

**PREVALENCE AND TYPES OF PERIPHERAL NEUROPATHY
IN HIV INFECTED PATIENTS ON STAVUDINE - BASED HAART
REGIMEN AT KENYATTA NATIONAL HOSPITAL**

BY

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**A DISSERTATION SUBMITTED IN PART FULFILLMENT OF
THE DEGREE OF MASTER OF MEDICINE IN INTERNAL
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DECLARATION

I declare that this is my own original work and has not been published elsewhere or presented for a degree in any other university.

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DEDICATION

This work is dedicated to my dear wife Evelyn and my daughter Nangira who sacrificed so much for me.

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ABBREVIATIONS

KNH	- Kenyatta national hospital
AIDS	- Acquired immune deficiency syndrome
HIV	- Human immunodeficiency virus
WHO	- World health organization
CD4	- CD4+ T Lymphocytes
CCC	- Comprehensive care clinic
UON	- University of Nairobi
ELISA	- Enzyme linked immunosorbent assay
DNA	- Deoxy ribonucleic acid
NRTI	- Nucleoside reverse transcriptase inhibitor
DSPAN	- Distal sensory painful axonal neuropathy
HAART	- Highly active antiretroviral therapy
ddC	- Zalcitabine
ddI	- Didanosine
d4T	- Stavudine
3TC	- Lamivudine
TK	- Thymidine kinase
Mt DNA	- Mitochondrial DNA
AZT	- Zidovudine
ARV	- Anti retroviral
NCS	- Nerve conduction studies
SLE	- Systemic lupus erythematosus
CDC	- Center for disease control
PI	- Principal investigator.

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ABSTRACT

Introduction: Peripheral neuropathy, which is abnormal function and structure of peripheral motor, sensory and autonomic neurons is important drug associated toxicity with the nucleoside reverse transcriptase inhibitors, which are used as anti retroviral backbone in management of HIV/AIDS.

The prevalence of peripheral neuropathy in patients on this class of antiretrovirals is unknown locally, especially with the up-scaling of ARV use where stavudine is a major backbone.

Objectives: To determine the prevalence and types of peripheral neuropathy in HIV infected patients on stavudine-based regimen, and compare with those naïve to antiretrovirals but eligible for HAART at KNH.

Design: Cross sectional comparative study.

Setting: Comprehensive care clinic of Kenyatta National Hospital

Study population: Adults (>13 years) with HIV infection on stavudine-based regimen for a period of at least three months and those naïve to antiretrovirals but eligible for HAART.

The study targeted WHO III/IV HIV patients.

Methods: Sixty four (64) patients with HIV infection, 32 on stavudine-based regimen for a period of at least three months and another 32 naïve to antiretrovirals but eligible for HAART (32 of each group matched for age to the nearest 5 years, sex and CD4 category). Neurological history, examination and electrophysiological study were done for every patient.

Results: The mean age for those patients on ARVs was 38.8 ± 6.4 years, range 24 – 50 years, while for the comparison group, the mean age was 38.4

± 7.6 years, range 24 – 55 years, there being no statistically significant difference, p value of 0.93.

Most patients (75% of the ones on treatment and 68.75% of the ones naïve to treatment) were in WHO clinical stage 4. Their mean CD4+ cell count was 115.6 ± 53.9 (range 6 – 190) for those on ARVs and 123.6 ± 65.3 (range 12 – 198) for the HAART naïve group. There was no statistically significant difference, p value of 0.6

The mean duration of ARV use for the group on ARVs was 22.6 months, range 10 – 42 months.

Fifteen patients (46.9%) on ARVs compared to eight patients (25%) of the naïve group, were symptomatic for peripheral neuropathy (p value = 0.08).

The most common symptoms in the two groups were burning sensation followed by paraesthesiae. The most common physical findings on neurological examination were impaired vibration perception sense followed by impaired proprioception in the naïve patients. Those on ARVs had most of the findings spread out with slight predominance of reduced tone and muscle power followed by impaired touch sensation.

Twenty one (65.6%) patients on stavudine-based regimen had evidence of peripheral neuropathy as compared to eleven (34.4%) naïve patients (p = 0.02). Patients on ARVs had significantly more axonopathy at a p value of 0.05. The naïve patients had predominant demyelination.

Conclusion: Peripheral neuropathy predominantly, axonopathy is common in patients on stavudine-based regimen of antiretrovirals. The toxicity of stavudine-based antiretrovirals may limit the use of the regimen and reduce drug adherence.

INTRODUCTION

In 1981, there was a report of an unusual cluster of cases of pneumocystis pneumonia and Kaposi sarcoma in previously healthy homosexual males in the United States of America. Two years later (1983), cytopathic retroviruses were identified. In 1985, diagnostic serologic tests for HIV – 1 were unveiled followed by monotherapy of Zidovudine in 1987. Much later, in 1997, HAART was rolled out aggressively as the EUROSIDA study of pre – HAART and later HAART (1982 – 2002) found sustained decrease in mortality and progression to AIDS with ongoing HAART (1).

However, HIV/AIDS continues to have a devastating impact on all sectors of the society especially in the developing world. HIV global estimates for adults and children in 2005 are as follows (2):

- People living with HIV 38.6 million
- New HIV infections in 2005 4.1 million
- Deaths due to AIDS 2.8 million.

With these soaring numbers however, treatment is not readily and widely available in developing countries due to cost and lack of clinical infrastructure.

Kenyan data

Locally, the prevalence of HIV infected individuals has dropped from 10% in 1998 to 7% in 2003 and further down to 6% in the year 2006. The cost of HAART has also dropped significantly from about 10,000 USD/person/year in 2000 to about 70 USD/person/year in the public sector and 700 USD/person/year in the private sector by 2006. In line with the WHO goals, the government of Kenya is committed to progressively deliver effective antiretroviral therapy to 95,000 patients by the end of 2005 and 140,000 by 2008 (2).

LITERATURE REVIEW

Use of a combination of antiretroviral drugs has led to dramatic decline in HIV- related morbidity and mortality. However, clinically important drug toxicities can limit the use of these agents (3).

With effectiveness of HAART and the consequent decline in the incidence rates of CNS opportunistic infections, HIV dementia, HIV associated neuropathies has become the commonest neurological disorder (17)

Peripheral neuropathy, defined as abnormal function and structure of peripheral motor, sensory and autonomic neurons is a frequent adverse effect of all dideoxynucleosides (3).

However, peripheral neuropathy is common in patients with HIV/AIDS and has many aetiological factors some of which include (4):

- (i) Human immune deficiency virus. This is a frequent cause of neuropathy and may take a variety of forms; early in the disease, an acute inflammatory demyelinating polyneuropathy resembling GBS may occur. In others, a progressive or relapsing-remitting inflammatory neuropathy resembling chronic inflammatory demyelinating polyneuropathy (CIDP) has been noted. Patients present with progressive weakness, areflexia, and minimal sensory changes. Peripheral nerve biopsy reveals a perivascular infiltrate suggesting an autoimmune aetiology. Another autoimmune peripheral neuropathy seen in these patients is mononeuritis multiplex due to a necrotizing arteritis of peripheral nerves. It could also be due to a direct effect of the virus through immunological dysregulation.
- (ii) Neurotoxic antiretrovirals: commonly seen with the dideoxynucleoside group of antiretrovirals. These drugs commonly give a distal sensory polyneuropathy.
- (iii) Opportunistic infections: e.g cytomegalovirus infection; which causes a radiculopathy that is asymmetrical

- (iv) Drugs used in the management of opportunistic infections e.g. anti-tuberculous drugs, dapson, metronidazole, anti epileptics e.g. phenytoin that may be useful as adjunct therapy in intracranial space occupying lesions.

Patients treated with nucleoside analogue reverse transcriptase inhibitors develop a varying degree of neuropathy after long-term therapy (3). Stavudine, Zalcitabine, Didanosine and Lamivudine are the NRTIs associated with neuropathy (3).

PATHOGENESIS

It is known that distal sensory polyneuropathy becomes more prevalent with advanced immunosuppression and increased viral replication, but can also increase with the use of combined dideoxynucleoside therapy through its neurotoxic effects, even in the presence of improved viral suppression. These two seemingly opposed possibilities raise important questions in the era of HAART: which mechanism will be more influential in the development of neuropathy, is it the reduction and eventual suppression of the viral load or the exposure to neurotoxic drugs used as part of HAART?

At least one previous study (5) showed an improvement in the physiological measures of neuropathy in patients who responded to antiretroviral therapy, in spite of increased exposure to neurotoxic medications. Two recent case reports present findings that may suggest a therapeutic effect from HAART in Guillain – Barre syndrome (GBS), in one case with concomitant anti – cytomegalovirus therapy. One anti retroviral naïve patient with acute GBS and advanced HIV infection appeared to improve after the introduction of HAART, with an improvement in viremia and CD4 cell measures (6).

Although only a single case and confounded by the self limited nature of GBS, the report raised the possibility of a direct effect of improved viral suppression with HAART and a potential effect of viral replication in this demyelinating neuropathy. An additional report of an antiretroviral naïve

patient with evidence of advanced HIV infection and with GBS associated with acute cytomegalovirus infection (7), showed a dramatic recovery after the concomitant use of HAART and gancyclovir. Both cases show that GBS may occur in advanced stages, and is not limited to the time of seroconversion or early stages.

An additional case report presented an opposite effect from HAART and improved viral suppression (8). An antiretroviral naïve patient developed a relapse of a demyelinating polyneuropathy (probably chronic inflammatory demyelinating polyneuropathy) after treatment with HAART and a rapid recovery of immune parameters. The authors argued that the relapse was the result of the improved viral suppression with immune reconstitution. Although difficult to prove, the coincidental and vigorous increase in CD4 lymphocytes supported a very provocative argument about the exact causation of the polyneuropathy. Was it an adverse effect of HAART or a result of recovery from the extreme immune suppression? (8)

One important aspect that has arisen with the use of dideoxynucleosides relates to the possibility of a Stavudine - associated, rapidly ascending syndrome of neuromuscular weakness and respiratory failure, mimicking GBS (18). The syndrome may be associated with hyperlactatemia.

Mechanism of dideoxynucleoside – associated neuropathy

Although the precise cause is not known, there is abundant indirect evidence of mitochondrial dysfunction as the principal mechanism. One possibility that had been reported earlier (9) was a deficiency in serum levels of acetyl-carnitine, a critical substrate for normal mitochondrial function. This has been challenged by results from a recent study of a much larger sample of patients who participated in the nerve growth factor (NGF) trial (10). Comparing patients with dideoxynucleoside associated polyneuropathy and primary HIV neuropathy, the investigators failed to observe a significant difference in total, free carnitine, or acetyl carnitine

between the two groups, or an association with other clinical and physiological markers of neuropathy.

Dalakas and colleagues (11) provided direct, pathology evidence of mitochondrial abnormalities in sensory nerves of patients with Zalcitabine induced neuropathy. Using quantitative methods and Sural nerve biopsy specimens from four HIV infected patients with Zalcitabine associated neuropathy, they were able to demonstrate an increased number of abnormal mitochondria in the axons and schwann cells, as well as mitochondrial DNA depletion. Sural nerve specimens from Zalcitabine naïve HIV infected patients and non-HIV neuropathy patients, showed a much smaller number of abnormal mitochondria and no evidence of mtDNA depletion.

The paper provided compelling evidence of mitochondrial damage (by biopsy) as the cause of dideoxynucleoside neuropathy. This mitochondrial dysfunction is attributed to the inhibition of DNA polymerase gamma, the enzyme responsible for mtDNA replication. One possible mechanism to explain the enhanced susceptibility for toxic neuropathy in some but not all individuals exposed to dideoxynucleosides could be genetic variations in the polymerase gamma.

Chen and colleagues (12) investigated whether CAG repeat expansions or mutations in the DNA polymerase gamma gene explained this susceptibility. They were unable to find any correlations between CAG repeat expansions and the presence of neuropathy or mutations in the coding regions and lactic acidosis. The study was one of a few examining specific mechanisms that could explain the differences or increased susceptibility from a superimposed, genetically encoded variant.

How can one monitor or detect mitochondrial toxicity in early or presymptomatic stages?

Cherry et al (13) reported an improved method to measure mtDNA from subcutaneous fat samples obtained from skin biopsies. In a group of sixty (60) patients enrolled in a study of distal sensory polyneuropathy, 50% of whom had clinical neuropathy, a significant correlation was shown between reduced mtDNA in subcutaneous fat and exposure to NRTIs. The reduction was more prominent with exposure to dideoxynucleosides, but interestingly, as a cross – sectional measurement it did not correlate with the presence of neuropathy or lipoatrophy. This may prove to be a valuable method to detect mitochondrial toxicity in pre symptomatic stages, or alternatively a way to monitor for mitochondrial toxicity in patients exposed to antiretroviral drugs.

Although infrequent, vasculitic neuropathy is known to occur in HIV infected patients. In the immunocompromised host these may be associated with infections by cytomegalovirus or varicella zoster virus. A recent paper (14), from Asia continent described four cases of patients with vasculitic neuropathies as the presenting manifestation of HIV infection. All patients showed elevated erythrocyte sedimentation rate without evidence of other rheumatological conditions. Clinically, the presentation was that of an asymmetric sensorimotor, predominantly axonal, polyneuropathy with additional facial nerve involvement in some cases.

Can dideoxynucleosides aggravate a pre existing motor neuropathy?

In a recent report of a patient with Charcot-Marie-Tooth 1A (15), a predominantly motor inherited demyelinating neuropathy; the authors suggested that the absence of a worsening of motor parameters indicated that dideoxynucleosides did not aggravate the pre existing neuropathy. Although an interesting argument, the rapid onset of intense paraesthesiae that the authors described could be construed as evidence of aggravation, because Charcot-Marie-Tooth type 1A affects both motor and sensory axons, and because dideoxynucleosides preferentially affect sensory neurons. An additional report underscored the need to consider the

possibility of a coexistent inherited neuropathy in patients with HIV associated neuropathies (15).

What are the markers of severity?

The diagnosis of the HIV associated peripheral neuropathy still relies on a careful clinical and electro diagnostic examination.

In distal sensory polyneuropathy, however, there is prominent involvement of small myelinated and unmyelinated fibers, and these are difficult to evaluate clinically or electro diagnostically. Skin biopsies with nerve fiber density evaluation are of value in the assessment of peripheral neuropathies with prominent involvement of small fibers, including distal sensory polyneuropathy.

An analysis of intraepidermal nerve fiber (IENF) densities from skin biopsies obtained from 60 subjects enrolled in the NGF trial in HIV sensory neuropathy study (16) revealed that intraepidermal nerve fiber density was significantly and inversely correlated with some measurements of neuropathic pain. Intraepidermal nerve fiber densities were also associated with measures of HIV activity, specifically lower CD4 cell counts and higher plasma HIV – RNA levels.

Overall, the study provided additional important information that helped validate this novel technique (analysis of intraepidermal nerve fiber densities from skin biopsies) as an added measure of severity of neuropathy and a reflection of the influence of viral replication in distal sensory polyneuropathy.

Previous studies (17,19) have shown that increased viral replication, with resultant high viral loads and low CD4 cell counts, is a risk factor for prevalent and incident distal sensory polyneuropathy. This implies therefore that the patients in the late stage disease will be at a higher risk of developing peripheral neuropathy even before HAART commencement.

Among all antiretroviral drugs, toxicity to the peripheral nerves has been observed only with NRTIs, either singly or in combination. All NRTIs except zidovudine are neurotoxic to a varying degree and in a dose dependent manner but they are not myotoxic except zidovudine, which is myotoxic and has been associated with cardiomyopathy (17)

Two factors must be considered before concluding that an NRTI is responsible for neuropathy in patients with AIDS.

First, there is frequent presence of pre-existing clinical or sub clinical neuropathy related to AIDS and secondly, there is almost identical clinical symptomatology of NRTI – associated neuropathy and the distal sensory painful axonal neuropathy (DSPAN) of AIDS.

The following features may help distinguish the NRTI – related peripheral neuropathy from DSPAN:

- a) Temporal association between onset or rapid worsening of neuropathic symptoms with initiation of NRTI treatment.

- b) Clinical or electromyographic improvement of symptoms and signs after cessation of therapy or reduction of the dose compared to continuous worsening of neuropathic symptoms in AIDS – related DSPAN.

The clinical symptoms of NRTI - related peripheral neuropathies are identical to those of DSPAN and include:

- Burning sensation in the feet and legs.
- Shooting pain and cramps in the legs.
- Impaired temperature and pain sensation and to a lesser degree vibration sensation.
- Absent ankle jerks and minimal muscle weakness in the toe extensors.

Electro physiologically, the sensory nerve axon potentials are characterized by low amplitude and normal latency consistent with sensory axonal degeneration.

In a recent large study, the incidence of drug related neuropathy after HAART therapy was 31.2% (18) compared with 10% found in a study by Ashok Verma (37) before the introduction of HAART.

NRTI – related neuropathy has not been appreciated in children even if doses used are higher (19)

Another risk factor for development of neuropathy is the combination therapy; zalcitabine is more neurotoxic than didanosine, stavudine and lamivudine but the combination of didanosine and stavudine is more toxic than didanosine or stavudine alone.

Zalcitabine

In the initial clinical trial involving a series of patients who received 1 of 4 ddC dose regimens, all patients who received high dose therapy (0.12-0.24mg/kg/day) as well as 80% of patients who received an intermediate dose (0.04mg/kg/day) developed neuropathy (18,20)

In other trials, about 30-40% of patients even without history of neuropathy, receiving low dose ddC (0.02mg/kg/day) developed neuropathic symptoms. With high dose treatment almost all patients on ddC may develop neuropathy. Upon drug withdrawal, up to 80% of patients improve (21).

The time to recovery varies; it can be as long as 19 weeks in patients who received high dose therapy. Usually, there is clinical and electrophysiological improvement 6-8 weeks after withdrawal of ddC (22).

Didanosine

Painful sensory polyneuropathy is common with ddl therapy and is also a dose-limiting factor in the use of this drug in AIDS patients. Although the incidence of toxic neuropathy varies with different ddl doses and schedules

(23) a reversible neuropathy occurs in up to 23% of patients after 10 months of treatment with ddI. Overall the neuropathy related to ddI seems to be slightly less frequent than the one related to ddC.

Stavudine

The dose – dependant neuropathic effects of stavudine were defined in a randomized trial involving doses of 0.5mg/kg/day, 1.0mg/kg/day and 2.0mg/kg/day in 152 patients with a median CD4 cell count of 246/mm³. Polyneuropathy was observed in 6%, 15% and 31% of patients respectively within 8 – 16 weeks after initiation of therapy. Patients with pre existing neuropathy, low CD4 cell count or low hemoglobin level were at increased risk for developing polyneuropathy during treatment with stavudine (18,24,25).

Lamivudine

This is also neurotoxic, exaggerating pre existing neuropathy (26). The lamivudine-associated neuropathy appears to be less common than with the other NRTIs, even though lamivudine has not been systematically evaluated.

Combinations of NRTIs may have a synergistic neurotoxic effect in mitochondrial toxicity, as shown in vitro. All side effects attributed to NRTIs such as polyneuropathy, myopathy, cardiomyopathy, pancreatitis and lactic acidosis resemble the spectrum of clinical manifestations seen in inherited mitochondrial diseases (29,30)

Locally, highly active antiretroviral therapy has been scaled up significantly and stavudine is the backbone of the first line therapy owing to its lower cost compared to other NRTIs in its class. Studies (3,4,20,44,47,48) done elsewhere shows that for stavudine, the reported figures differ according to the diagnostic method used: a low incidence for clinical diagnosis and a high incidence (up to 31%) for electrophysiological diagnosis.

GUIDELINES ON FIRST LINE THERAPY

Current evidence (2) supports the use of two basic regimens: an NNRTI – based regimen or a ritonavir boosted (pi/r) based regimen. When choosing the initial treatment regimen, the following factors should be considered:

1. Co-morbidity or co-existing conditions such as tuberculosis, liver disease, pregnancy, or pregnancy potential.
2. Adherence potential
3. Dosing convenience with regard to frequency of dosing and pill burden and food and fluid considerations
4. Potential adverse drug effects
5. Potential drug interactions with other medications.

In general, a minimum combination of three drugs from at least two different classes in the following combinations is preferred:

1. 2 NRTIs + NNRTI
2. 2NRTI +Pi/r (ritonavir boosted Pi)

On current evidence, single Pi based therapy is no longer considered as a preferred regimen due to reduced potency compared to the above. It may however sometimes be necessary to use this in specific patient groups.

Triple nucleoside combination therapy is also currently not recommended for first line treatment; such combinations have been shown to be inferior to the standard two class recommended regimens. There are however occasions when this combination may be the only suitable treatment in some patient groups.

Monotherapy or dual therapy should not be used due to inadequate potency. The combination of didanosine and stavudine should be avoided particularly in pregnancy because of increased risk of fatal lactic acidosis with hepatic steatosis and/or pancreatitis. This combination should be used only when other NRTI based drug combinations have failed or have caused unacceptable toxicity or side effects.

Based on the above guidelines, the ministry of health has decided on standardized antiretroviral drug regimens.

This process took into account the needs of a public health approach to scaling up of ART, which has taken into account cost, efficacy, tolerability and availability.

First line regimen for adults and adolescents:

Stavudine (d4T) or Zidovudine (AZT)
+
Lamivudine
+
Nevirapine (NVP) or Efavirenz (EFV)

The zidovudine/lamivudine combination while more costly than stavudine/lamivudine is also effective and better tolerated. However, since anemia is a common presentation in HIV-infected patients (40) either secondary to nutritional deficiencies or as a result of HIV, opportunistic infections or other diseases related to HIV, stavudine or other NRTI that do not cause bone marrow suppression may be preferable to zidovudine as initial therapy in this setting.

Doses of these first line drugs are:

Stavudine: body weight > 60kg- 40mg bid
< 60kg- 30mg bid

Lamivudine: 150mg bid or 300mg OD

Zidovudine 300mg bid

Nevirapine 200mg OD × 14 days, then 200mg bid

Efavirenz 600mg OD

Stavudine stands out in this first line therapy as the drug commonly associated with peripheral neuropathy.

STUDY JUSTIFICATION

1. Up-scaling of HAART has created larger numbers of people surviving HIV but are developing toxicities like peripheral neuropathy. Neuropathies, amongst other toxicities, impact negatively on the quality of life.
2. The prevalence of peripheral neuropathy in this group of patients is not known several years and it is difficult to address this important adverse effect if its exact magnitude is not known.
3. Previous studies done elsewhere shows that peripheral neuropathy is a common adverse drug reaction in patients with HIV on antiretrovirals (stavudine in particular). Since this might affect adherence to HAART, the burden of the problem needs to be addressed.
4. The knowledge from this study will be useful in defining the place of stavudine in future antiretroviral regimen.
5. This study will also serve as a basis for future studies.

MAIN OBJECTIVE

To determine the prevalence and types of peripheral neuropathy in HIV infected patients on stavudine based HAART regimen at Kenyatta National Hospital.

SPECIFIC OBJECTIVES

1. To determine the prevalence of peripheral neuropathy by clinical findings and nerve conduction studies in HIV infected patients:
 - Naïve to HAART but eligible for commencement.
 - On stavudine-based HAART regimen for ≥ 3 months.

2. To determine the types of peripheral neuropathy using nerve conduction studies in HIV infected patients:
 - Naïve to HAART but eligible for commencement.
 - On stavudine-based HAART regimen for ≥ 3 months.

3. To compare the prevalence and types of peripheral neuropathy in the two groups of patients.

METHODOLOGY

STUDY DESIGN

A cross sectional comparative study

SAMPLE SIZE CALCULATION

The minimum sample size was estimated using the formula for calculation of sample size in a comparative study as shown below.

$$N = \frac{(p_0q_0 + p_1q_1) (z_{1-\alpha/2} + z_{1-\beta})^2}{(p_1-p_0)^2}$$

In which; p_1 = prevalence of disease among cases.

p_0 = prevalence of disease among the comparison group.

$$q_1 = 1 - p_1$$

$$q_0 = 1 - p_0$$

$z_{1-\alpha/2}$ = value of the standard normal distribution corresponding to a significance level of alpha of 0.01 in this study.

$z_{1-\beta}$ = value of the normal distribution corresponding to the desired level of power of 80% in this study.

For this study, the prevalence of peripheral neuropathy in cases was taken as 31% based on previous studies (18), whereas, that of comparison group was taken as 10% (37).

The confidence level was taken as 90% and the power as 80%.

The minimum sample size required was 31 in each arm. We recruited 32 patients in each group

STUDY AREA

This was a hospital-based study conducted at the Comprehensive Care Clinic of Kenyatta National Hospital.

Kenyatta is a tertiary referral hospital for Kenya and the neighboring countries located in Nairobi; the administrative and business capital of Kenya. Most patients live within Nairobi, a good proportion are referrals from the district and provincial hospitals all over the country.

The comprehensive care clinic of Kenyatta is among the few HIV clinics in the public hospitals that care specifically for HIV infected patients. Most patients seen at KNH are of low socioeconomic status and most ethnic groups are represented.

STUDY POPULATION

Patients aged 13 or more years confirmed to have HIV infection on ELISA and on stavudine-based regimen for a period of at least three months utilizing the health services at Kenyatta National Hospital's Comprehensive Care Clinic.

The comparison group was made of patients sent to the Comprehensive Care Clinic for work up for commencement of HAART. They were eligible for HAART based on CD4 count and WHO clinical stage but not yet started on HAART.

First line i.e. drug groups of interest was: stavudine/ lamivudine/nevirapine or stavudine/lamivudine/efavirenz.

CASE DEFINITION

Peripheral neuropathy was defined as: presence of a symptom, and/or a sign, with or without impairment in nerve conduction studies or such impairment without a sign or symptom. Such impairment was in the following parameters:

- Nerve conduction velocity
- Amplitude
- Distal latency/peak onset latency
- F – wave response

The various measures were compared to the controls, values done and supplied with the machine (see appendix iii, g)

Axonopathy was defined as a reduction in the amplitude of the action potentials of various nerves with preservation of the nerve conduction velocities (43). The amplitudes used as references, were the ones that the machine used for this study normally uses which are from the manufacturer (software stated in the methods). The measures vary according to the nerve in question (see appendix iii)

Values below the reference range were considered suggestive of axonopathy.

Demyelination was defined as a reduction in conduction velocity in the tested nerve to below the reference range for the machine used with prolongation in distal latencies below what was considered normal for this particular machine (see appendix for iii).

The neuropathy was considered as sensory neuropathy if only nerves or components of nerves subserving sensory modalities were affected. It was considered motor if motor nerves or their components were affected and sensorimotor if both the sensory and motor components were affected.

Mononeuritis multiplex was considered if simultaneous or sequential involvement of individual noncontiguous nerve trunks, either partially or completely were involved.

The motor nerves or their components, were assessed by stimulating the nerve electrically at two or more sites, and recording from the muscle innervated. The same electrical stimulation was done for the sensory nerves or components but the recording was done at another site on the stimulated nerve trunks.

SYMPTOMS DIAGNOSTIC OF PERIPHERAL NEUROPATHY (43)

Paraesthesiae

Numbness

Tingling sensation

Pins and needles sensation

Hyperpathia

Loss of specific sensory modalities e.g. pain, temperature, touch in the peripheral distribution.

Neuralgia

SIGNS DIAGNOSTIC OF PERIPHERAL NEUROPATHY (43)

Impaired sensation to touch, pain, vibration, temperature and proprioception in the peripheral distribution.

Decreased muscle tone

Loss of power not attributable to muscle disease or spinal cord lesions

Absence of deep tendon reflexes

Muscle wasting

PATIENT SELECTION

Inclusion criteria

Treatment group

- Adults \geq 13 years testing HIV positive by ELISA.
- On stavudine-based regimen for at least three months
- Informed consent.

Comparison group

- Adults \geq 13 years with HIV on ELISA
- Naïve to HAART but eligible for treatment.
- Informed consent

Exclusion criteria

Treatment group

- Diabetes mellitus
- Physical injuries affecting nerves
- Excessive alcohol intake
- Known case of pernicious anemia
- Known case of rheumatoid arthritis and other connective tissue diseases e.g. SLE, polymyositis, scleroderma.
- Chronic renal failure
- Patients on anti tuberculous medications
- Amputees and those with foot ulcerations

Comparison group

- Diabetes mellitus
- Physical injuries affecting nerves
- Excessive alcohol intake
- Known case of pernicious anemia

- Known case of rheumatoid arthritis and other connective tissue diseases e.g. SLE, polymyositis, scleroderma.
- Chronic renal failure
- Patients on anti tuberculous medications
- Patients on stavudine/ARVs
- Amputees and those with foot ulcerations

SAMPLING AND CLINICAL PROCEDURE

Eligible patients were recruited into the study by random sampling. The Principal investigator (PI) visited the CCC and reviewed files of patients with HIV/AIDS on antiretrovirals in the CCC. Those on stavudine-based regimen for a period of at least three months were recruited into the study. The comparison group was recruited from the patients sent to the CCC for work up for commencement of antiretrovirals.

Files of patients in the clinic were reviewed and after the preliminary interview those meeting inclusion criteria had their files assigned a number, this was done on a piece of paper which was folded and put in a container. Two pieces of paper were picked and the corresponding files and therefore the patients were enrolled. The comparison group was matched for every case to the nearest five years and also matched to sex. If any reason came up that led to the patient exclusion, the procedure was repeated. Thorough history and physical examination were done on the successful candidates. The candidates were taken for electrophysiological studies at the neurology center at General Accident House on Ralph Bunche road after being attended to at the CCC. If for some reason the study could not be done on the same day, the patients were given some allowance to facilitate their return trip. After the procedure, the patients and their relatives were dropped off at the bus station where they normally caught their transport back home.

Important information required for the study was obtained from both the file and the patient and entered into the study proforma for every patient.

Interview and recruitment of patients in the CCC was done between 9.00am and 12.00pm on weekdays until the desired sample size was reached.

History included:

- Demographic data –age, sex, occupation, residence (see proforma)
- Past medical history – including whether they had been treated for HIV complications, treatment given and the duration, emphasis on diseases mentioned in the exclusion criteria
- Family history of diseases in the exclusion criteria above
- Social history – alcohol abuse/use
- Drug history – recent, past, or present intake of these drugs
 - Phenytoin
 - Anti tuberculous drugs
 - Vincristine.
 - Any other drug known to have effect on the peripheral nervous system
- The current antiretroviral regimen.

PHYSICAL EXAMINATION INCLUDED:

- General examination – dry skin and loss of hair, skin ulcerations, scars, oral thrush, pallor, jaundice, lymphadenopathy, edema.

SENSATION

- Fine touch was tested using soft cotton wool and coarse touch using blunt end of a ballpoint pen with the patient's eyes closed
- Pain was tested by pricking on the surface of the skin using a pin with the patients eyes closed.
- Vibration perception was tested using tuning fork – 128Hz over bone prominences
- Skin temperature perception was tested using a glass of warm and cold water

PROPRIOCEPTION

Proprioception was tested by examining joint movements of the big toe, and the middle finger with eyes closed and asking the patient which direction the digit had moved

MOTOR SYSTEM

Muscles were inspected and palpated for evidence of wasting.

Power was tested in the standard way and graded 0 – 5 according to MRC classification at the ankle, knee, shoulder, elbow, and wrist joints and the handgrip.

Tone was tested in the standard way and described as hypotonia, normal tone and hypertonia.

Reflexes – Deep tendon and superficial tendon reflexes were tested and graded as absent, present (as a normal ankle jerk), brisk (as a normal knee jerk), very brisk and clonus.

NERVE CONDUCTION STUDIES

The tests were done according to standard procedure (see appendix iv).

All tests were carried out in the same lab at room temperature

Nerve conduction studies were done in all patients.

Five nerves were tested; the median, the ulnar, the peroneal, the sural and the tibial nerves.

Data for each patient was collected on a proforma

For each nerve the following were done

- Amplitude
- Dispersion
- Distal latency/peak onset latency.
- Conduction velocity
- F – wave response

The neuropathies found on nerve conduction studies were classified into the following pathological lesions and syndromes:

Pathological:

- Axonopathy
- Demyelination

Syndromes:

- Sensorimotor neuropathy
- Sensory neuropathy
- Motor neuropathy
- Mononeuritis multiplex

DATA MANAGEMENT

Data collected was coded, verified, cleaned, validated then analyzed using SPSS version 15.0.

Analysis involved descriptive statistics such as mean, median, and standard deviations for continuous variables and proportions/percentages and frequency distributions for categorical variables

Study population was described in terms of age, gender, occupation, CDC CD4 category, duration of antiretroviral drug use, and the type of neuropathy found.

Point prevalence was determined as percentages of the study population.

Chi – square test was used to compare the prevalence and types of peripheral neuropathy in the two groups.

Associations were measured and considered statistically significant at a p value of 0.05 or less.

Summarized data was presented in form of tables, pie charts, and graphs.

ETHICAL CONSIDERATION

The study was undertaken after approval by the department of internal medicine and therapeutics of the university of Nairobi and the KNH ethics review committee.

Eligible patients were recruited after going through the consent process outlined below:

1. They were informed that the project involved research and were told the purpose of the research.
2. The procedures of the research were explained clearly with full details of all the tests to be done.
3. They were assured that participation would be voluntary and that no medical attention would be denied should they decline to participate
4. They were informed of the medical benefits and the physical discomfort that may be experienced during NCS prior to being recruited into the study.
5. Full and free access to their results was assured, and therapeutic interventions would be recommended where the need arose according to accepted standards of practice.

6. It was asserted that confidentiality would be strictly maintained and that all data would be securely stored and only revealed upon a need to know basis.
7. All costs regarding investigations in the study were borne by the principal investigator.

Following the full explanation and acceptance by the patient of the above, the patient was requested to sign the consent form (see appendix vi).

RESULTS

The study was conducted between February 2007 and August 2007. Sixty-four patients: 32 cases and 32 controls (age matched to the nearest five years and sex matched) were enrolled into this study.

The mean age was 38.8 ± 6.4 years (range 24 – 50) for those patients on HAART and 38.4 ± 7.6 years (range 24 – 55) for the ARV naïve group, no statistically significant difference ($p=0.93$).

The peak age for the cases was 31-40 years. As can be seen from figure 1 and 2, majority (66% of the cases, 75% of the comparison group) of the patients were married. Overall there was no statistically significant difference between the cases and the comparison group.

Figure 1: Distribution of patients by marital status (ARVs)

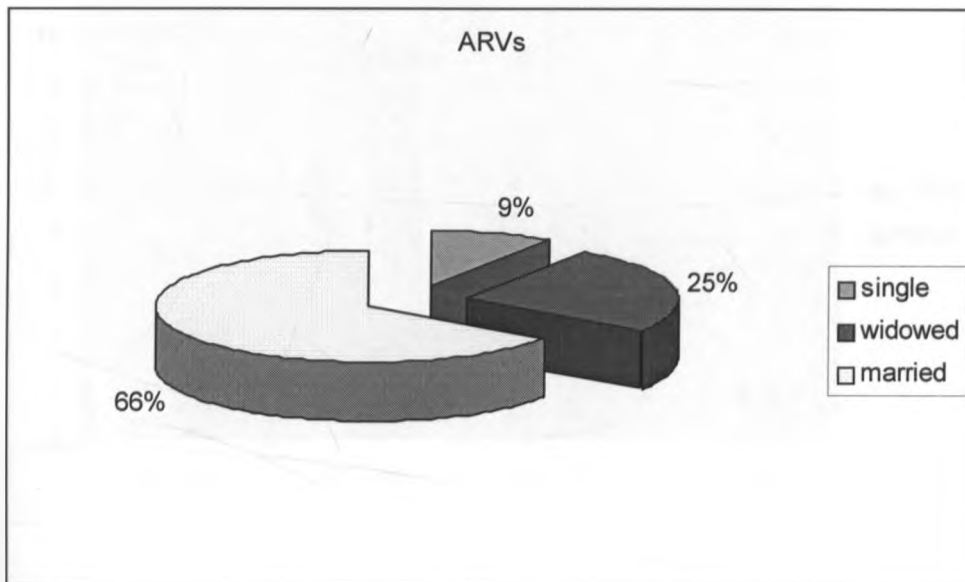


Figure 2: Distribution of patients by marital status (Naïve)

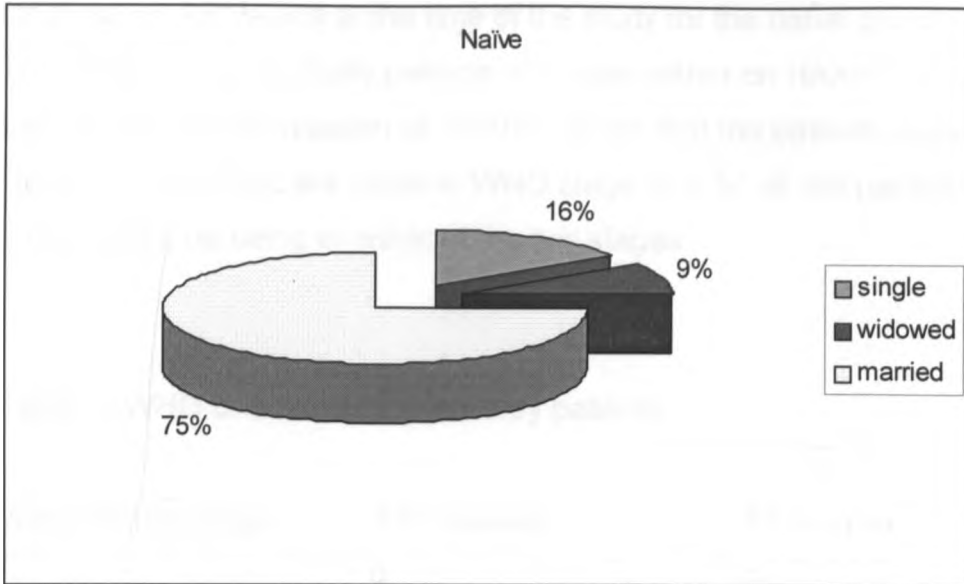
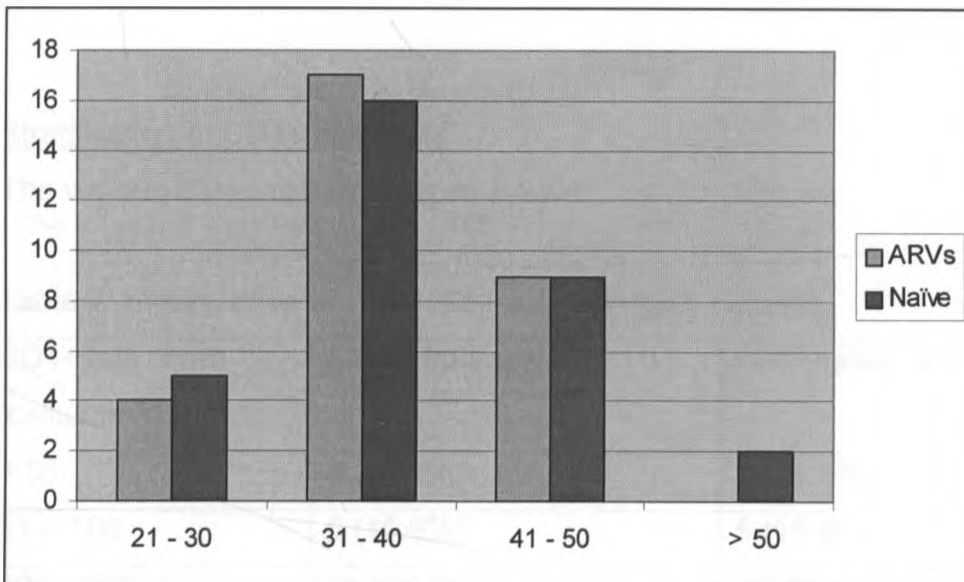


Figure 3: Age distribution.



WHO Clinical stage

Majority of the patients in both groups were in WHO clinical stage IV. The rest of the patients were in stage III. No patient was in stage I or II.

Table 1 shows the WHO clinical stage of the patients at initiation of HAART for those on ARVs and at the time of the study for the naïve group.

This study set out to study patients who were either on HAART or who were being prepared for initiation of HAART. Given that the patients started on HAART in this clinic are either in WHO stage III or IV, all the patients in this study ended up being in either of the two stages.

Table 1: WHO clinical staging of study patients.

WHO clinical stage	ARV-treated	ARV-naive
I	0	0
II	0	0
III	8	10
IV	24	22

Stratification of CD4+ cell count

The various CD4+ cell strata is as follows

Table 2: Stratification of CD4+ Cell count of study patients.

CD4+ cell count (cells/mm3)	ARV-treated, N = 32 (%)	ARV-naïve, N = 32 (%)
< 50	6 (18.8%)	7 (21.9%)
51 – 100	5 (15.6%)	5 (15.6%)
101 – 200	21 (65.6%)	20 (62.5%)

Mean CD4+ cell count

The mean CD4+ cell count for the groups and the range is shown in Table 3.

The difference in the mean for the two groups did not achieve statistical significance; p value 0.59

Table 3: Mean and range of CD4+ Cell count.

	Mean CD4+ cell count	CD4+ cell count - range
ARV-treated	115.6 ± 53.9	6 – 190
ARV-naïve	123.6 ± 65.3	12 – 198

Duration of ARV usage

The study included patients who had been on treatment for at least 3 months or more. However, the shortest duration of treatment was ten months and the longest was 42 months.

The mean duration of ARV usage was 22.6 months

Majority of the patients (75%) were on stavudine, lamivudine and nevirapine, while 25% were on stavudine, lamivudine and efavirenz.

Signs and symptoms of peripheral neuropathy

Fifteen patients (46.9%) were symptomatic for peripheral neuropathy among the patients who were on ARVs compared to 8 patients (25%) among the HAART naïve patients; p value = 0.08.

All patients who had neurological symptoms had either or some of the following: pain, pins and needles prick sensation, burning sensation and numbness in the soles of the feet.

Table 4: Symptoms of peripheral neuropathy.

Symptoms	Frequency – ARVs	Frequency – naïve
Paraesthesiae	9	5
Burning sensation	11	6
Numbness	3	0

The table above shows the frequency of various neurological complaints at the time of presentation. This represents the patients suspected to have neuropathy from the complaints alone before the examination.

Paraesthesiae were mostly of the painful type involving the soles largely but to a small extent the palms. They were disabling in a few cases.

Some patients had mixed paraesthesiae and burning sensations in both the groups

Table 5: Signs of peripheral neuropathy.

Signs	Frequency - ARVs	Frequency – naïve
Impaired vibration sense	4 (12.5%)	11 (34.4%)
Impaired proprioception	5 (15.6%)	9 (28.1%)
Depressed reflexes	5 (15.6%)	5 (15.6%)
Hyperpathia	4 (12.5%)	2 (6.3%)
Impaired pain sensation	4 (12.5%)	1 (3.1%)
Impaired touch sensation	6 (18.8%)	3 (9.4%)
Reduced tone/muscle power	8 (25%)	3 (9.4%)

The table above shows the frequency of various clinical neurological findings at the time of examination. This group was suspected to have peripheral neuropathy on clinical examination.

NERVE CONDUCTION STUDIES

The nerve conduction studies were done on five nerves in each patient, which included the median, ulnar, peroneal, tibial and sural nerves.

THE MEDIAN NERVE

Four parameters were tested in this nerve: the motor nerve conduction velocity, amplitude, latency and F-response. These were done in the two groups.

Motor nerves

Table 6: mean – median nerves.

	Cases	Comparison group	pvalue
CV (m/s)	58.5 (SD ±4.87)	60.5 (SD ±7.24)	0.18
Amplitude (Mv)	4.6 (SD ±2.11)	4.2 (SD ±2.13)	0.50
Latency CV (ms)	7.3 (SD ±0.64)	7.3 (SD ±0.74)	0.93
F-response (ms)	23.6 (SD ±1.99)	23.8 (SD ±2.67)	0.85

Table 7: mean – ulnar nerves.

	Cases	Comparison group	pvalue
CV (m/s)	61.2 (SD ±6.98)	59.0 (SD ±7.77)	0.22
Amplitude (Mv)	2.6 (SD ±2.37)	2.8 (SD ±2.20)	0.69
Latency CV (ms)	5.8 (SD ±0.68)	6.0 (SD ±0.87)	0.39
F-response (ms)	25.3 (SD ±8.32)	23.5 (SD ±4.40)	0.31

Table 8: mean – tibial nerves.

	Cases	Comparison group	pvalue
CV (m/s)	50.7 (SD ±7.33)	52.7 (SD ±10.29)	0.35
Amplitude (Mv)	4.7 (SD ±3.05)	3.5 (SD ±2.10)	0.05
Latency CV (ms)	12.7 (SD ±1.87)	12.3 (SD ±1.73)	0.36
F-response (ms)	41.7 (SD ±8.92)	37.2 (SD ±11.13)	0.09

Table 9: mean – peroneal nerves.

	Cases	Comparison group	pvalue
CV (m/s)	47.8 (SD ±4.18)	47.9 (SD ±5.61)	0.95
Amplitude (Mv)	3.9 (SD ±1.86)	4.4 (SD ±2.53)	0.36
Latency CV (ms)	10.7 (SD ±1.61)	10.5 (SD ±1.45)	0.66
F-response (ms)	33.3(SD ±12.67)	31.7 (SD ±13.32)	0.52

SENSORY NERVES/ SENSORY COMPONENT

Table 10: mean – median nerves.

	Cases	Comparison group	pvalue
CV (m/s)	61.1 (SD ±7.78)	62.4 (SD ±9.34)	0.49
Amplitude (Mv)	45.6 (SD ±16.57)	45.7 (SD ±14.17)	0.97
Latency CV (ms)	3.1 (SD ±1.46)	2.8 (SD ±0.35)	0.42

Table 11: mean – ulnar nerves.

	Cases	Comparison group	pvalue
CV (m/s)	60.8 (SD ±7.28)	62.9 (SD ±10.10)	0.34
Amplitude (Mv)	32.5 (SD ±19.88)	38.5 (SD ±20.34)	0.20
Latency CV (ms)	2.8 (SD ±0.69)	2.8 (SD ±0.78)	0.82

Table 12: mean – sural nerves.

	Cases	Comparison group	pvalue
CV (m/s)	32.1 (SD ±17.17)	48.2 (SD ±34.63)	0.04
Amplitude (Mv)	29.7 (SD ±25.71)	43.1 (SD ±27.70)	0.04
Latency CV (ms)	6.9 (SD ±3.13)	6.8 (SD ±3.10)	0.58

SUMMARY OF THE FINDINGS

The presence of peripheral neuropathy was based on findings of symptoms, signs of peripheral neuropathy and / or nerve conduction studies.

Eleven (11) patients on ARVs had what is referred to as positive symptoms i.e. the paraesthesiae and burning sensations while three (3) patients of the same group had what is referred to as negative symptoms of numbness.

Among the comparison group, only six (6) had positive symptoms while none had negative symptoms.

Neurological examination was able to add three more patients with neuropathy among the patients on ARVs; though the patients who had numbness as their presentation did not have obvious clinical findings on examination.

Among the patients in the comparison group five more patients with signs of peripheral neuropathy were detected.

All the patients found to have peripheral neuropathy in the comparison group had impaired vibration sense, at least, but had combination of other signs including impaired proprioception, depressed reflexes, impaired touch sensation.

Among the patients on ARVs, a total of 17 patients had at least one sign suggestive of neuropathy though many had a combination of signs as shown in table 5.

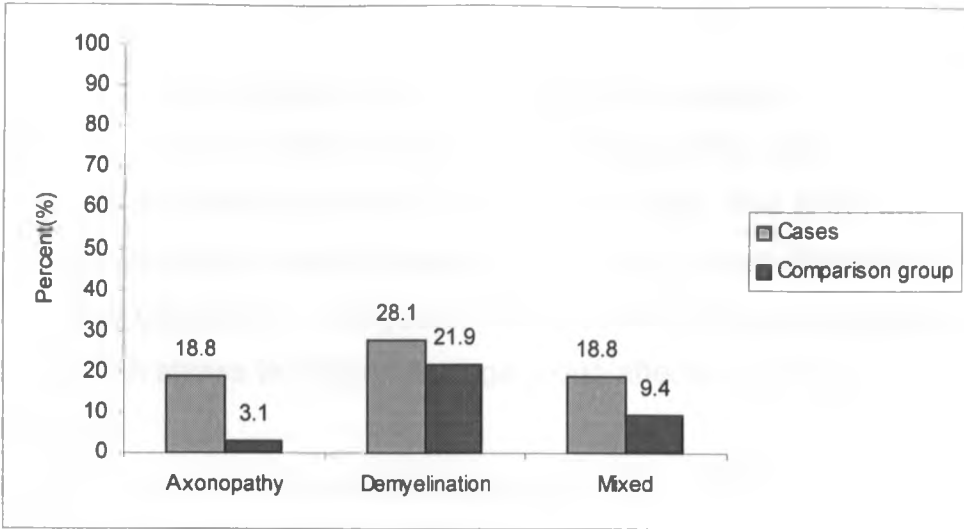
When the electrophysiological studies were done, an additional four (4) patients in the treatment group were found to have evidence of peripheral neuropathy. Interestingly, no additional patient in the comparison group was found to have evidence of neuropathy in excess of what had been found on examination

The study was important however in classifying neuropathies as demyelination or axonopathic and pattern of involvement in the two groups. In summary, 21 patients (65.6%) of the patients on ARVs had evidence of peripheral neuropathy compared to 11 (34.4%) of the patients who were naïve.

The diagnosis of neuropathy was based on symptoms, signs and electrophysiological studies.

The graphs below summarize the findings i.e. whether neuropathy was demyelinating, axonopathic or mixed and whether there was sensory, motor, sensorimotor or mononeuritis multiplex pattern of involvement.

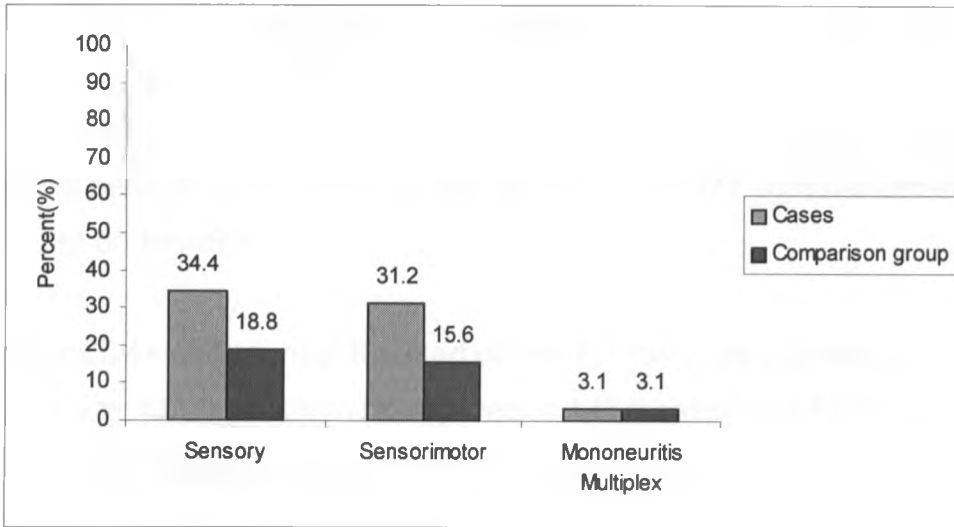
Figure 4: Pathological classification



Axonopathy p-value 0.05, Demyelination p-value 0.56, Mixed p-value=0.47

The p-values compare the statistical significance between the two groups in terms of prevalence of axonopathy, demyelination and mixed axonopathy and demyelination in that order.

Figure 5: Syndromic or pattern of nerve involvement.



Sensory p-value =0.25, Sensorimotor p-value=0.23

The p-values compare statistically significant differences between the two groups in terms of prevalence of sensory or sensorimotor involvement.

DISCUSSION

The two groups were matched for sex and age to the nearest five years. Majority of the patients, 53% of those on HAART and 50% of the comparison group were in the age group 31 – 40 years. This is the age bracket most affected by the HIV pandemic. The age range of patients in this study was between 24 – 55 years. This is consistent with the national statistics, which shows that this is the age group affected by the HIV pandemic (2)

Dr Mbuya S, O et al (33), found an age range of 16 – 55 years, which compares closely to that found in this study.

Most of the patients, 24 in the HAART group and 22 in the comparison group, were in WHO clinical stage 4; the rest were in stage 3. These patients were therefore in more advanced level of HIV infection.

Though the study was not designed to recruit mainly stage 4 disease patients, it ended up recruiting these patients mainly because this is the stage with severe disease and will naturally qualify for HAART commencement, which was the entry criteria. Stage 1 and 2 patients were missed out because they did not qualify either for HAART commencement or were not on HAART.

The mean CD4+ cell count at the start of HAART for those patients on treatment was 115.6 cells/mm³ compared to 123.6 cells/mm³ for those patients eligible but naïve. The difference was not statistically significant (p value = 0.59).

The low CD4+ cell count also emphasises the severity of the disease in the study population and the eligibility.

The patients on ARVs had been on treatment for at least ten months with the longest being forty-two (42) months. This had allowed enough time to reflect the possible effect of the drugs on the peripheral nervous system. Most literature (3,4) indicate three months as the shortest time of exposure

required for development of neuropathy though as short a duration as six weeks has been reported.

The most common symptom of peripheral neuropathy was burning sensation, which was present in all symptomatic patients in the two groups. The next commonest was paraesthesiae, which was present in all symptomatic patients except two on ARVs, and absent in only one of the symptomatic patients in the comparison group.

This is comparable to findings by Mbuya S, O et al "Peripheral neuropathy in a group of AIDS patients at KNH"(33), in which he found the commonest symptoms at presentation being paraesthesiae and burning sensation in the glove and stockings distribution.

Three patients in the ARVs group had numbness. This group of patients did not have much clinical signs on examination.

The commonest signs were combined reduction in power and tone followed by impaired touch sensation. There was also impaired pain sensation, hyperpathia and depressed reflexes. This was among the patients on HAART. However, in naïve patients, impaired vibration sense and loss of proprioception were predominant.

In the study by Mbuya S, O et al (33), which recruited patients who were not on HAART, the two findings (impaired vibration sense and loss of proprioception) were the commonest.

Vibration sense may be preferentially affected in demyelinating neuropathies, which was the commonest finding among the naïve patients (37, 38).

In study by Mbuya et al (33) done in HAART naïve patients, found the commonest pathology being demyelination.

The group on HAART had predominant axonopathic lesions and therefore the impairment in vibratory sense and proprioception was not prominent.

The prevalence of peripheral neuropathy in this study was 65.6% among patients on stavudine containing regimen compared to 34.4% in patients who were not on ARVs.

This prevalence is higher than what has been documented in other studies done elsewhere. The prevalence of neuropathy in most studies done in Europe and North America was found to be between 31 and 60%.

Locally, Mbuya S, O et al (33), assessed patients with AIDS but not on HAART found a prevalence of peripheral neuropathy of 100%. This group should compare well with the comparison group in our study that was naive; however, our prevalence was much lower than his. This might have been because all patients in his study were in WHO clinical stage 4.

They were also very sick patients, as all were inpatients and obviously had co morbidities: the reason for their hospitalisation.

The patients in this study were all outpatients, ambulant and some did not even have evidence of opportunistic infections or co morbidities.

Maschke et al 2000 (18), found a stavudine related peripheral neuropathy of 31.2% compared to 20.4% in those patients not on HAART/neurotoxic antiretrovirals.

Reliquet V et al 2001 (3) working in France assessed patients on stavudine with a CD4+ cell count of at least 100 cels/mm³ with a mean of 220cells/mm³ found a prevalence of 11.8%for the naïve patients and 29% for those on HAART.

The prevalence of neuropathy was lower in the two studies above largely because of their selection criteria, which was significantly different from this study.

Majority of our patients were in WHO clinical stage 4 while majority of their patients (3, 18) were in stage 3 with a significant number in stage 2.

Patients in this study had a CD4+ cell count that was way below 200 cells/mm³ compared to the other studies (3,18) that had patients with a count of more than 200cells/mm³.

This means that our patients had all the predictors of severe disease i.e severe immune suppression and very low CD4+ cell count which either contribute to or worsen the pre existing neuropathy.

Our patients could have had some co morbidities as compared to their patients who did not have significant co morbidities.

Also, the monitoring and the dosing in relation to weight might not have been stringent locally. It was not unusual to find patients weighing less than 60kg on 40mg of stavudine. It is clear that the neuropathy is dose related so frequent monitoring and dose adjustment is needed.

In addition, some of the studies (11, 21) had sural nerve biopsies done and even muscle biopsies especially in cases where stimulation of some of the nerves could not be easily achieved.

Contrary to expectation, we found fewer patients diagnosed to have peripheral neuropathy on the basis of history and clinical examination compared to electrophysiological diagnosis. Normally, it is expected that patients with involvement of the small fibre will have complains of paraesthesiae but electrophysiological studies will be normal unless sural nerve biopsies are done. In our study, we picked 4 more patients on electrophysiological studies to have peripheral neuropathy.

Relative subjectivity of clinical diagnosis might have contributed to this phenomenon.

In patients who had axonopathy, more (18.8%) were on stavudine-based treatment compared to 3.1% who were treatment naïve. The p value was just significant at 0.05. In demyelination and mixed axonopathy and demyelination there were still more patients who were on stavudine regimen though this did not achieve statistical significance (figure 4).

In patients who had sensory and sensorimotor involvement, more were those on stavudine though this again did not achieve statistical significance (figure 5).

Stavudine associated neuropathy is usually axonopathic and tends to affect sensory nerves more than the motor ones. Patients in this study had sensory pattern of involvement and also tended to have axonopathies as opposed to demyelination. This may imply that stavudine may be a key player in the pathogenesis of the neuropathy.

Mbuya S, O et al in his study (33) found that the predominant pathology was demyelination. We did find the same in our group of patients who were naïve to HAART but for those on treatment, axonopathic pathology was predominant.

Reliquet et al (3) and Maschke et al (18) in their studies found axonopathies predominating among the patients on stavudine.

Given the high prevalence of peripheral neuropathy in this group of patients on stavudine-based regimen, it's possible that this could significantly impact on adherence to this type of treatment. More needs to be done to educate the patients and the healthcare workers to avoid the possible toxicity, which might go unnoticed and lead to poor compliance to HAART in an attempt to avoid the side effects.

STUDY LIMITATIONS

Full compliance to antiretrovirals was assumed in this study.

Sural nerve and muscle biopsies were not done. This could have been particularly important in those cases where clear nerve stimulation was not achieved.

Due to logistical and financial constraints, the numbers in this study might not have been enough to do sub group analysis especially in comparing the types of peripheral neuropathy.

Although an attempt was made to exclude other possible causes of neuropathy, some causes might not have been fully excluded.

CONCLUSIONS

There was a high prevalence of peripheral neuropathy in patients on stavudine-based HAART (65.6%) to naïve patients (34.4%). These were patients with severe immune suppression.

Axonopathies were the predominant pathological lesions found in patients on stavudine-based regimen. They also had predominant sensory pattern of involvement.

RECOMMENDATIONS

Patients on stavudine based HAART should have frequent assessment for peripheral neuropathy in view of the high prevalence.

A bigger and more powered study needs to be done to clearly determine the type of neuropathies in these patients.

Dosing studies to balance viral suppression with safety in this population needs to be done.

Sural nerve biopsies should be included in future studies especially in cases where nerve stimulation for nerve conduction studies is not achieved.

There is need to assess the impact of the neuropathy on the quality of life.

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APPENDIX 1

PROFORMA.

1. Number Name: -----
Sex M F Age
Occupation: ----- Weight: -----
Residence: -----
Married Single Divorced Separated

2. Past Medical History

- T.B
- Painful Skin Rash Epilepsy
- Anemia Pins And Needles
- Paralysis Burning Sensation
- Paraesthesiae Kidney Failure

3. Drugs ----- ----- -----

4. Antiretrovirals Being Taken.

- Stavudine -----
- Efavirenz -----
- Lamivudine -----
- Nevirapine -----

5. Duration Of Antiretrovirals Usage-----

6. Systemic Enquiry

- Pins And Needles
- Hyperpathia
- Loss Of Pain Sensation
- Loss Of Temp Sensation
- Tingling Sensation
- Numbness
- Painful Sensation
- Loss Of Touch Sensation

Muscle Wasting ()

Loss Of Power In Any Limb ()

PHYSICAL EXAMINATION

Impaired Sensation

Touch () Pain () Vibration () Temperature () Proprioception ()

Muscles	Tone	Power
Ankle Flexors	()	()
Ankle Extensors	()	()
Knee Flexors	()	()
Knee Extensors	()	()
Hip Flexors	()	()
Hip Extensors	()	()
Hand Grip		()
Elbow Extensors	()	()
Elbow Flexors	()	()
Shoulder Joint Extensors	()	()
Shoulder joint Flexors	()	()
Shoulder adductors	()	()
Shoulder abductors	()	()

Tendon Reflexes	Normal	Increased	Decreased
Ankle	()	()	()
Knee	()	()	()
Triceps	()	()	()
Biceps	()	()	()
Plantar Reflex	Flexor	()	Extensor

Investigations

CD4 Count-----

APPENDIX II

WHO staging system for HIV infection and disease in adults and adolescents (2)

Clinical stage I

Asymptomatic
Primary HIV infection
Persistent generalized lymphadenopathy

Performance scale 1: asymptomatic, normal activity

Clinical stage II

Weight loss, <10% of body weight
Minor mucocutaneous manifestations (seborrheic dermatitis, papular pruritic eruption, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
Herpes zoster within the last five years (uncomplicated)
Recurrent upper respiratory tract infections (i.e. bacterial sinusitis, otitis media) in past 12 months
Thrombocytopenia not responsive to steroids

And/or performance scale 2: symptomatic, normal activity

Clinical stage III

Weight loss, >10% of body weight and/or BMI <18.5, unexplained.

Unexplained chronic diarrhoea, >1 month

Unexplained prolonged fever (intermittent or constant), >1 month

Oral candidiasis (thrush)

Oral hairy leukoplakia

Pulmonary tuberculosis within the past year

Severe bacterial infections (i.e. pneumonia, pyomyositis, bacterial meningitis, bacteraemia)

Bacillary angiomatosis

Herpes zoster: complicated (recurrent, disseminated, multidermatomal)

And/or performance scale 3: bedridden <50% of the day during the last month

Clinical stage IV

HIV wasting syndrome, as defined by the Centers for Disease Control and Prevention^a

Pneumocystis carinii pneumonia

Toxoplasmosis of the brain

Cryptosporidiosis, Isosporiasis, Microsporidiosis with diarrhoea >1 month

Cryptococcosis, extrapulmonary

Cytomegalovirus disease of an organ other than liver, spleen or lymph nodes

Herpes simplex virus infection, mucocutaneous >1 month, or visceral any duration

Progressive multifocal leukoencephalopathy

Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis, Penicilliosis)

Candidiasis of the oesophagus, trachea, bronchi or lungs

Non-tuberculous mycobacteriosis, disseminated

Non-typhoid *Salmonella* septicaemia

Extrapulmonary tuberculosis

Lymphoma

Kaposi's sarcoma

HIV encephalopathy, as defined by the Centers for Disease Control and Prevention.^b

Invasive cervical carcinoma

American trypanosomiasis-reactivation

Major aphthous ulceration: ulcers of GI tract >5mm and for >1 month

Nephropathy

Cardiomyopathy, unexplained

Visceral leishmaniasis

Strongyloides hyperinfection syndrome

And/or performance scale 4: bedridden >50% of the day during the last month

Note: both definitive and presumptive diagnoses are acceptable.

- a. HIV wasting syndrome: weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>1 month) or chronic weakness and unexplained prolonged fever (>1 month).
- b. HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection which could explain the findings.

APPENDIX III

NERVE CONDUCTION STUDY REFERENCE RANGES.

MOTOR NERVES.

Median nerve.

Conduction velocity $\geq 49\text{m/s}$

Amplitude $\geq 4.0\text{mv}$

Distal latency $\leq 4.4\text{ms}$

F response $\leq 31\text{ms}$

Ulnar nerve

Conduction velocity $\geq 49\text{m/s}$

Amplitude $\geq 6.0\text{mv}$

Distal latency $\leq 3.3\text{ms}$

F response $\leq 32\text{ms}$

Tibial nerve

Conduction velocity $\geq 41\text{m/s}$

Amplitude $\geq 4.0\text{mv}$

Distal latency $\leq 5.8\text{ms}$

F response $\leq 56\text{ms}$

Peroneal nerve

Conduction velocity $\geq 44\text{m/s}$

Amplitude $\geq 2.0\text{mv}$

Distal latency $\leq 6.5\text{ms}$

F response $\leq 56\text{ms}$

Sensory nerves

Median nerve

Conduction velocity $> 50\text{m/s}$

Amplitude $> 20\text{mv}$

Distal latency $< 3.5\text{ms}$

Ulnar nerve

Conduction velocity $> 50\text{m/s}$

Amplitude $> 17\text{mv}$

Distal latency $< 3.1\text{ms}$

Sural nerve

Conduction velocity ≥ 40 m/s

Amplitude ≥ 6.0 mv

Distal latency ≤ 4.4 ms

APPENDIX IV: NERVE CONDUCTION STUDY PROCEDURE.

This was done using the following standard method:

The nerves are stimulated proximally and distally at supramaximal current strength using an electronic stimulator type SEM 4101, at a current duration of 0.05 – 0.1 msec and a voltage of 100 – 200 volts. There is no discomfort in the procedure.

The stimulator provides a trigger current, which can be used to trigger sweeps on the electromyograph machine and the storage oscilloscope type 564B of Tetronix Inc, USA and is also equipped with a timer signal, which can be stored and reproduced by the oscilloscope. The response is fed into the electromyograph through its pre – amplifier.

The median and ulnar nerves are stimulated at the elbow and wrist for proximal and distal latencies respectively. The muscle action potentials of both are picked up by a single set of surface electrodes on the thenar eminence.

The muscle action potential of the peroneal nerve is picked by similar electrodes placed on the extensor digitorum brevis and the nerve is stimulated at the head of the fibula and at the ankle.

For the H – responses, the tibial nerve is used.

APPENDIX V

CONSENT EXPLANATION

Introduction

My name is Dr. Wabwire Silvanus. I am a postgraduate student pursuing a master's degree in internal medicine, University of Nairobi. I am in the second year of study. The curriculum requires that I write a thesis, which entails research collecting and analyzing data on various aspects of diseases. My research is on prevalence and types of peripheral neuropathy in patients on stavudine-based antiretrovirals at KNH.

To do this I will require a thorough history and physical examination from each participant. I will also require the participants to undergo a nerve conduction study outside KNH to help establish the presence of the neuropathy. Decency will be maintained at all stages of history taking and physical examination and during the nerve conduction procedure. The extent of discomfort (minor) during venepuncture and nerve conduction studies will be explained and fears allayed.

Benefits

This study is intended to establish the prevalence and types of peripheral neuropathy in patients on stavudine-based regimen at KNH. This will help in planning the care of patients with HIV infection especially the choice of antiretrovirals to be used in the community that utilize KNH and the country in general. Participants found to have neuropathy will be treated and referred to their primary physician for further follow-up especially in connection with the choice of the antiretrovirals.

Risks

History taking and physical examination have no risks. Taking venous blood for CD 4 count and putting the needles for nerve conduction studies have some level of minor discomfort. Use of sterilized needles, and syringes with proper aseptic techniques will ensure no risk to the participants.

Participation

Participation in this study is purely voluntary. All information collected will be confidential. A written consent will be required. Participants have a right to

withdrawal from the study at any stage. They also have a right to know results of all tests done.

About a half of the patients have been given their results especially the ones who had significant neuropathy. The rest will be given their results as soon as their files are traced when they come to the clinic.

Current treatment

This study will not in any way jeopardize standard treatment participants are on during the study.

APPENDIX VI

CONSENT FORM

Consent by patients / next of kin for participation in the study.

I Of
..... Hereby consent to participate in this study
/ research, the nature of which has been fully explained to me by:
DR. / MR......

I will be required to give 4ml venous blood for CD4 counts and other blood tests in cases where this would not have been done already. I will be required to go for an electrophysiological study at the neurology center at general accident house. This is a slightly invasive procedure with minimal discomfort the procedure of which has been explained to me to my satisfaction. I understand that Dr. Wabwire shall use the results of these tests for research work only.

Date **Sign**

I confirm that I have explained to the patient the nature of the study and the tests to be done.

Date **Sign**