage	III or IV vs. I or II	1.72 (1.07, 2.77)	0.77 (0.24, 2.54)
Current WHO stage	III or IV vs. I or II	1.80 (1.12, 2.89)	1.53 (0.44, 5.31)
Anti TB treatment	1 vs. 0	2.13 (1.23, 3.69)	1.70 (0.84, 3.44)
	2 vs. 0	1.11 (0.21, 5.85)	1.40 (0.21, 9.31)
Presence of	Hypertension	3.81 (1.75, 8.32)	**3.26 (1.40, 7.57)**

UOR – Unadjusted Odds ratios, AOR – Adjusted odds ratios

The effect of age on HIV-SN: after adjusting for the other covariates, age was found to be associated with HIV-SN, OR: 1.04 (95% CI: 1.01, 1.06). That is older participants were more likely to be diagnosed with HIV-SN and the odds was 4% higher for a participant who was a year older.

Participants who had higher baseline CD4 count (CD4>350 cells/mm^3) had 49% reduced odds of HIV-SN, OR: 0.51 (95% CI: 0.28, 0.99).

The effect of hypertension on the presence of HIV-SN, after adjusting for the other covariates, was more than threefold, OR: 3.26 (95% CI: 1.40, 7.57).

After adjusting for the other covariates, other variables that were significant in the bivariate analysis were no longer associated with the presence of HIV-SN.

CHAPTER FIVE: DISCUSSION

5.1 Prevalence of HIV-SN

The prevalence of HIV-SN in patients attending Webuye County hospital CCC was 30.0% (102 out of 340 subjects) and median duration of sensory neuropathy symptoms was 2.0 years. This prevalence is comparable to what has been found in other studies. Globally HIV-SN affects between 30% and 60% of ambulatory HIV-positive individuals, meaning that an estimated 10.5 to 21 million individuals have the neuropathy and are at a high risk of having pain (IASP, 2014). Higher prevalence has been found in developed world compared to our study. Smyth et al., (2006) in Melbourne Australia screened 100 patients and found a prevalence of forty-two per cent. Ellis et al., (2010) conducted a study between 2003 and 2007 in Six US academic medical centres. One thousand five hundred thirty-nine HIV-infected individuals were enrolled in the CNS (Central Nervous System) HIV Anti-Retroviral Therapy Effects Research (CHATER) study. They found HIV-SN in 881 participants (57.2%). In a study by Pettersen et al., (2006) in Canada, among the 221 patients examined, 101 had HIV-SN (45.7%). In Asia, Affandi et al., (2008) found a neuropathy prevalence of 34% among HIV patients in Jakarta who were exposed to d4T and Dubey et al., (2013) in Central India studied HIV neuropathy in pre-HAART patients, out of 75 patients studied, 40% had clinical HIV-SN.

Data available in Africa documents the prevalence of HIV-SN ranging from 30% to 60%. In a study carried out in South Africa by Maritz et al., (2010) a total 598 HIV-infected adults were studied and almost half (49%) of the study population were diagnosed with HIV-SN. Wadley et al., (2011) recruited 404 Black HIV-positive Africans in Johannesburg and assessed HIV-SN using the AIDS Clinical Trials Group

BPNS. Of those exposed to stavudine, 57% (226/395) had HIV-SN. In another study done in Lagos, Nigeria, by Oshinaike et al., (2012), the prevalence of sensory neuropathy was 39.0%. Some studies have reported lower prevalence than this study e.g. according to a study done in Douala General Hospital in Cameroon by Luma et al., (2011) out of 295 patients studied, 21% had HIV-SN. The researchers attributed this low prevalence to the fact that the study was done in an expensive tertiary institution where there could have been selection bias. In East Africa the same varied prevalence is documented. In a study by Tumusiime et al., (2014) in Rwanda, peripheral neuropathy prevalence was 59%. Biraguma et al., (2012) found the prevalence of neuropathy among PLWHA attending the outpatients' clinic at Rutongo Hospital in the Rulindo district of Rwanda to be 40.5%.

Mehta et al., (2010) looked at 102 patients receiving antiretroviral therapy in Mombasa, 36% had peripheral neuropathy which was comparable to our study. The varied prevalence is probably due to the differences in inclusion criteria and patient profile (e.g. inpatient vs. outpatient, HAART naive patients, and use of d4T) as well as diagnostic tool variance. Further on-going changes in the guidelines for management of HIV may have occasioned changes in prevalence owing to earlier initiation of HAART and phasing out stavudine.

5.2 Determinants of HIV-SN

Concerning the various determinants for HIV-SN, after bivariate analysis, our study established that older age was associated with the presence of HIV-SN. Viral load, baseline CD4 count, and WHO clinical stage were all associated with the presence of HIV-SN. Participants with higher distributions of current viral load were associated with the presence of HIV-SN.

History of use of anti-TB treatment was associated with the presence of HIV-SN, while history of alcohol drinking problem was not linked to the presence of HIV-SN. Hypertension comorbidity was significantly associated with diagnosis of HIV-SN. Similarly, the presence of diabetes was significantly associated with diagnosis of HIV-SN.

5.2.1 Age association with HIV-SN

Older participants were more likely to be diagnosed with HIV-SN and the odds was 4% higher for a participant who was a year older than another. An association between increasing age and the risk of HIV-SN has been an almost universal finding in recent observational studies. Smyth et al., (2006) in Melbourne Australia found that age was independently associated with HIV-SN, the same strong association was seen in many other studies (Wright et al., 2008; Ances et al., 2009; Anziska et al., 2011; Oshinaike et al., 2012; Wadley et al., 2011; Tumusiime et al., 2014).

This finding is consistent with declining neurological function with age (Cherry et al., 2009). This is because peripheral nerves by their length and size are known to have increased vulnerability with aging due to continual metabolic stress, exposure to toxic substances, according to Luma et al., (2012) and increased risk of many disorders including most types of polyneuropathies (Smyth et al., 2006). Furthermore, increased life expectancy in the HAART era predisposes to longer exposure to the HIV virus and to dideoxynucleoside analogues (Skopelitis et al., 2006). With the aging HIV population expected to increase due to widespread access to effective ART, we should expect a potential increase in prevalence of HIV-SN, independent of changes to modifiable risk factors such as exposure to neurotoxic ART, due to the positive association of HIV-SN with age.

Monitoring or screening for the occurrence of HIV-SN is therefore important for possible and appropriate management in this group, stressing the importance of early identification and management of the neuropathic pain symptoms in primary care to improve the quality of life (Haanpaa et al., 2009).

5.2.2 Baseline CD4 count association with HIV-SN

Participants who had higher baseline CD4 count (CD4>350 cells/mm^3) had 49% reduced odds of HIV-SN, OR: 0.51(95% CI: 0.28, 0.99). Severe prior immune-suppression based on CD4 count as a marker of immune suppression has been found to be an important determinant of HIV-SN (Lichtenstein et al., 2005).

The risk of HIV-SN is higher for patients with advanced HIV disease. Early studies emphasized low CD4 count and high viral load as risk factors, but with successful therapy these associations, specifically viral load have become less important (Morgello et al., 2004). There is evidence that successful HIV treatment as reflected by higher CD4 cell count is associated with a lower risk of neuropathy than found in those whose CD4 responses are lower. Nadir CD4, in treatment-naive cohort represented by the baseline CD4, also is associated with greater risk of peripheral neuropathy (Smyth et al., 2006; Ellis et al., 2010; Dubey et al., 2013). In Africa Luma et al., (2011) found a similar association but Wadley et al., (2011) in South Africa, Oshinaike et al., (2012) in Nigeria, and Tumusiime et al., (2014) in Rwanda did not find any association between either nadir and current CD4 T-cell counts and HIV-SN. Low CD4 count is a reflection of advanced HIV disease, low baseline CD4 count suggests most patients were symptomatic even before HAART and probably direct nerve damage could have already occurred primarily from the HIV infection (Evans et al., 2011). Ellis et al., (2010) in the US found that the elevated risk of HIV-SN in participants with low CD4

nadirs was independent of HAART success as indexed by virologic suppression. Thus, among participants with virologic suppression, those who had started HAART after their CD4 counts fell to less than 350/µL were significantly more likely to have HIV-SN than were those who started HAART before the CD4 dropped to less than 350/µL, even after adjusting for age, estimated duration of HIV infection, and D-drug use. This finding suggests that it may be possible to protect patients from HIV-SN by initiating HAART early (Hammer et al., 2008).

5.2.3 Hypertension association with HIV-SN

Hypertension was also found to be strongly associated with HIV-SN in our study. The effect of hypertension on the presence of HIV-SN, after adjusting for the other covariates, was more than threefold, OR: 3.26 (95% CI: 1.40, 7.57). Over the past decade there have been significant demographic changes in the HIV epidemic. The overall population of people living with HIV/AIDS is aging. The effect of HAART, aging and resulting comorbidities, such as hypertension, and diabetes add new complexity to HIV and related conditions such as HIV-SN (Hahn & Husstedt, 2011).

Two Metabolic Syndrome components, that is elevated triglycerides level (>150mg/dl) and Diabetes Mellitus type II have been associated with idiopathic Sensory Neuropathy in HIV infected populations (Ances et al., 2009). In a previous cross-sectional study of age-associated peripheral neuropathy (AAPN), and Diabetic neuropathy, it was found that a history of hypertension was protective (Cho, Mold, & Roberts, 2006). More recently, a review of the literature concluded that exposure to statins, commonly used in patients with metabolic syndrome including elevated blood pressure may increase the risk of polyneuropathy and that statins should be considered the risk factor when other etiologies have been excluded (Miron et al., 2009). Our search found that not many HIV

neuropathy studies include diabetics and associated comorbidities so the degree of interaction of these problems has not been well described. Whereas the number of diabetic patients in our study was so small that it was excluded in the multiple logistic regression, our data from bivariate analysis suggest that diabetes raises the likelihood of having HIV-SN.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

1. There is high prevalence of HIV-SN in patients attending Webuye County Hospital CCC.
2. Age is independently associated with HIV-SN.
3. Baseline CD4 count is also independently associated with HIV-SN.
4. Hypertension, a less studied factor (comorbidity) is strongly associated with HIV-SN.

6.2 Recommendations

1. Since the prevalence of HIV-SN is 30% and age is independently associated with HIV-SN, we recommend the routine screening of adult patients for HIV-SN during clinic visits by health care workers through the easy to use BPNS tool.
2. Further study to evaluate the role of hypertension in HIV-SN.

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APPENDICES

1. Informed consent form Study No----------

‘**Determinants of sensory neuropathy among HIV/AIDS patients attending Comprehensive Care Clinic at Webuye County Hospital’**

Invitation to participate

You are invited to participate in this research study investigating relationship between various determinants and HIV associated sensory neuropathy in adults attending CCC at Webuye County Hospital.

Basis for selection

You are eligible to participate in this study because you have been recruited in order to help us investigate relationship between various determinants and HIV associated sensory neuropathy in adults attending CCC at Webuye County Hospital.

Purpose of study

The main aim of this study is to determine the relationship between various determinants and HIV associated sensory neuropathy in adults attending CCC at Webuye County Hospital.

Procedures

You will be asked some questions about your point of entry into care, date of diagnosis, your past health and social life and whether you experience extremity pains, numbness or tingling sensation and then you will be taken through minimal clinical examination.

Potential benefits

There is no reward for participation in this study. Patients with HIV-SN will be started on treatment and booked to the physician's clinic for follow-up. They will also potentially help improve the knowledge of determinants of HIV-SN.

Potential risks

There are no risks in this study.

Guarantee of confidentiality

To ensure confidentiality, at no time will your name appear on any materials or reports of the research findings (including web-site postings of the results, conference presentations, or professional publications). Materials associated with this study will be kept under lock and key in a cabinet. Your signed consent form will be stored separately from your data to insure complete confidentiality. At the conclusion of this study, all materials will be destroyed.

Withdrawal from participation

Participation in this study is voluntary. Your decision to participate or not to participate Will not affect your follow up at the comprehensive care clinic If you decide to participate, you are free to withdraw your consent and to discontinue your participation at any time.

Offer to Answer Any Questions

If you have any questions about the procedures at any time, please do not hesitate to ask. If you think of questions later, please feel free to contact the principal investigator. All questions about the procedures and this study in general will be answered. However,

some questions may not be answered until after you have completed the procedures to ensure that your responses will not be affected by your knowledge of the research.

Participant's statement

I am voluntarily making the decision to participate. My signature certifies that I have heard and understand the aforementioned information. My signature also certifies that I have had an adequate opportunity to discuss this study with the research investigator and have had all of my questions answered to my satisfaction. I understand that by signing this document, I waive no legal rights.

_____ _____

Participant's Signature Date.

Research Investigator's Statement

In my judgment, the aforementioned participant is voluntarily and knowingly giving Informed consent and possesses the legal capacity to do so.

_____

Research Investigator's Printed Name.

_____ _____

Research Investigator's Signature and Date.

0720911086, P.O Box 1002 Webuye. Email: jerngugi@yahoo.com

Research Investigator's Telephone Number Research Investigator's E-mail Address

2. Fomu ya idhini Namba ya uchunguzi……..

Uhusiano kati ya kufa ganzi na uchungu kwa mikono na miguu na maradhi ya ukimwi kwa watu wanaopata matibabu kwenye kliniki ya CCC ya Hospitali ya kaunti ya Webuye.

Mwaliko wa kushiriki

Unaalikwa kushiriki katika utafiti, "Uhusiano kati ya kufa ganzi na uchungu kwa mikono na miguu na maradhi ya ukimwi kwa watu wanaopata matibabu kwenye kliniki CCC ya Hospitali ya kaunti ya Webuye".

Madhumuni ya somo hili

Lengo la utafiti huu ni kusaidia kujua uhusiano kati ya kufa ganzi na uchungu kwa mikono na miguu na maradhi ya ukimwi kwa watu wanaopata matibabu kwenye kliniki CCC ya Hospitali ya kaunti ya Webuye na inatarajiwa matokea yatasaidia kupanga mikakati ya kugundua wenye changamoto hii na kuzuia wengine kupata.

Taratibu

Utaulizwa maswali kuhusu wakati na mahali ulipopimwa na hali yako ya kiafya na kama huwa unapata shida ya kufaganzi ama uchungu kwenye miguu na mikono kisha kufanyiwa uchunguzi mdogo wa kiafya.

Faida ya utafiti

Hakuna malipo au zawadi kwa ajili ya kushiriki katika utafiti huu. Watakaopatikana na shida ya kufa ganzi na uchungu kwa mikono na miguu wataanzishwa matibabu na kufuatiliwa kwenye kliniki. Kushiriki katika utafiti huu pia kutachangia pakubwa katika

kuelewa shida ya kufaganzi ama uchungu kwenye miguu na mikono kwa watu wenye maradhi ya ukimwi.

Hatari za utafiti

Hakuna hatari zinazotokana na kushiriki kwako katika utafiti.

Dhamana ya kuweka siri

Kuhakikisha siri, jina lako halitaonekana kwenye nyenzo yoyote au taarifa ya matokeo ya utafiti (ikiwa ni pamoja na mtandao, matangazo ya matokeo, maonyesho ya mkutano huo, au machapisho ya kitaaluma). Vifaa vinavyohusiana na uchunguzi vitahifadhiwa na mpelelezi mkuu na ataziweka siri zote.

Kujitoa kutoka kushiriki kwa utafiti

Kushiriki katika utafiti huu ni kwa hiari. Uamuzi wako wa kushiriki au kutoshiriki hautaadhiri matibabu na kufuatiliwa katika kliniki. Uko huru kujitoa wakati wowote na kuacha kushiriki bila madhara yoyote.

Kuuliza na kujibu maswali yoyote

Kama una maswali kuhusu taratibu wakati wowote, tafadhali usisite kuuliza.
Kama utakuwa na maswali baadaye, tafadhali jisikie huru kuwasiliana na mpelelezi mkuu. Maswali yote juu ya taratibu na utafiti huu kwa ujumla yatajibiwa. Hata hivyo, baadhi ya maswali yatajibiwa baadaye ili yasiadhiri uchunguzi.

Taarifa ya mshiriki

Mimi nimefanya uamuzi kushiriki kwa hiari katika utafiti. Sahihi yangu inaonyesha ya kwamba nimeelewa habari niliyoelezewa pia ni dhihirisho kuwa nimepata muda wa kutosha kujadiliana na watafiti wanaohusika na nimeridhishwa na majibu niliyopewa. Ninaelewa kuwa kwa kutia sahihi yangu kwenye hati hii sijaziondoa haki zangu za kisheria.

_____ _

Sahihi ya mshiriki Tarehe

Mpelelezi

Katika maoni yangu, mshiriki aliyetajwa ana hiari na amepewa habari ya kutosha kuweza kutoa ridhaa na ana uwezo wa kisheria kufanya hivyo.

_____

Jina la mpelelezi.

_____

Sahihi ya Mpelelezi wa utafiti na tarehe.

0720911086, P.O BOX 1002 Webuye, email: jerngugi@yahoo.com

Simu ya Mpelelezi wa utafiti, anwani ya Mpelelezi wa Utafiti, na barua pepe

3. Study Questionnaire

Demographic and Anthropometric data.

Date.....

Age..... Gender/Sex Male ☐ Female ☐

Weight..... Height..... BMI.....

Clinical data

Date enrolled on HIV care.....

Duration of HIV infection-from the time of diagnosis (yrs.).....

Baseline CD4 Count (cells/mm^3)……

Current viral load (copies/ml)..... Highest ever viral load (copies/ml).....

WHO stage (initial)..... Current WHO stage.....

HAART Regimen (i)..... Duration (Years).....

(ii)..... Duration (Years).....

(iii)..... Duration (Years).....

TB Treatment: Current ☐ Past ☐ Never ☐ Duration (yrs).....

Alcohol drinking problem YES ☐ NO ☐ Duration (yrs).....

HIV-SN (From BPNS) YES ☐ NO ☐ Duration (yrs).....

Comorbidities: Hypertension: YES ☐ NO ☐ Duration (yrs).....

Diabetes M: YES ☐ NO ☐ Duration (yrs).....

Renal Disease: YES ☐ NO ☐ Duration (yrs).....

4. ACTG Brief Peripheral Neuropathy Screen (BPNS) tool

Source: NIAID Adult AIDS Clinical Trials Group

1. Elicit Subjective Symptoms

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

Always Been Normal	Currently Absent	Mild ←→ Severe									
11	00	01	02	03	04	05	06	07	08	09	10
Symptoms										R	L

a. Pain, aching, or burning in feet, legs

b. "Pins and needles" in feet, legs

c. Numbness (lack of feeling) in feet, legs

2. Grade Subjective Symptoms

Use the single highest severity score from Question 1 above to obtain a subjective sensory neuropathy score. If all severity scores are "00" or "11," the subjective sensory neuropathy score will equal "0."

Subjective Sensory Neuropathy Score (based on highest severity rating)

01 - 03 = grade of 1

04 - 06 = grade of 2

07 - 10 = grade of 3

11 or 00 = grade of 0

R	L

3. Evaluate Perception of Vibration

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

Vibration perception

a. Great toe DIP joint perception of vibration in seconds

b. Vibration perception score

0 = felt >10 seconds (normal)

1 = felt 6-10 seconds (mild loss)

2 = felt <5 seconds (moderate loss)

3 = not felt (severe loss)

8 = unable to or did not assess

R	L

4. Evaluate 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 examiner's hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon is struck. Use reinforcement by having the subject clench his/her fist before classifying the reflex as absent.

Ankle Reflexes Score

0 = absent

1 = hypoactive

2 = normal deep tendon reflexes

3 = hyperactive

4 = clonus

8 = unable to or did not assess

R	L

5. Study Approval Documents

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET

Reference: IREC/2013/178
Approval Number: 0001130

28th January, 2014

Dr.Jeremiah Kinuthia Ngugi
Moi University,
School of Medicine,
P.o Box 4606,
ELDORET –KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
28 JAN 2014
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr.Jeremiah,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee have reviewed your research proposal titled:-

"Determinants of Sensory Neuropathy among HIV/AIDs Patients attending Comprehensive Care Clinic at Kangundo District Hospital."

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 1130*** on 28th January, 2014. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 27th January, 2015. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

28/1/2014
DR. W. ARUASA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc Director - MTRH Dean - SOM
Principal - CHS Dean -

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference
IREC/2013/178
6th October, 2014

Approval Number: 0001130

Dr. Jeremiah Kinuthia Ngugi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
06 OCT 2014
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Ngugi,

RE: APPROVAL OF AMENDMENT

The Institutional Research and Ethics Committee has reviewed the amendment made to your proposal titled:-

"Determinants of Sensory Neuropathy among HIV/AIDS Patients Attending Comprehensive Care Clinic at Kangundo District Hospital".

We note that you are seeking to make an amendment as follows:-

1. To change study site from Kangundo Sub County Hospital to Webuye Sub County Hospital.

The amendment has been approved on 6th October, 2014 according to SOP's of IREC. Your title now reads as follows:-
"Determinants of Sensory Neuropathy among HIV/AIDS Patients Attending Comprehensive Care Clinic at Webuye County Hospital".

You are required to submit progress(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change(s) or amendment(s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc: Director - MTRH, Dean - SPH, Dean - SOM
Principal- CHS, Dean - SOD, Dean - SON

Academic Model Providing Access To Healthcare
Telephone: 254 53 2033471/2P.O. BOX 4606, ELDORET Fax: 254 53 2060727

RESEARCH

Ref: RES/STUD/12/2014 **November 5, 2014**

To: In Charge AMPATH Webuye Clinic

RE: PERMISSION TO CONDUCT RESEARCH AT AMPATH

This is to kindly inform you that **Dr. Jeremiah Kinuthia,** has been granted permission to conduct research at the Webuye AMPATH Clinic. His study; *"Determinants of Sensory Neuropathy among HIV/AIDS Patients Attending Comprehensive Care Clinic at Webuye County Hospital "* has been reviewed by IREC and reviewed by the AMPATH Research Program Office.

His research activities should not in any way interfere with the care of patients. This approval does not support access to AMRS data at AMPATH.

The researcher is to submit a final report of their findings to the AMPATH Research Program Office.

Should the researcher wish to publish their findings, permission has to be sort from AMPATH Publications Committee. Please contact the AMPATH Research Office in case of any enquiry regarding this matter.

Thank you,

AMPATH CENTRE * RESEARCH * 05 NOV 2014 * P.O. Box 4606-30100, Eldoret

Jepchirchir Kiplagat
Assistant Program Manager for Research

CC.

- Chief of Party, AMPATH
- Deputy Chief of Party, Research and Training
- Associate Program Manager, Research and Training