The prevalence, characteristics and morbidity of neuropathic pain in AIDS patients, prior to the use of HAART, at the Kalafong Hospital HIV Clinic, Pretoria

by

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Declaration

I, Sonia Anne Hitchcock, hereby declare that this dissertation which I hereby submit as partial fulfilment for the degree MPhil Palliative Medicine, at the University of Cape Town, is original and my own work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been submitted, or is being submitted for another degree at this or any other university.

Signed Signed by candidate Date 8/5/2008

Abstract

Title:

The prevalence, characteristics and morbidity of neuropathic pain in AIDS patients, prior to the use of HAART, at the Kalafong Hospital HIV clinic, Pretoria.

Introduction:

Neuropathic pain, of which a distal sensory polyneuropathy (DSP) is the most frequent cause, is a common problem in patients with HIV infection and AIDS.

The researcher is concerned that neuropathic pain in patients with AIDS tends to be under-diagnosed and under-treated. There are several reasons for this, one of which may be a lack of awareness of the extent of the problem, as well as the impact it has on patients' lives. Several studies around the world have noted the problem of under-diagnosis and under-treatment of pain and more specifically, neuropathic pain, in patients with AIDS.

A review of the literature reveals a wide variation in the prevalence of neuropathic pain and peripheral neuropathy in AIDS patients.

Aim:

To determine the prevalence, characteristics, severity and morbidity of neuropathic pain in AIDS patients, attending the Kalafong HIV Clinic, prior to the initiation of HAART.

Methods:

A prospective, cross sectional and descriptive study was done at the Kalafong Hospital HIV Clinic. Data was collected from a systematic sample of 354 AIDS patients, who were referred to this HIV clinic to be initiated on HAART.

An interviewer-administered questionnaire and focused neurological examination were used. This included a recently validated instrument, the DN4, for identifying pain which is neuropathic in origin. Selected sections of the Brief Pain Inventory (BPI) were used to determine the severity of the neuropathic pain, as well as pain-related interference on aspects of daily living.

Results:

Twenty one percent (95% CI: 16.8% to 25.2%) of AIDS patients had pain of predominantly neuropathic origin (POPNO). This pain was significantly more frequent in patients who were male, had lower CD4 cell counts or higher viral load levels and those with a history of recent or current use of treatment for tuberculosis. The majority of patients (79.7%) with POPNO experienced substantial pain (worst pain severity ≥ 5 out of 10 on a numerical rating scale). Pain-related interference with aspects of daily living was highest for enjoyment of life, mood and the ability of these patients to work. Abnormalities of tactile and pinprick sensation and vibration sense were the commonest neurological findings in patients identified as having POPNO.

Conclusion:

Pain of predominantly neuropathic origin results in substantial suffering and impaired functioning in patients with AIDS. It is therefore imperative that clinicians should carefully assess patients with AIDS for the presence and severity of neuropathic pain and treat it, using the most recent evidence based guidelines, regarding the management of neuropathic pain.

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Definitions of variables

Neuropathic pain:

Pain initiated or caused by a primary lesion or dysfunction in the nervous system. This lesion or dysfunction may be peripheral or central in origin, giving rise to the terms peripheral neuropathic pain and central neuropathic pain (IASP, 1994).

Nociceptive pain:

Pain produced by the stimulus of specific peripheral receptors (nociceptors) and conveyed by neurons dedicated to transmitting pain.

Allodynia:

Pain due to a stimulus which does not normally provoke pain (IASP, 1994). Different types of allodynia have been identified, such as mechanical allodynia and thermal allodynia. Mechanical allodynia may be static or dynamic.

Static mechanical allodynia:

Pain obtained by applying a single non-noxious stimulus, such as light pressure, to a defined area.

Dynamic mechanical allodynia:

Pain obtained by moving a non-noxious stimulus, such as a piece of cotton wool, over the sensitized area.

Thermal allodynia:

Pain due to a non-noxious warm or cool stimulus (Dworkin et al, 2003 & Backonja et al, 1998).

Hyperalgesia:

An increased response to a stimulus which is normally painful (IASP, 1994).

Dysesthesia:

An abnormal unpleasant sensation- whether evoked or spontaneous (IASP, 1994).

Paresthesia:

An abnormal, although not unpleasant sensation- whether evoked or spontaneous (IASP, 1994).

AIDS:

Infection with the Human Immunodeficiency Virus, together with a history of a AIDS-defining condition or a CD4 lymphocyte count of less than 200 cell/mm^3 (based on the 1993 Centers for Disease Control case definition criteria for AIDS) (CDC, 1993).

CD4 cell count:

The concentration, in the blood, of T lymphocytes, that express the CD4 receptor. This measurement is expressed as cells/µl or cells/mm^3.

HIV Viral load:

The concentration, in the blood, of free virus, identified by measuring HIV1 RNA. The measurement is expressed as viral copies/ml.

National Department of Health HIV Antiretroviral Programme:

The public health sector programme in South Africa, whereby several regimens of HAART (Highly Active Antiretroviral Therapy) is made available to all patients, who are dependent on public health facilities and meeting the criteria for this treatment.

CHAPTER 1

INTRODUCTION

As a family physician with a special interest in palliative medicine, the researcher has encountered many patients with HIV (Human Immunodeficiency Virus) infection, with troublesome neuropathic pain. These patients were seen both at the Kalafong Hospital, as well as in the hospice situated nearby the hospital. The Kalafong Hospital is an 850-bed regional state hospital in Pretoria (Tshwane). According to the National Health policy, HIV infected patients who do not yet require ARV (antiretroviral) therapy and who are clinically stable, are managed by a general practitioner or primary health care clinic. Patients dependent on the public health system, requiring ARV therapy, are referred to the HIV clinic of the Kalafong Hospital. The Leratong Hospice is an 18 bed unit situated 8 km from the Kalafong Hospital. The majority of admissions to this hospice have advanced AIDS (Acquired Immune Deficiency Syndrome) and require supportive care, symptom control or terminal care. With the increasing availability of ARV therapy in the public health sector, many of these patients require disease-specific curative management, rather than terminal care. There is a close working relationship between this hospice and the clinicians at the Kalafong Hospital.

The human immunodeficiency virus has a predilection for nerve tissue. Therefore the peripheral nerves, the spinal cord and the brain are frequently affected in HIV/AIDS, resulting in a high incidence of neuropathic pain (Belgrade, 1999). It is thought that up to 40% of pain in patients with HIV is due to neuropathic pain syndromes (Stephenson, 1996).

Neuropathic pain is currently defined by the International Association for the Study of Pain (IASP) as "pain initiated or caused by a primary lesion or dysfunction of the nervous system" (IASP, 1994). The lesion may be within the central nervous system, at the level of the dorsal root ganglion, or a peripheral nerve. This injury may lead to structural and functional changes in the nervous system, resulting in altered peripheral and central neural processing of sensory input (central sensitisation) (Dworkin et al, 2003 & Galer et al, 1997). Consequently, pain may persist long after healing of the original injury (Brunton, 2004). Pain, other than neuropathic pain, is elicited by the activation of unmyelinated C fibres and thinly myelinated Aδ fibres. When there is no noxious stimulus, these afferent fibres are silent (Holdcroft et al, 2005). In the situation of injury to the nervous system, however, spontaneous afferent activity may occur, resulting in neuropathic pain (Holdcroft et al, 2005).

Neuropathic pain syndromes typically present with both negative and positive sensory symptoms and signs, (Dworkin et al, 2003 & Backonja et al, 1998) in the anatomical area corresponding to the damaged nerve or central lesion (Holdcroft, 2005). The usual qualities

of neuropathic pain are burning, pricking, shooting or aching (Holdcroft, 2005). This may be accompanied by hyperalgesia (increased pain in response to a noxious stimulus), allodynia (elicitation of pain in response to a non-noxious stimulus), dysesthesia (abnormal unpleasant sensation) or paresthesia (abnormal sensation which is not unpleasant). Negative sensory symptoms such as numbness are common. After-sensation (pain continuing after the stimulation has ceased), referred pain (pain felt in a place apart from the stimulated area) and wind-up pain (abnormal temporal summation of pain), may also occur in the situation of neuropathic pain (Holdcroft, 2005). Pain may be spontaneous or evoked. Evoked pain could result from stimuli such as pressure of clothing or cold temperatures. (Dworkin et al, 2003). Motor symptoms and signs occur less commonly. These too, can be viewed as negative or positive. Negative signs include hypotonia, decreased muscle strength and decreased endurance. Positive signs are increased muscle tone, tremor, dystonia or incoordination (Backonja et al, 1998).

Neuropathic pain can be divided into three broad categories namely; peripheral mononeuropathy (e.g. trigeminal neuralgia, nerve compression by a tumour or post-herpetic neuralgia), peripheral polyneuropathy (e.g. diabetic, alcoholic and HIV neuropathy) and central neuropathy (e.g. post-stroke syndrome and HIV myelopathy) (Dworkin et al, 2003 & Brunton, 2004).

The clinical differentiation between nociceptive pain and neuropathic pain is not always clear-cut, because there is considerable overlap in patients' descriptions of their pain symptoms. Furthermore, the clinical diagnosis of neuropathic pain is open to error because of the absence of a consistent, clear and testable definition of neuropathic pain (Bennett et al, 2005 & Bouhassira et al, 2005). It has been suggested that neuropathic pain is not necessarily a dichotomous phenomenon of "it is", or "it is not" but may be part of a spectrum where the pain is "more or less neuropathic" in origin (Smith et al, 2007; Torrance et al, 2006; Attal et al, 2004). This gave rise to the concept of pain of predominantly neuropathic origin (POPNO) (Torrance, 2006).

No single symptom or sign is pathognomonic of neuropathic pain. The European Federation of Neurological Societies' guidelines on neuropathic pain assessment, emphasises the importance of a thorough neurological examination, especially the sensory aspects thereof (Cruccu et al, 2004). At the same time, the absence of neurological signs does not rule out the presence of neuropathic pain (Backonja et al, 1998). The finding of both negative and positive sensory symptoms or signs in the same anatomical area of pain, is a strong predictor of neuropathic pain (Dworkin et al, 2003). The anatomical distribution of neuropathic pain is one of its most distinguishing features, be it stocking-glove, dermatomal or indicative

of a spinal cord level (Belgrade, 1999). Unlike most other pains, neuropathic pain is often worst at night (Belgrade, 1999).

The often-confusing set of symptoms and signs associated with neuropathic pain, necessitate patients to be instructed, before the examination, to carefully describe exactly what they feel. Any stimulus should be applied first to an unaffected area and then to the painful area. Patients need to respond whether the stimulus in the painful area is the same, less or worse than the unaffected area (Dworkin et al, 2003).

There is no single diagnostic special investigation which will identify pain as being neuropathic. Abnormal nerve conduction studies occur in approximately 81% of patients with a distal sensory polyneuropathy (DSP), whilst the remaining 19% show no abnormality (Tagliati et al, 1999). Since conventional nerve conduction studies are not able to assess the function of the small myelinated and unmyelinated fibres involved in pain and temperature sensation, there is frequently no relationship between painful symptoms and electrophysiological alterations (Dworkin et al, 2003 & Bouhassira et al, 1999).

The commonest cause of neuropathic pain in patients with HIV infection is a peripheral neuropathy (Stephenson, 1996). A variety of sensory neuropathies may occur throughout the course of HIV infection, including acute and chronic inflammatory demyelinating polyneuropathy, mononeuritis multiplex (sometimes associated with cytomegalovirus and varicella zoster virus) and progressive polyradiculopthy (Keswani et al, 2002 & Brinley et al, 2001). The most common and clinically important neuropathy is a distal sensory polyneuropathy (DSP) (Brinley et al, 2001 & Watters et al, 2004), which is thought to be due to neurotoxic substances of both HIV viral and monocyte/macrophage origin (Brinley et al, 2001 & Verma et al, 2005). A toxic neuropathy from ARV drugs is an increasingly common cause of peripheral neuropathy in patients with HIV infection. The nucleoside reverse transcriptase inhibitors (NRTI's), such as didanosine, stavudine and zalcitabine are the worst offenders in this regard (Brinley et al, 2001). This drug-induced neuropathy may produce such severe symptoms that patients are forced to use alternative ARV medication, which reduces future treatment options (Brinley et al, 2001). The decision whether to change ARV medication is made difficult by the fact that HIV-associated DSP and antiretroviral toxic neuropathy are clinically indistinguishable and many patients have contributions from both causes (Verma et al, 2005 & Simpson et al, 2003). NRTI-induced neuropathies tend to be reversible, although symptoms may continue to worsen for a while, even after discontinuation of the drug (Brinley et al, 2001; Verma et al, 2005; Berger et al, 1993). In South Africa, where tuberculosis and HIV infection frequently occur concurrently, the anti-tuberculous drug, isoniazid (INH), may also lead to a peripheral neuropathy in many cases (Wilson et al, 2002).

Neuropathic pain in HIV-infected patients may also be due to malignancies, which occur with increased frequency in HIV-infected patients. These sometimes infiltrate nerves resulting in neuropathic- or mixed neuropathic and nociceptive pain. There is some evidence that the incidence of cerebrovascular incidents is increased in patients with HIV infection (Cole et al, 2004). These may give rise to neuropathic pain of central origin. Herpes zoster in immunodeficient patients tends to be multidermatomal and recurrent (Wilson et al, 2002). This and its complication of post herpetic neuralgia is an additional cause of neuropathic pain, in this group.

In patients with a symptomatic neuropathy, pain occurs predominantly in the lower limbs, especially in the toes and soles of the feet. Painful symptoms include burning or deep pain, intense pins and needles, hyperesthesia (with sensitivity to contact e.g. with socks or bed sheets), paroxysmal shooting pains or combinations of these. Numbness may also be present (Bouhassira et al, 1999 & Verma et al, 2005). Patients with DSP may alter their gait to avoid painful pressure on their feet and they may have disturbed sleep. Symptoms may be severe and may significantly impair a patient's quality of life and functional ability (Verma et al, 2005 & Simpson et al. 2003).

Treatment of painful peripheral neuropathy in HIV infection is difficult. No treatment is known to reverse its course (Keswani et al, 2002 & Simpson et al, 2003), therefore treatment is aimed at improving symptoms. Consistent and prolonged suppression of viral load using HAART results in a decline of the development of DSP (Brinley et al, 2001). Any neurotoxic drugs that the patient may be using, should be discontinued. Several drugs may result in a significant degree of relief for *neuropathic pain in general*. These results have been confirmed in published double-blind, placebo-controlled, randomised studies. First-line agents include certain antidepressants (i.e. tricyclic antidepressants [TCA's] and dual reuptake inhibitors of both serotonin and norepinephrine [SNRI's]), the anticonvulsant, gabapentin and in selected circumstances, opioid analgesics (Dworkin et al, 2007). Certain of these agents have been tested in trials specifically looking at efficacy in HIV sensory neuropathies. The results have been less promising than for neuropathies of other aetiologies. The only therapies shown to offer symptomatic treatment of HIV neuropathies, in randomized placebo-controlled studies, are lamotrigine and recombinant human nerve growth factor (Keswani et al, 2002 & Simpson et al, 2003).

Although neuropathic pain in AIDS patients is common and results in significant patient suffering and functional impairment, it is frequently under-diagnosed and under-treated. A study in the USA found that 63% of patients with symptomatic peripheral neuropathy had not been diagnosed by their clinicians prior to the study (Estanislao, 2003). Stephenson, 1996 suggests that a lack of awareness of the extent of the problem, may contribute to the

inadequate diagnosis of neuropathic pain in AIDS patients. However, both Stephenson, 1996 and Larue et al, 1997 found that even when HIV-related pain is recognised, the majority of patients with significant pain do not receive any or adequate analgesic treatment. Larue et al, 1997 found that inadequate assessment of pain and under-estimation of its severity and its impact on patients' quality of life, may result in poor management of pain. Furthermore, failure to recognize when neuropathic pain mechanisms predominate, results in failure to treat patients with the most appropriate drug regimens, which include adjuvant medication such as certain antidepressants and anticonvulsants. In a study of pain in HIV patients, Breitbart et al, 1996b found that only 10% of patients were prescribed an adjuvant drug, despite the fact that almost 50% of the pain was related to neuropathic pain syndromes.

The present study aimed to identify the prevalence, severity and impact of pain that is predominantly neuropathic in origin, in patients with AIDS, prior to the initiation of HAART (highly active antiretroviral treatment). It is hoped that greater awareness of the extent of the problem may prompt clinicians to perform a more thorough evaluation of their patients' pain, leading to a more specific diagnosis and appropriate prescribing of analgesia and adjuvant medication.

In addition, since this study focused on neuropathic pain in pre-HAART subjects, the findings of this study could be used as a baseline from which to assess the influence of HAART, on the prevalence of neuropathic pain in patients with AIDS.

A further objective of the study was the identification of the most frequent symptoms and signs found with neuropathic pain, which can be used by clinicians in the discrimination between different types of pain in patients with AIDS.

CHAPTER 2

LITERATURE REVIEW

Literature search and Key words:

A literature search was done using the MEDLINE database. Google Scholar was used to extend the search and an expert in the field assisted with literature that he considered important. The following key words were used: neuropathic pain, peripheral neuropathy, polyneuropathy, HIV, AIDS, pain assessment, pain interference.

Neuropathic pain in HIV/AIDS

Pain is a significant problem in patients with HIV infection and AIDS, comparable to that experienced by cancer patients (Lebovits et al, 1989). In a study of ambulatory AIDS patients in the USA, Breitbart et al,1996a found that 62% reported frequent or persistent pain during the past two weeks. One or more pains were reported by 80% of AIDS subjects, in a Los Angeles study of male patients by Singer et al, 1993. Norval, 2004 studied AIDS patients registered with the Soweto Hospice Association Programme in South Africa and found pain to be the most prevalent symptom amongst the sample, with 98% experiencing pain. This particularly high incidence in the Norval study may be due to the fact that hospice patients are likely to have advanced disease.

Only limited evidence could be found in the scientific literature, regarding the prevalence of neuropathic pain *in general,* in AIDS patients. In a study of ambulatory AIDS patients in New York, Breitbart et al, 1996a found 46% of a subset of patients with pain had one or more neuropathic pains. No study could be found that had determined the prevalence of neuropathic pain *in general* in AIDS patients, within the entire sample. Numerous studies have examined the prevalence of *distal sensory polyneuropathy (DSP)* in HIV infected patients. Many of these studies included both symptomatic and asymptomatic neuropathy. Only those studies reporting on symptomatic peripheral neuropathy are discussed. In a USA study, Schifitto et al, 2002 found that 35% of pre-HAART AIDS patients met the criteria for a symptomatic DSP, while 37% of HIV-infected subjects in a Hawaii study of Watters et al, 2004, had a symptomatic DSP. In this study, symptomatic DSP occurred significantly more frequently in patients older than 50 years, as compared to the younger patients. A small study of hospitalized AIDS patients in San Francisco by So et al, 1988, found a DSP prevalence of 35%. A study in Los Angeles by Singer et al, 1993, found that peripheral neuropathy was responsible for the pain in 59% of AIDS patients with pain. Another aspect of neuropathic pain was examined by a New Jersey dental school. In this study, Fischoff et al, 1995 found that 21% of their HIV infected patients suffered from *orofacial* neuropathic

pain. Studies from the African continent, focusing on neuropathic pain in HIV-infected patients, indicate widely variable prevalence rates of peripheral neuropathy. In a recent study in Uganda, Nakasujja et al, 2005 found the prevalence of peripheral neuropathy in HIV-infected patients at different stages to be 44%, of whom just over half were asymptomatic. This would produce a prevalence of symptomatic peripheral neuropathy in HIV patients, of approximately 20%. A much higher prevalence of symptomatic peripheral neuropathy was found in a study by Mbuya et al, 1996, of AIDS patients admitted to a Kenyan hospital. Here, 45% of patients had symptoms of a peripheral neuropathy. The commonest symptom was a dysesthesia and the commonest sign was a loss of vibration sense. This high prevalence may relate to the fact that hospitalized patients tend to have more advanced disease or other complications of HIV infection. No neuropathic pain prevalence study originating from South Africa was identified.

A number of studies examined risk factors for the development of DSP in patients with HIV infection. Tagliati et al, 1999, demonstrated that a lower CD4 cell count, older age, male gender and Caucasian race were associated with a higher incidence of DSP. Morgello et al, 2004 also found a definite significant correlation between DSP and older age and male gender. In this study, initial statistical analysis also found patients with DSP to have lower CD4 cell counts, however, no association between DSP and plasma viral load was indicated. The severity of the pain in HIV-associated peripheral neuropathy was shown by Simpson et al, 2000, to be significantly worse in patients with a higher HIV viral load. Other sources indicate a lower CD4 cell count and advanced disease to be associated with a greater risk of HIV-infected patients developing DSP (Brinley et al, 2001 & Verma et al, 2005). Naturally, concurrent causes of neuropathy, such as diabetes mellitus, alcoholism and deficiencies of vitamin B12 and thiamine, may increase the risk of developing DSP (Brinley et al, 2001).

Assessment of pain and neuropathic pain

The definition of pain, according to the International Association for the Study of Pain (IASP), is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP, 1994). Pain is a subjective experience. What a patient communicates about his pain, verbally or non-verbally, is therefore an important aspect of the measurement of that pain (Ong et al, 2004). A patient's self report, may provide the most valid measure of the experience of pain and is considered the gold standard of pain measurement (Brunton, 2004 & Turk et al, 1992).

A pain measurement test needs to be reliable (giving the same test scores when measuring the same thing on different occasions), valid (referring to the extent to which it measures that

which it is supposed to measure) and sensitive (as far as possible covering the whole dimension of what it is intended to measure) (Ong et al, 2004).

The requirements of this study were first to identify the number of patients in the sample, who had POPNO and then to quantify this pain experience and its impact on the patient's functioning. Several instruments have been developed with the purpose of identifying neuropathic pain or POPNO. These include the Leeds Assessment of Neuropathic Symptoms and Signs Scale (LANSS), the Neuropathic Pain Questionnaire (NPQ) and more recently, the Neuropathic Pain Diagnostic Questionnaire (DN4).

The LANSS was developed at the Chronic Pain Management Service at St James University Hospital in Leeds (Bennet, 2001). It is a simple and valid 7-item tool, using a binary response (yes or no) to the presence of five symptoms (sensory description) and two clinical signs (examination of sensory dysfunction) (Bennet, 2001 & Bennet et al, 2005). When used to differentiate neuropathic from non-neuropathic pain, the LANSS has a sensitivity of 83% and specificity of 87% (Krause et al, 2003). One difficulty with using the LANSS Pain Scale, relates to the symptom of skin colour change. This was likely to pose a problem in this study's population, where many of the patients are dark-skinned.

The NPQ was developed to function as a diagnostic and measurement tool. The intensity of 12 neuropathic symptoms is assessed and discriminate function coefficients are used to calculate the total score. No examination is included in this tool (Bennet et al, 2005 & Krause et al, 2003).

The French Neuropathic Pain Group recently developed a 10-item clinician-administered questionnaire named the Neuropathic Pain Diagnostic Questionnaire (DN4) (Bouhassira et al, 2005 & Jensen, 2005). As with the LANSS Pain Scale, it measures the presence of a number of sensory symptoms and signs. This includes 7 pain qualities and three examination items (hypoesthesia to touch and pinprick and allodynia). Each positive item is given a score of 1 and negative items are scored as 0. The cut-off value for the diagnosis of neuropathic pain is 4/10. This tool was validated in a single study and was found to have a sensitivity of 82.9% and specificity of 89.9% for identifying neuropathic pain (Bouhassira et al, 2005 & Jensen, 2005). The relatively small number of items to be measured and the simplicity of the scoring method of the DN4 made this instrument an appropriate option for this study, which was likely to include several ill or debilitated patients. The DN4 could potentially be a useful tool in palliative medicine research and clinical practice. It should be noted that none of these scales have yet been widely used, nor used in HIV/AIDS populations and have therefore only preliminary validation (Cruccu et al, 2004).

Other measurement tools for neuropathic pain are the Neuropathic Pain Scale (NPS) and the Neuropathic Symptom Inventory (NPSI). While both these tests discriminate between different categories of neuropathic pain and their scores have been shown to change in response to treatment of the pain, they were not developed to discriminate neuropathic pain from non-neuropathic pain (Galer et al, 1997; Bennet et al, 2005; Krause, 2003). Cherry et al, 2005 evaluated The Brief Neuropathy Screening Tool and found it to be a valid screening tool for detecting HIV-associated sensory neuropathies. It was, however, used to detect peripheral nerve dysfunction, rather than a symptomatic neuropathy and was therefore not considered appropriate for this study.

Several instruments are available for the measurement of a patient's pain experience. Unidimensional scales, such as the numerical rating scale (NRS) or visual analogue scale (VAS), are used to determine a score of a patient's pain intensity. The validity of these scales has been well documented and they are simple for patients to understand and easy to use. While a NRS could be used to measure the severity of pain in this study, this unidimensional scale would only measure pain intensity and a multidimensional pain scale was indicated to measure functional and emotional dimensions of the pain.

Examples of multidimensional pain scales are the McGill Pain Questionnaire (MPQ) and the Brief Pain Inventory (BPI). The MPQ attempts to assess the three dimensions of the pain experience, namely the sensory, affective and evaluative components of pain. There is a checklist of 87 descriptors of the sensory qualities of a patient's pain and related emotions. The reliability and validity of this scale have been confirmed in many studies. It has been used to measure a variety of different kinds of pain, but not specifically neuropathic pain. Its disadvantage is that it is time-consuming and requires patients to possess a fairly sophisticated vocabulary (Ong et al, 2004). It was therefore not considered suitable for this study setting, where, for several patients, the study questions had to be translated into another language. The BPI is a widely used and validated instrument, which measures the severity of pain and its interference with daily functioning (Zelman et al, 2005 & Daut et al, 1983). Its brevity and ease of use make it particularly useful in both clinical and research settings (Poundja et al, 2007). The BPI has been used in several different clinical settings, including patients with HIV disease (Poundja et al, 2007). A French study by Larue et al, 1997 and a New York study by Breitbart et al, 1996b, on the undertreatment of pain in AIDS patients, used the BPI as a measure of pain. The BPI measures worst, least and average pain levels, during the last 24 hours, on an 11-point numerical rating scale. Pain location is recorded on a pain drawing. An NRS is also used to rate the degree to which pain interferes with multiple aspects of life. Some of these aspects include ability to work, walking ability, sleep, mood and relations with other people (White, 2004 & Holdcroft et al, 2005).

Summary:

- Neuropathic pain is the result of injury to the peripheral or central nervous system. It has several aetiologies in patients with HIV and AIDS, the commonest being a type of peripheral neuropathy known as a distal sensory polyneuropathy.
- There is more evidence relating to the prevalence of AIDS-related peripheral neuropathy than neuropathic pain in general.
- The prevalence of peripheral neuropathy in patients with HIV and AIDS varies considerably in different studies around the world.
- No study, that originated in South Africa, relating to the prevalence of neuropathic pain or peripheral neuropathy in AIDS patients, was found.
- Assessment of neuropathic pain is difficult, due to both the lack of a clear clinical definition, as well as neurological guidelines for the diagnosis of neuropathic pain. The Neuropathic Pain Diagnostic Questionnaire (DN4) may provide a simple and practical tool for neuropathic pain research and clinical practice.

CHAPTER 3

AIM AND OBJECTIVES

The aim of this study is to determine the prevalence, characteristics and morbidity of neuropathic pain in AIDS patients, who attended the Kalafong HIV Clinic, prior to the initiation of HAART.

Primary Objectives

- To identify what percentage of AIDS patients, attending the Kalafong HIV Clinic, have POPNO, prior to the initiation of HAART.
- To identify the perceived intensity of pain in those patients with POPNO.
- To assess the perceived impact of the POPNO on patients' physical and psycho-social functioning.
- To identify the most prevalent symptoms and signs of POPNO in AIDS patients.

Secondary Objectives

- To improve awareness amongst clinicians, regarding the extent and impact of neuropathic pain in AIDS patients.
- To produce baseline data to be used in comparing the prevalence of POPNO in patients, prior to the initiation of HAART, with those who are using ARV therapy.

CHAPTER 4

STUDY METHODOLOGY

Study design

This is a prospective, cross sectional and descriptive-analytic study.

Subjects and sampling

The study population included all patients attending the Kalafong HIV Clinic for the first time. The majority of patients referred to this clinic, meet the requirements for the National Department of Health's HIV ARV programme. This means that they are patients with confirmed AIDS , either with a history of an AIDS-defining condition or a CD4 cell count of less than 200 cell/mm^3.

All patients attending the Kalafong HIV clinic for the first time, are required to attend a preparation visit, during which they are counselled and informed regarding the use of ARV's. These preparation visits take place on the Monday and Thursday of each week. All the patients attending each of these preparation visits, were invited to participate in the study. Only those patients meeting the inclusion criteria were included in the sample. Sampling continued until the desired sample number was reached.

To determine the sample size, the following approximate formula was used:

$$n = \frac{p(100-p)Z_{\alpha}^2}{d^2}$$

where n = sample size

p = proportion

d = level of accuracy

Note: $Z_{\alpha}^2 = 1.96^2$

The prevalence of pain in this study population was estimated as 50% and neuropathic pain as 5% - 10%. It was therefore expected that about 50% of subjects would be classified as being positive to the study variable. Using the mentioned formula, given different sample sizes (n) and using a 95% level of confidence, ($Z_{\alpha}^2 = 1.96^2$), d is calculated as:

n	Accuracy level
50	13.9%
100	9.8%
150	8.0%
200	6.9%
250	6.2%
300	5.7%
350	5.2%
400	4.9%
450	4.6%
500	4.4%

Therefore, with the sample of 354 subjects, an accuracy level of 5.2% should have been achieved.

Study Procedure

Lay counsellors do pre- and post-test HIV as well as ARV counselling at the Kalafong HIV clinic. Six of these counsellors were available as research assistants on their off-duty days. One research assistant was on duty each research day and he/she handed each of the patients attending the clinic for a preparation visit, the study information sheet (Appendix 1). In the times before or after the preparation sessions, the research assistant approached each patient individually and explained any parts of the study information sheet that were unclear. He/she then assisted those patients who were willing to participate in the study, to sign the informed consent form (Appendix 2). Both the information sheet and the informed consent form were available in English, Afrikaans, Tswana and Zulu. The research assistants were all competent in these same languages and almost all the patients attending this clinic are able to communicate in one of these languages. The research assistants were trained in issues of patient communication, research ethics (such as avoiding any influence or coercion) and confidentiality.

Inclusion criteria:

1. Patients with a confirmed diagnosis of AIDS i.e. HIV infection with either a history of an AIDS-defining condition or a CD4 cell count of less than 200 cell/mm^3.
2. Patients 18 years and older.
3. Patients who were willing and consented to participate in the study.

Exclusion criteria:

1. Patients who were unable to understand or answer the questionnaire due to cognitive impairment or language difficulties, in spite of the availability of the translator.

2. Patients with severe systemic illness, who may have experienced the additional questioning and examination as too burdensome.

3. Patients attending the Kalafong HIV Clinic for the first time, but who were already using ARV agents, prescribed by another institution or clinician.

Data collection method

The research data was collected using an interviewer-administered paper questionnaire, which included a focused neurological examination (Appendix 3). In this questionnaire, the method used to identify the subsection of the sample who had *pain in general,* was adapted from a question used to identify patients with pain, in a large study of pain in ambulatory patients with AIDS in the USA (Breitbart et al, 1996a & Hewitt et al, 1997). In this USA study, patients were asked the question: "During the past two weeks, have you experienced persistent or frequent pain of any type?" The language of this question was adjusted to make it more meaningful for the present study's population. Several aspects of this questionnaire were based on the Brief Pain Inventory (BPI). Although the BPI is a valid and reliable measure of pain, the focus of this study was neuropathic pain and a further instrument was required to identify those patients with POPNO. For this purpose, the DN4 was chosen, from several clinical instruments used to measure neuropathic pain, due to the relative simplicity of its questions and examination items. This was considered to be important for this study in a palliative care setting, where many of the subjects may be feeling ill, weak or fatigued. The DN4 has been shown, in a single study, to be a valid tool for the identification of neuropathic pain (Bouhassira et al, 2005 & Jensen, 2005). It has, however, not been subject to other validation studies, nor has it been used for studying HIV populations.

Both the questions and the neurological examination, were administered by the researcher, with the help of a translator (one of the research assistants) where required. The researcher read the questions to the patients and recorded their responses. This method enhanced the quality of the data because the interviewer could clarify, but not amplify, the questions or instructions. Patients were also able to motivate their answers.

Tools of measurement

The questionnaire was divided into the following sections:

- A demographic section which included age, gender and use of tuberculosis treatment. The CD4 cell count, on the referral note of the patient to the HIV Clinic, was recorded in this section of the questionnaire. On the day of the first visit to the HIV Clinic, the HIV viral load is measured in all patients who qualify to use ARV's. This result was obtained and recorded from the records of the ARV Clinic, once it was available.

- The presence of pain was assessed by asking all patients the following question: "During the past two weeks, have you experienced any pain that has troubled you a lot?" Only the subsection of patients identified as having pain, continued with the questionnaire.

- A body map for patients to indicate the location of their pain(s).

- The Neuropathic Pain Diagnostic Questionnaire (DN4):
  Using this instrument, each patient was asked to answer "yes" or "no" to the following seven pain qualities or sensations in his/her area of pain: burning, painful cold, electric shocks, tingling, pins and needles, numbness and itching. This instrument included three examination items, to check for the presence of hypoesthesia to touch, hypoesthesia to pain and dynamic allodynia of the skin overlying the area of pain. The painful area was compared to an adjacent or contra lateral non-painful area of skin. Cotton wool was used for the modality of touch, a cocktail stick was used to elicit pinprick pain and brushing with cotton wool was used to elicit any allodynia. Each positive item was given a score of 1 and negative items were scored as 0. The cut-off value for the diagnosis of pain of predominantly neuropathic origin (POPNO) was 4/10.

  Only patients, whose pain was identified as neuropathic in origin by using the DN4, were required to complete the remaining sections of the questionnaire. These included:

- A focused neurological examination to identify any sensory or motor deficits in the area identified as having pain of predominantly neuropathic origin:
  The following sensory aspects were tested; tactile, pinprick, and vibration sense, static mechanical allodynia, dynamic mechanical allodynia, warm thermal allodynia

and cold thermal allodynia. (Certain of these had already been measured during the application of the DN4). Dynamic allodynia was tested by brushing the skin with cotton wool, while static allodynia was tested by blunt pressure with a finger, at a pressure that does not evoke pain in a normal area. A tuning fork heated in water of 40 degrees Celsius and cooled in water of 15 degrees Celsius, was used for the thermal allodynia testing. All stimuli were applied first to an adjacent or contra lateral non-painful area and then to the painful area. Patients were asked to say whether the stimulus felt "the same", "less intense" or "more intense". For vibration sense, a 128 Hz tuning fork was used. The stimulus was first applied to a joint in a non-painful area, such as the wrist. It was then applied to joints in the area of pain, such as the knee, medial malleolus and IP joint of the big toe. Vibration sense was recorded as "present" or "decreased or absent".

Motor aspects of this examination included distal muscle strength and the deep tendon reflexes. Where the lower limbs were painful, the strength of the big toe and ankle dorsiflexion was compared to finger spread and recorded as either "the same" or "weaker". Depending on the area of pain, the ankle or supinator reflex was compared to a more proximal reflex and recorded as "the same" or "absent or decreased". In cases where the pain was situated in an area other than a limb, vibration sense, muscle strength and the deep tendon reflexes were not tested.

- A section regarding temporal aspects of the neuropathic pain and whether any analgesia had been prescribed in the month prior to the study.

- Intensity of pain of predominantly neuropathic origin:
  Numerical rating scales were used to rate the intensity of worst and average pain. Patients were asked to select a number from 0-10 to indicate the intensity of their pain during the past week. Zero was labeled as "no pain" and 10 was labeled as "unbearable pain".

- Impact of pain of predominantly neuropathic origin:
  Patients were asked to rate how much the pain interfered with their walking, working ability, sleep, relations with other people, mood and enjoyment of life, during the past week. They were asked to select a number on an 11-point numerical rating scale to indicate the degree to which the pain interferes with each aspect of their daily functioning. Zero was labeled as "no interference" and 10 was labeled as "complete interference".

The questions regarding intensity and impact of pain were adapted from the Brief Pain Inventory. This instrument has been validated in several studies of various kinds of pain, including diabetic peripheral neuropathy and pain in AIDS patients (Zelman et al, 2005; Poundja et al, 2007; Keller et al, 2004).

Analysis of data:

Data was analysed using SPSS for Windows statistical software.

Descriptive statistics were produced to examine the study sample, the prevalence of POPNO (DN4 score of 4 or more), the severity of the POPNO and pain-related interference. Means ± standard deviations were used for continuous variables and frequency distributions for categorical variables.

Factors associated with the presence of POPNO and the severity of POPNO were identified using Chi squared tests of Independence.

Statistically significant differences between the severity of POPNO and interference items were evaluated by means of non-parametric tests using the Kruskal Wallis statistics. The Pearson's Correlation Coefficient was also calculated to identify significant linear relationships between variables.

Statistical significance was evaluated at the 95% level of confidence.

The analysis focused on the following aspects:

1. The prevalence of pain that is predominantly neuropathic pain in origin.
3 Factors associated with the occurrence of POPNO.
4. The severity of POPNO.
5. The perceived interference of POPNO on certain aspects of daily functioning.
6. The correlation between the severity of POPNO and pain-related interference with daily functioning.
7. Frequently occurring symptoms and signs of POPNO, as demonstrated by the DN4 instrument and focused neurological examination.

Ethical considerations

All possible candidates for the study received information by means of the study information sheet and by a research assistant. They were assured that participation in the study was entirely voluntary and that if they chose not to participate or to withdraw from the study, they would still receive standard care as offered at the clinic.

Care was taken to ensure that participation in the research study did not negatively influence the patients' management at the ARV Clinic. No clinical or counselling session was delayed in favour of the research interview. Certain patients, however, needed to stay at the clinic a while longer following their clinical sessions, to be able to participate in the study.

All information obtained from the study participants was treated as confidential and no patient names appeared on the study questionnaires. Any publication resulting from this study will be presented in such a fashion that patients remain unidentifiable.

In cases where significant pain or other problems were identified during the data collection procedure, a referral to the doctor on duty at the HIV clinic was offered to the patient. Several patients, with acute or severe problems, benefited from the direct and fast referrals they received in this manner.

This study received full approval from the Research and Ethics Committees of the University of Cape Town and the University of Pretoria.

CHAPTER 5

RESULTS

Sample characteristics

The characteristics of the study sample are shown in Table I and Table II.

Table I. Sample characteristics (n=354)

	n or Mean	% of total or SD
Variable		
Gender		
Male	96	27.1%
Female	258	72.9%
Age		
<30 yrs	73	20.6%
30-39 yrs	163	46.0%
40-49 yrs	91	25.7%
50+ yrs	27	7.6%
Mean age	36.3	8.6
CD4 cell count		
Up to 50	94	26.6%
51-100	63	17.8%
101-200	167	47.2%
>200	27	7.6%
Not specified	3	0.8%
Mean CD4 cell count	111.2	70.8
Viral load		
Up to 10 000	42	12.1%
10 000-99 000	116	33.3%
100 000-499 000	109	31.3%
500 000 & more	81	23.3%
Not specified	6	1.7%
Current or recent TB treatment	74	20.9%
Frequent or persistent pain	220	62.1%

Table II. Sample characteristics with gender ratios

		Male	Female	P-value
Age	**n**	96	258	
<30 yrs		6.3%	26.0%	
30-39 yrs		45.8%	46.1%	
40-49 yrs		37.5%	21.3%	
50+ yrs		10.4%	6.6%	<0.001
Mean		40.0	35.0	<0.001
SD		8.5	8.2	
CD4 cell count	**n**	95	258	
Up to 50		46.3%	19.5%	
51-100		20.0%	17.2%	
101-200		28.4%	54.7%	
200+		5.3%	8.6%	<0.001
Mean		77.9	123.6	<0.001
SD		64.9	69.0	
Viral load	**n**	94	254	
Up to 10 000		8.5%	13.4%	
10 000-99 999		27.7%	35.4%	
100 000-499 999		29.8%	31.9%	
500 000 and more		34.0%	19.3%	0.028
Current or recent TB treatment	**n**	96	258	
Yes		40.6%	13.6%	
No		59.4%	86.4%	<0.001
Frequent or persistent pain	**n**	96	258	
Yes		72.9%	58.1%	
No		27.1%	41.9%	0.011

This study included 354 patients diagnosed with AIDS, with a mean age of 36.3 years (± 8.6) and ranging from 18 to 67 years.

More than 90% of the sample was under the age of 50 years. Almost half (46.0%) of the patients were in the 30 to 39 year old group. Female patients were significantly younger than male patients (P<0.001). 26% of the female sample fell in the under-30 year old age group, as compared to only 6.3% of the male sample.

Female patients made up the majority of the sample (72.9%).

More than half of the patients had a CD4 count of more than 100 cells/mm^3. The average CD4 cell count was significantly lower for males than females (P<0.001).

Most patients (54.6%), had high viral loads of 100 000 copies/ml and over. In male patients, these were significantly higher than in female patients (P=0.028).

Twenty one percent of the patients had used treatment for tuberculosis in the past two weeks. By far the majority of these were male, with those using treatment for tuberculosis comprising 40.6% of the male sample, as compared to only 13.6% of the female sample (P<0.001).

Pain of any type within the total patient sample

The prevalence of frequent or persistent pain of any type within the whole sample was 62.1% (220 patients). Male patients experienced significantly more pain (P=0.011), with 72.9% having pain, compared to 58.1% of female patients.

Figure 1 shows the prevalence of frequent or persistent pain, of any type, for different levels of CD4 count.

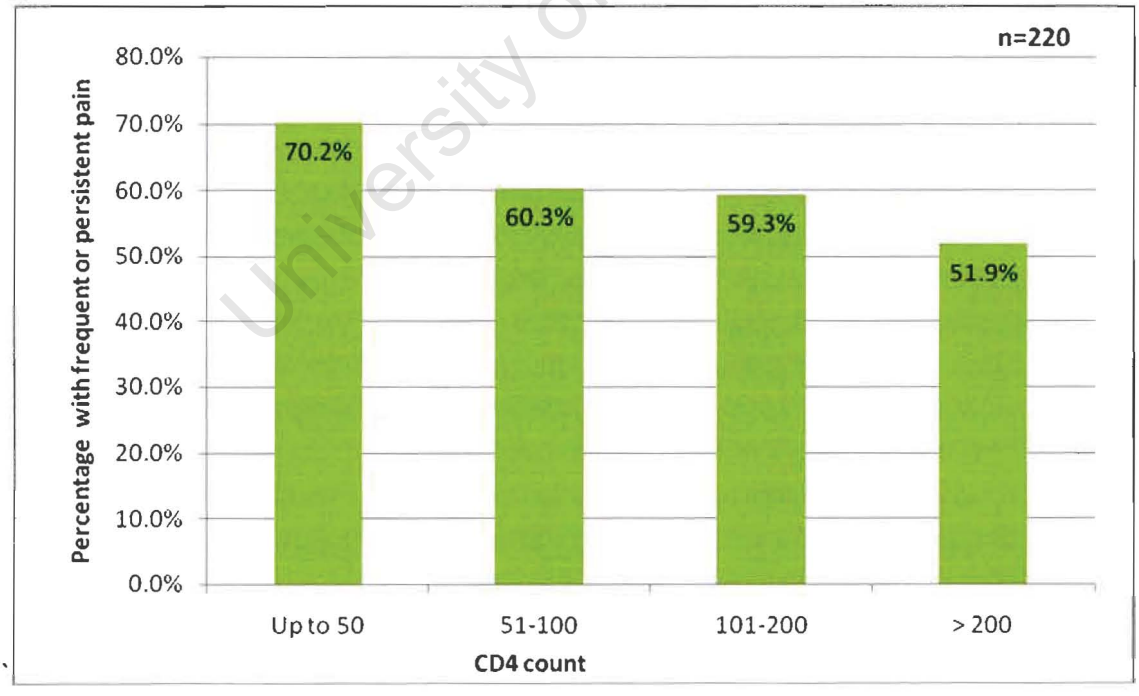


Figure 1. The association between the presence of frequent or persistent pain of any type and CD4 count level

There is a trend towards an increased prevalence of pain as the CD4 cell count becomes lower, however, a statistically significant difference was not found (P=0.216).

Figure 2 shows the anatomical distribution of frequent or persistent pain, of any type.

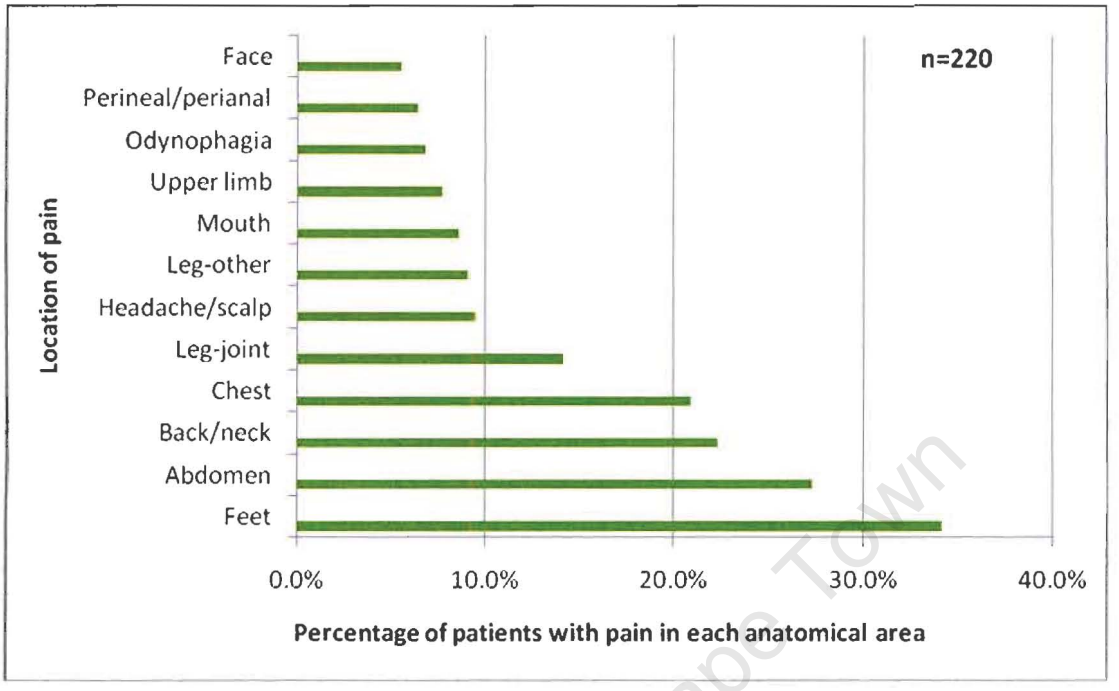


Figure 2. Anatomical distribution of frequent or persistent pain, of any type (n=220)

The commonest sites of pain were the feet (34.1%), the abdomen (27.3%), the back and neck (22.3%), the chest (20.9%) and joints of the lower limb (14.1%).

Prevalence of pain of predominantly neuropathic origin

All of the 220 patients (62.1%) with frequent or persistent pain were tested for the presence of pain of predominantly neuropathic origin (POPNO), using the DN4 instrument. These results are shown in Table III. The frequencies for patients without any pain are included in this table, to demonstrate the prevalence of POPNO in the total sample.

Table III. Presence of pain of predominantly neuropathic origin as indicated by the DN4 score (n=354)

DN4 total score	n (%)
No pain (DN4 not done)	134 (37.9%)
DN4 total score 0-3	146 (41.2%)
DN4 total score 4-10	74 (20.9%)
Total	354 (100%)

This shows that 74 patients (20.9%) in the total sample have pain that is predominantly neuropathic in origin, as indicated by a DN4 score of 4-10 (95% CI= 16.8% to 25.2%). Of the 220 patients in the subsample that had pain, 33.6% had POPNO.

The distribution of DN4 scores for the 220 patients with pain is displayed in Figure 3.

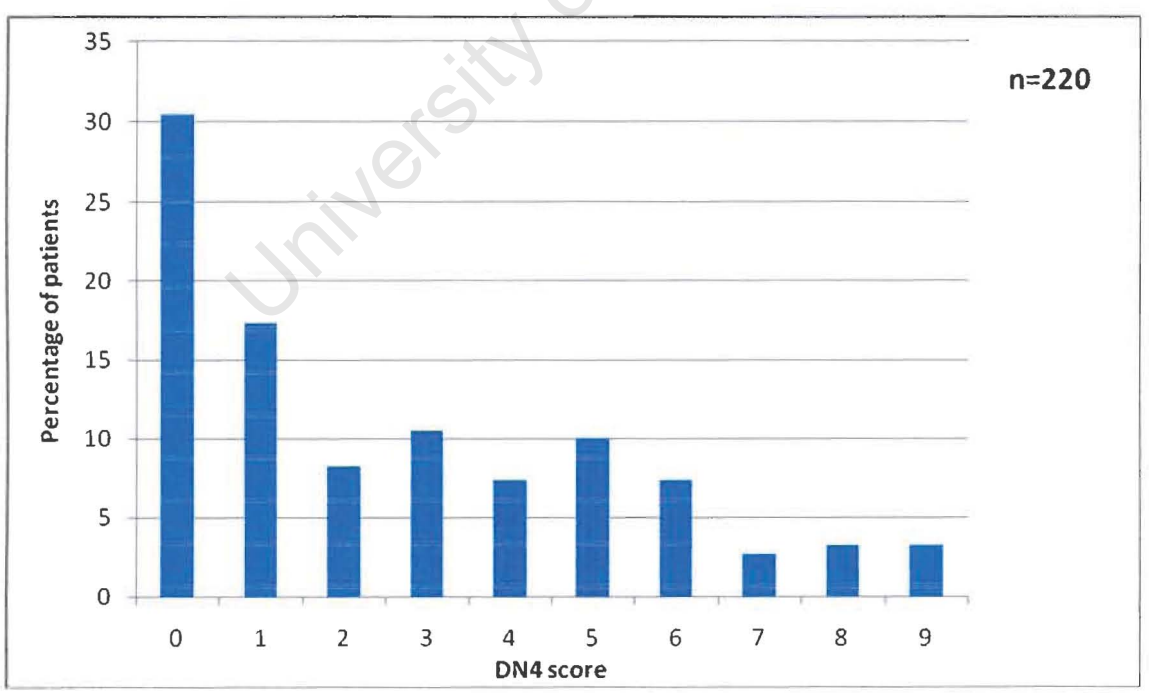


Figure 3. Distribution of DN4 scores in patients with pain of any type

Chi-Squared analysis was done to assess the impact of the following variables on the prevalence of pain of predominantly neuropathic origin: gender, age, CD4 count, viral load and the use of treatment for tuberculosis. The results of this are displayed in table IV.

A significantly higher percentage of male patients (31.3%), as compared to 17.1% of the female group, had a score indicative of POPNO (P=0.003).

There was a trend towards older patients having a higher prevalence of POPNO, however, the analysis did not demonstrate significant differences between age groups.

Patients with lower CD4 cell counts (P=0.009) and those with higher viral load values (P=0.006) showed a significantly higher prevalence of POPNO.

Those patients with a history of recent or current use of treatment for tuberculosis demonstrated a far greater prevalence of POPNO (P<0.001).

TABLE IV. The association between the study variables and the prevalence of POPNO

	DN4 scores 4-10 n	
Total sample	74	
Gender		
Male	30	31.3%
Female	44	17.1%
P-value (Chi-Square)		0.003
Age		
<30 yrs	11	15.1%
30-39 yrs	30	18.4%
40-49 yrs	27	29.7%
50+ yrs	6	22.2%
P-value (Chi-Square)		0.095
CD4 cell count		
Up to 50	31	33.0%
51-100	13	20.6%
101-200	26	15.6%
200+	4	14.8%
P-value (Chi-Square)		0.009
Viral load		
Up to 10 000	3	7.1%
10 000-99 000	19	16.4%
100 000-499 000	25	22.9%
500 000 and more	26	32.1%
P-value		0.006
Current or recent use of TB treatment		
Yes	30	40.5%
No	44	15.7%
P-value		<0.001

The DN4 instrument

Figure 4 indicates how frequently each of the items (symptoms and signs) of the DN4 instrument was present in the group of 74 patients with POPNO.

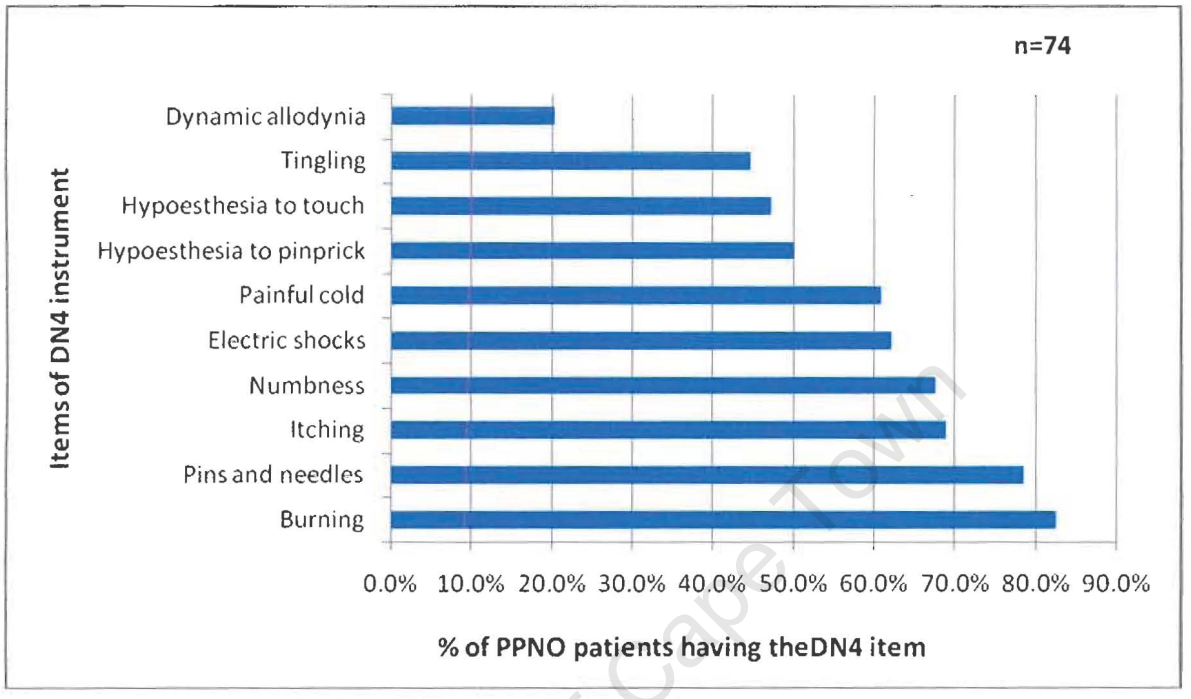


Figure 4. Frequency of each of the DN4 items, in patients identified as having POPNO (n=74)

The most frequent symptoms encountered were burning pain in 61 patients (82.4%) and abnormal pain-related symptoms, such as pins and needles, in 58 patients (78.4%), itching in 51 patients (68.9%) and numbness in 50 patients (67.6%).

As evident from the above figure, the examination items occurred less frequently than most of the symptom items.

Characteristics of pain of predominantly neuropathic origin

Anatomical location of POPNO:

The location of the pain in patients identified as having POPNO is shown in Figure 5.

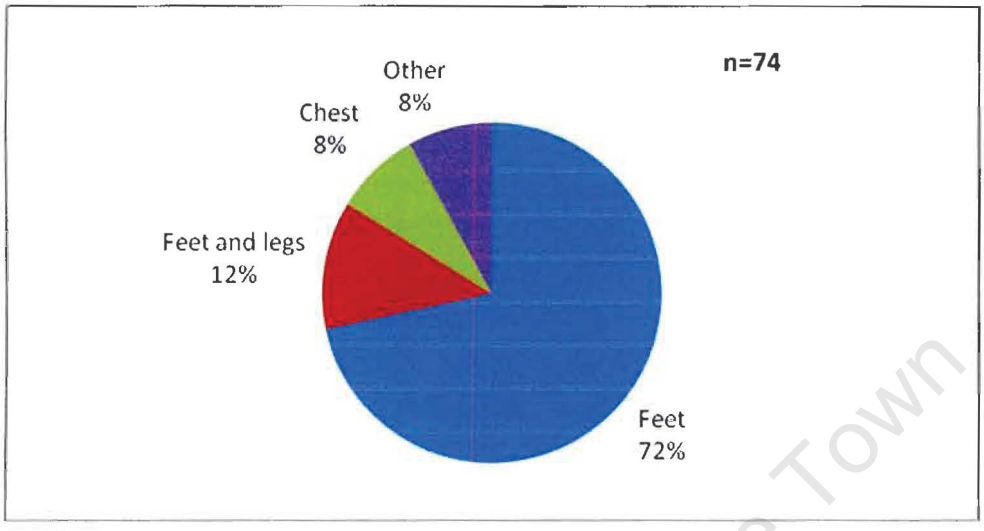


Figure 5. The location of pain in patients with POPNO

By far the majority of patients (62 out of 74) had pain in their feet only or both feet and legs. Two of the patients (not indicated on the chart) had POPNO in two different sites.

Temporal aspects of POPNO:

In most patients (52.7%), the pain had been present for months, while in 18.9%, it had been there for several years. 85.1% reported the pain to be present both day and night, of whom 66.7% found it worse at night.

Analgesic medication prescribed:

Only 29.7% of the patients with POPNO could remember having analgesic medication being prescribed for the pain, by their doctor or clinic, in the past month. It was beyond the scope of this study to determine how many of the patients had actually consulted a doctor or clinic in the preceding month.

Neurological signs:

In order to determine some of the clinical characteristics of pain of predominantly neuropathic origin in this population, a focused neurological examination was done on all the patients identified as having POPNO (74 patients).

Figure 6 shows the frequency of an abnormal examination result for each aspect of the focused neurological examination. Items, such as vibration sense, distal reflexes and muscle strength were not applicable to all POPNO patients. In these cases, the frequency was calculated as a percentage of the total number of patients tested in this regard (n=66).

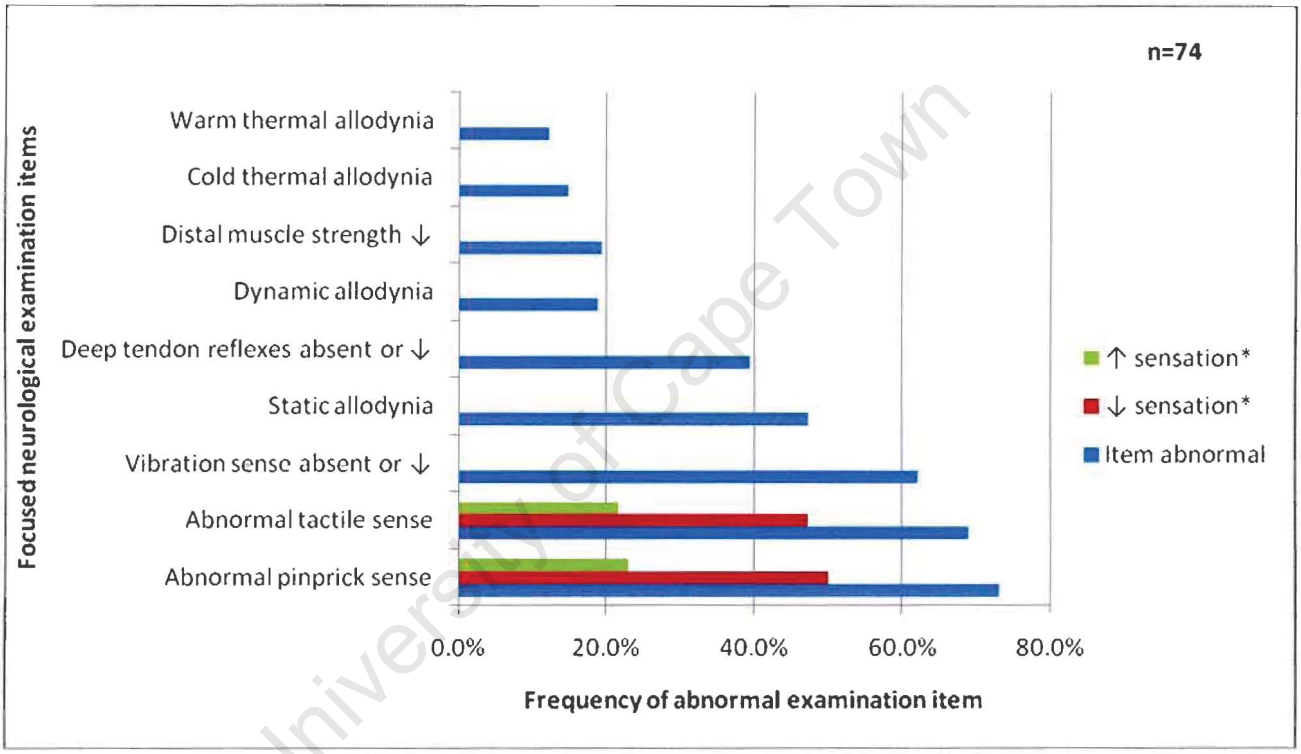


Figure 6. Frequency of abnormal examination for each aspect of the focused neurological examination

*Both increased and decreased tactile and pinprick sense were regarded as abnormal. The clustered bars indicate the frequencies of each of these.

The most frequent abnormal examination findings were abnormal pinprick sense in 54 patients (73%), most of whom demonstrated a decreased pinprick sense (50.0%). Testing of tactile sense revealed similar results, with 51 patients (68.9%) showing abnormalities, of whom most showed a decreased tactile sense (47.3%). Other commonly-occurring neurological abnormalities were decreased or absent vibration sense (62.1% of patients), static mechanical allodynia (47.3%) and decreased or absent deep tendon reflexes (39.4%).

In order to further characterise patients with pain of predominantly neuropathic pain, the number of abnormal neurological examination items per patient was analysed. The focused neurological examination consisted of nine items. Therefore, any one patient could have a maximum of nine abnormalities. These results are displayed in figure 7.

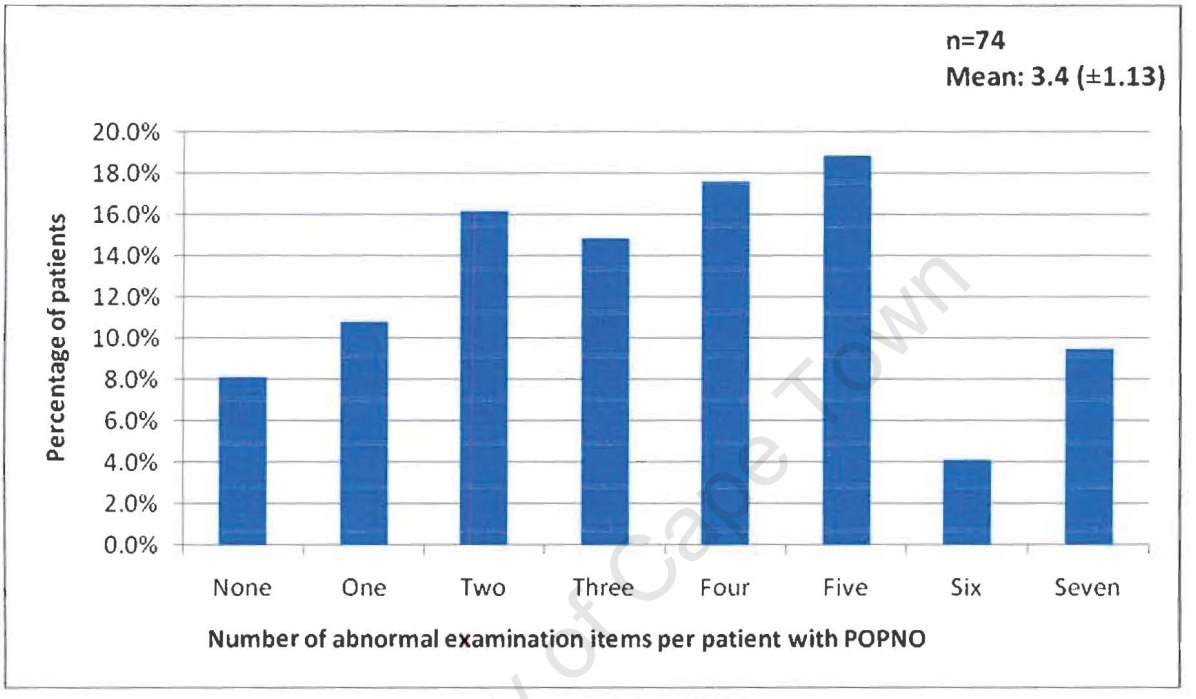


Figure 7. Number of abnormal neurological examination items per patient with POPNO

Using the focused neurological examination, six of the 74 patients (8.1%) displayed no neurological abnormalities. At the opposite end of the spectrum, 7 patients (9.5%) had abnormal findings for seven of the nine examination items. These results show that most, but not all patients with POPNO, exhibit at least one or more objective neurological abnormality.

Intensity of pain of predominantly neuropathic origin

One of the objectives of the study was to determine the perceived intensity of the pain of predominantly neuropathic origin. Each patient identified as having POPNO was asked to rate his/her worst and average pain, during the past week, on a numerical rating scale. "0" on the scale was labelled as "no pain" and "10" was "unbearable pain". These results are displayed in table V.

Table V. Intensity rating of pain of predominantly neuropathic origin

	n (%)				
	Mild pain (1-3)	**Moderate pain (4-7)**	**Severe pain (8-10)**	**Mean pain score**	**SD**
Worst pain	9 (12.2%)	34 (45.9%)	31 (41.9%)	6.31	(2.57)
Average pain	54 (73.0%)	16 (21.6%)	4 (5.4%)	2.41	(1.79)

These results show that when the pain is at its worst, a large percentage (41.9%) experienced it as severe. It was only in a few of the respondents (12.2%) that the pain was never experienced as more than mild.

Chi-squared analysis was done to assess whether the variables of gender, age, CD4 count, viral load and the use of treatment for tuberculosis had any impact on the severity of the pain at its worst. The results are shown in table VI.

From this table, it can be seen that none of these variables had a significant influence on the severity of the POPNO, at its worst.

Table VI. The impact of study variables on the severity of pain at its worst

		Pain at its worst			
	n	**Mild (0-3)**	**Moderate (4-7)**	**Severe (8-10)**	P- value (Chi-Squared)
Total sample	74	12.2%	45.9%	41.9%	
Gender					
Male	30	13.3%	50.0%	36.7%	
Female	44	11.4%	43.2%	45.5%	0.753
Age					
<30 yrs	11	18.2%	36.4%	45.5%	
30-39 yrs	30	10.0%	46.7%	43.3%	
40-49 yrs	27	14.8%	44.4%	40.7%	
50+ yrs	6	0.0%	66.7%	33.3%	0.891
CD4 cell count					
Up to 50	31	16.1%	35.5%	48.4%	
51-100	13	0.0%	53.8%	46.2%	
101-200	26	15.4%	50.0%	34.6%	
200+	4	0.0%	75.0%	25.0%	0.891
Viral load					
Up to 10 000	3	0.0%	100.0%	0.0%	
10 000-99 999	19	21.1%	36.8%	42.1%	
100 000-499 999	25	4.0%	44.0%	52.0%	
500 000 and more	26	15.4%	46.2%	38.5%	0.289
Current or recent use of TB treatment					
Yes	30	16.7%	56.7%	26.7%	
No	44	9.1%	38.6%	52.3%	0.086

Impact of pain of predominantly neuropathic origin, on aspects of daily living

A further objective of the study was to determine the impact of the pain of predominantly neuropathic origin on certain aspects of daily functioning. Patients were asked to rate, on a numerical rating scale, how much this pain interfered with their walking, ability to work, sleep, mood, relations with others and enjoyment of life, during the past week. The results are shown in table VII.

Certain patients were unable to distinguish between interference by the POPNO and that of other problems such as generalised weakness. This accounts for the unspecified group.

Looking at the mean score for each item, the aspects of living most impacted upon by the POPNO were enjoyment of life (mean score 4.25), mood (mean score 4.23) and the ability to work (mean score 4.01). At least 25% of respondents experienced severe pain-related interference for these three aspects of living.

Almost one quarter of the patients (23.0%) had severe pain-related interference with their sleep, while 17.6% found their walking to be severely impaired as a result of the pain.

TABLE VII. Impact of pain of predominantly neuropathic origin on aspects of daily living (n=74)

Pain Interference Rating	n or mean	% or SD
Walking		
Mild (0-3)	38	(51.4%)
Moderate (4-7)	18	(24.3%)
Severe (8-10)	13	(17.6%)
Unspecified	5	(6.8%)
Mean score	3.59	(3.34)
Ability to work		
Mild (0-3)	34	(45.9%)
Moderate (4-7)	17	(23.0%)
Severe (8-10)	19	(25.7%)
Unspecified	4	(5.4%)
Mean score	4.01	(3.59)
Sleeping		
Mild (0-3)	41	(55.4%)
Moderate (4-7)	16	(21.6%)
Severe (8-10)	17	(23.0%)
Unspecified	0	
Mean score	3.61	(3.53)
Mood		
Mild (0-3)	35	(47.3%)
Moderate (4-7)	18	(24.3%)
Severe (8-10)	20	(27.0%)
Unspecified	1	(1.4%)
Mean score	4.23	(3.45)
Relations with other people		
Mild (0-3)	49	(66.2%)
Moderate (4-7)	13	(17.6%)
Severe (8-10)	10	(13.5%)
Unspecified	2	(2.7%)
Mean	2.07	(3.08)
Enjoyment of life		
Mild (0-3)	33	(44.6%)
Moderate (4-7)	21	(28.4%)
Severe (8-10)	19	(25.7%)
Unspecified	1	(1.4%)
Mean	4.25	(3.30)

Correlation between pain intensity and interference items

The correlation between the severity of POPNO at its worst and interference with aspects of daily living was tested using the Kruskal Wallis Test and Pearson's correlation coefficient. These results are shown in Figure 8 and Table VII.

Figure 8 shows a significant correlation between pain severity and the global or overall pain-related interference score (the combined mean score of all six items).

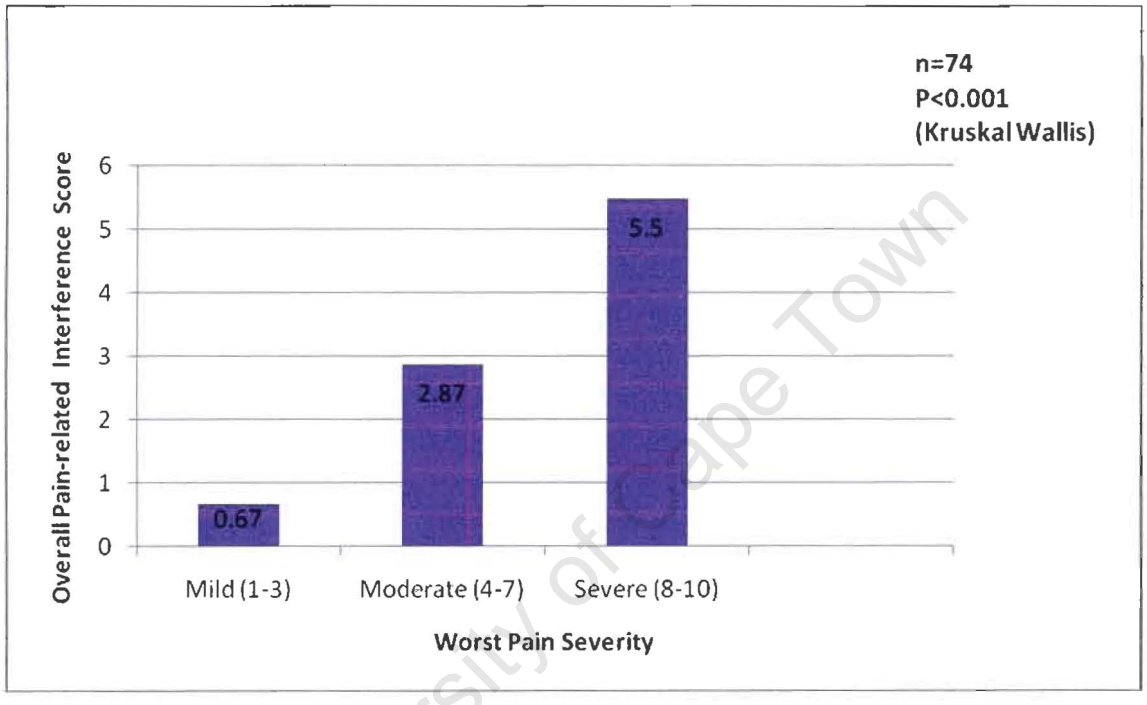


Figure 8. Correlation between severity of POPNO and overall pain-related interference score

Table VIII displays the correlation between worst pain severity and the mean pain-related interference score for the individual domains of daily living.

Table VIII. Correlation between POPNO at its worst and individual interference items (n=74)

	Pain at its worst		
	n	Pearson correlation coefficient	P-value
Walking	69	0.565	<0.001
Ability to work	70	0.558	<0.001
Sleep	74	0.518	<0.001
Relations with other people	72	0.303	0.010
Mood	73	0.456	<0.001
Enjoyment of life	73	0.555	<0.001

A significant positive correlation exists between worst pain severity and the overall pain-related interference score, as well as for the individual interference items.

CHAPTER 6

DISCUSSION

This study presents evidence of the prevalence, characteristics and impact of pain of predominantly neuropathic origin, in patients with AIDS, before the use of ARV therapy.

Demographics of sample

The majority of the study sample was female (over 70%) and under 40 years (66.6%). The higher percentage of females in the sample, corresponds with the usual gender ratio of patients attending this clinic, where two thirds of the patients are female. Patients in this sample had a mean age of 36.3 years, which is similar to that of a study of AIDS patients in Kenya, where the mean sample age was 33.0 years (Mbuya et al, 1996). The mean age of the male group of patients was 5 years older than that of the female group. This is consistent with a 2005 national study within the general population in South Africa, where the prevalence of HIV infection in females peaked in the 20-29 year-old age group, while in males this prevalence peaked 10 years later, in the 30-39 year old age group (Rehle et al, 2007).

The average CD4 cell count was 111 cells/mm^3. The male group was characterised by a significantly lower mean CD4 cell count, a significantly higher viral load and a significantly higher prevalence of the use of treatment for tuberculosis. This seems to indicate that, in general, the male patients, referred to this ARV clinic, have more advanced AIDS than the average female patient. Several factors could account for this. It might be that pregnancy has a positive spin-off for the female patients. Pregnant patients are routinely offered HIV testing during visits to antenatal care facilities. This might lead to earlier diagnosis of HIV infection within the female sector of the community, which is usually followed by timely referral for ARV therapy. It is also possible that many HIV-infected males in this community delay seeking health care from public health facilities, until their illness becomes more symptomatic. Furthermore, Prins et al, 1999, have shown that women seroconvert for HIV, develop AIDS and die at higher CD4 cell counts than men.

Prevalence of pain

Of the total sample, 62.1% experienced frequent or persistent pain within the preceding two weeks. This figure is similar to the studies of Larue et al, 1997; Breitbart et al, 1996a; Singer et al, 1993 and Schofferman et al, 1990, where 50% -80% of AIDS patients had pain.

Patients with frequent or persistent pain were more likely to be male (72.9% males with pain vs. 58.1% females with pain; P=0.011) and tended to have a lower mean CD4 count, although a significant difference in pain prevalence between different CD4 cell count levels, was not demonstrated (P=0.216). Since the male sample appeared to have more advanced disease, it is not unexpected that this group had a higher prevalence of pain.

The most frequent locations of pain were the feet (34.1% of patients with pain), the abdomen (27.3%), the back and neck (22.3%), and the chest (20.9%). This bears some resemblance to a USA study by Schofferman et al, 1990, of pain in far advanced AIDS, where peripheral neuropathy, abdominal pain, headaches and skin conditions (such as Kaposi's sarcoma and pressure sores) were found to be the four commonest causes of pain. A further study by Hewitt et al, 1997, from the USA, also found headache and peripheral neuropathy to be among the top four causes of pain in AIDS patients. These USA studies focused on pain aetiologies, rather than anatomical locations of pain and are therefore not directly comparable to the present study.

The high percentage of patients with pain in the feet, most likely relates to the high prevalence of various painful peripheral neuropathies in AIDS patients (affecting approximately one third of patients with CD4 cell counts below 200 cells/mm^3) (Wilson et al, 2002). A previous study of pain in ambulatory HIV-infected men, by Singer et al, 1993, found that of the patients with pain, 59% were related to peripheral neuropathy. Multiple pathologies may result in pain in the abdomen in patients with AIDS, including cryptosporidial and other infective diarrhoeas, mycobacterium avium-intracellulare infection, lymphoma, Kaposi's sarcoma, pancreatitis and acalculous cholecystitis (O'Neill et al, 1993).

Prevalence of Pain of Predominantly Neuropathic Origin

The prevalence of POPNO was based on achieving a score of 4 or more (range 0-10), using a relatively new neuropathic pain diagnostic questionnaire, the DN4 (Bouhassira et al, 2005). This instrument has been preliminarily validated and has a sensitivity of 82.9% and specificity of 89.9%, for neuropathic pain (Jensen, 2005). All of the 220 patients with frequent or persistent pain, completed this researcher-administered questionnaire and examination.

Using this method, 20.9% of the patients in the total sample were identified as having POPNO (CI=16.8%-25.2%) and within the subset of patients with pain, 33.6% had POPNO.

This study's POPNO prevalence of 20.9%, is somewhat lower than that found in previous studies. Two studies with patients with AIDS, done in the USA, found the prevalence of symptomatic DSP to be 35% (Schiffito et al, 2002 & So et al, 1988). One of these studies involved hospitalised patients, which could explain the higher prevalence. The present study's prevalence of POPNO concurred with a study of Nakasujja et al, 2005, done in Uganda, where the prevalence of a symptomatic peripheral neuropathy was found to be 20%. It should be noted that none of these studies are directly comparable with the present study, which examined *neuropathic pain in general*, as opposed to *symptomatic peripheral neuropathy* only. In Breitbart et al, 1996a's study of ambulatory AIDS patients in New York, 46% of the subset of patients with pain were identified as having neuropathic pain. The present study found that only 33.6% of the subset of patients with pain had POPNO. It is likely that many of the patients in the New York study were already using ARV's and a toxic neuropathy secondary to ARV's may have played a role in the higher frequency of neuropathic pain. Antiretroviral agents and drugs targeting opportunistic infections and malignancies are thought to cause up to 30% of neuropathic pain syndromes in patients with HIV infection (Stephenson, 1996).

In a study of underestimation and under treatment of pain in HIV disease, by Larue et al, 1997, it was found that pain severity was better assessed and possibly treated, by clinicians, when the source of the pain could be identified. While it was not within the scope of this study to identify the aetiologies of the neuropathic pain, the location of pain may be able to give some indications of these. Eighty-four percent (62 out of 74 patients) experienced the pain in their feet or both feet and legs. Predominantly neuropathic pain, located in the feet in patients with AIDS, is highly likely to be as a result of various AIDS-related or medication-related peripheral neuropathies. Therefore, more than 80% of POPNO in this study is probably related to peripheral neuropathy. The second most likely site of POPNO in this study was the chest. It can be speculated that post-herpetic neuralgia might frequently have been the cause of the POPNO in the chest. Other causes of neuropathic pain in AIDS patients, that might have played a role, are those related to nerve compression by malignancies such as Kaposi's sarcoma and lymphoma (Katz, 2000) and post-stroke pain (Dworkin et al, 2003). In the present study, patients were not asked specifically about the presence of diabetes mellitus or the use of alcohol. It is possible that peripheral neuropathy, secondary to diabetes or nutritional deficiency, could have contributed to neuropathic pain in the lower limbs (Dworkin et al, 2003).

The analysis of the association between the presence of POPNO in this sample and demographic and disease-related characteristics, revealed certain definite associations. A significantly higher prevalence of POPNO was found in male patients (P=0.003), those with a

lower CD4 cell count (P=0.009), those with a higher viral load (P=0.006) and those using treatment for tuberculosis (P<0.001). This confirms the findings of other studies, where lower CD4 cell counts (Tagliati et al, 1999 & Hewitt et al, 1997), higher viral loads (Brinley et al, 2001) and male gender (Tagliati et al, 1999) were significantly associated with a higher prevalence of polyneuropathy. Simpson et al, 2002, found a significant, albeit weak association between plasma viral load and the severity of peripheral neuropathy. Previous research also found Caucasian race and older age to be significantly associated with an increased prevalence of polyneuropathy (Tagliati et al, 1999). The present study did not find a significant difference in prevalence amongst different age groups. Race was not included in the questionnaire. The association between the use of certain anti-tuberculous drugs, such as INH and painful peripheral neuropathy, is well known (Wilson et al, 2002). It is therefore not unexpected that use of tuberculosis treatment was associated with a higher pain prevalence of POPNO.

Intensity of pain of predominantly neuropathic origin

Several studies indicated that pain management in HIV patients is inadequate (Stephenson, 1996; Larue et al, 1997; Breitbart et al, 1996b; Breitbart et al, 1998). One of the reasons cited for this was the underestimation of the severity of pain, by medical practitioners (Larue et al, 1997). In a study of Larue et al, 1997, it was found that clinicians had underestimated pain severity in 52% of HIV patients reporting pain. Of note is, that it was pain in the moderate and severe range that was most likely to be underestimated. One of the objectives of the present study was to increase awareness amongst clinicians, of the severity and impact of neuropathic pain in AIDS patients. This could potentially lead to improved management of this pain. For this reason, all patients with POPNO were asked to rate how they experience this pain, at its worst and on average.

A large percentage of patients (41.9%), experienced their "worst pain" as severe (rating of 8-10), while only 12.2% found that their POPNO was never more than a mild pain (rating of 1-3). The mean score for "worst pain" was 6.31 (±2.57) and the median 5.5.

Pain studies on HIV patients by Larue et al, 1997 & Cleeland et al, 1994, regarded "worst pain", that was rated as 5 or above, as substantial pain, because studies prior to these have shown that patients with a worst pain rating of ≥ 5, on a 0-10 scale, report disproportionately more functional impairment.

In the present study, 59 out of 74 (79.7%) POPNO patients rated their worst pain as 5 or higher and could therefore be regarded as having substantial pain. This is disturbing, considering the fact that fewer than a third of patients (29.7%), could remember having an analgesic prescribed for their pain, in the previous month, by a medical practitioner. It was,

however, beyond the scope of this study to determine what percentage of these patients had actually consulted a health care practitioner in the previous month. The problem of the under-treatment of pain related to HIV and AIDS, has been noted in several studies. Breitbart et al, 1996b found that 85% of ambulatory AIDS patients in their sample, received inadequate analgesia (based on WHO guidelines for analgesic therapy). Of the patients whose pain-severity warranted opioid analgesics, only 7% received these Research done by Breitbart et al, 1999 highlighted several barriers to adequate pain management in patients with AIDS and other chronic diseases, some relating to patient factors and others to the clinician or the health care system. One reason is under-diagnosis of painful conditions or under-estimation of the severity thereof. This may be the result of doctors focusing most of their attention on antiretroviral treatment and reversing opportunistic infections. In the busy primary care setting, little time is left for the management of symptoms. Both physicians and patients may have fears regarding the development of tolerance to the analgesia, as well as the addiction potential and side effects of opioid medication.

A French study of general pain in HIV patients by Larue et al, 1997, found that 16% of their out-patients and 51% of their in-patients had substantial pain (worst pain level ≥5). Cleeland et al, 1994 found that sixty two percent of patients with metastatic cancer, in the USA, scored their worst pain as 5 or higher, using the BPI. The substantial pain percentage in the present study was higher than in both of these studies, which suggests high levels of pain severity with neuropathic pain in AIDS patients. This is consistent with a United Kingdom chronic POPNO study within the general population by Smith et al, 2007, where the group with chronic POPNO reported higher pain severity and more pain-related interference than the non-POPNO group with chronic pain. Another study, however, of frequent or persistent pain of any type, in ambulatory AIDS patients in New York City, found that 48.7% of their sample reported their pain as severe (rating 8-10), with a mean worst pain intensity of 7.2 (2.1) (Breitbart et al, 1998). This suggests a similar pain severity in patients with POPNO or general HIV-related pain. These differences may relate to the different populations tested. More evidence is required in this regard.

The "worst pain" scores in the present study are similar to those found in other neuropathic pain studies. Torrance et al, 2006 reported a median pain severity score of 7.0 in the chronic POPNO study, within the general population, in the United Kingdom, while the mean worst pain severity score in studies of post-herpetic neuralgia and several studies of diabetic peripheral neuropathy were 6.0 (±2.4), 5.6 (±2.8) and 6.9 (±2.4) respectively (Galer et al, 2000; Oster et al, 2005; Gore et al, 2005). Other neuropathic pain studies used a pain severity index score, derived from the least, average, worst and current pain, and can

therefore not be used for comparison with the present study (Galer et al, 2000 & McDermott et al, 2006).

For "average pain", most patients (73.0%) experienced the pain as mild. Many of the respondents found the concept of average pain difficult to understand and it is likely that many of the "average pain" ratings, were in actual fact ratings of pain at its least. Even then, over 25% of patients experienced their average POPNO as moderate or severe. Twelve out of 74 patients (16.2%) indicated a score of 5 or higher for average pain.

Impact of POPNO

POPNO patients were asked to rate the degree to which their pain of predominantly neuropathic origin, affected six aspects of their daily living. The greatest degree of pain-related interference was reported for "enjoyment of life" (mean rating 4.25 ±3.30), "mood" (mean rating 4.23 ±3.45) and "ability to work" (mean rating 4.01 ±3.59). At least 25% of the POPNO patients experienced severe pain-related interference for these three aspects of functioning. In addition, almost one quarter of patients found that their sleep was severely affected by the pain (mean rating 3.61 ±3.53).

In a study by Oster et al, 2005 of patients with post-herpetic neuralgia, enjoyment of life, mood and sleep were most affected, with mean interference ratings of 4.5 (±3.1), 4.3 (±2.9) and 3.8 (±2.9) respectively. The interference ratings in this study are strikingly similar to those of the present study. Interference with sleep has been found to be among the most common pain-related problems reported by patients with neuropathic pain (Jensen et al, 2007).

When using the BPI, the seven pain interference subscales may be averaged to provide an overall measure of pain-related functional interference (Breitbart et al, 1996b). Studies of neuropathic pain in general, as well as trigeminal neuralgia and diabetic peripheral neuropathy, found overall pain-related interference scores of 4.5, 5.9 and >5 (range 0-10), respectively (Galer at al, 2000; McDermott et al, 2006; Tölle et al, 2006). Several USA studies of general pain in patients with HIV, found overall pain interference scores of 4.38 and 6.1 (range 0-10) (Breitbart et al, 1996b & Breitbart et al, 1998). The overall pain-related interference for the six items, adapted from the BPI, in the present study, was 3.6 (range 0-10).

The fact that patients with POPNO, in the present study, reported a lower overall pain-related interference than HIV patients with general pain, was unexpected. Limited evidence suggests that patients with chronic neuropathic pain have poorer scores for pain-interference items than non-POPNO chronic pain (Smith et al, 2007). One reason for the lower interference

scores in the present study could be due to the sampling in this study. It is possible that some of the most ill and disabled patients were unable to get to the HIV clinic, since most of the community served by this hospital are dependent on public transport. A further contributing factor could be cultural differences in how patients perceive and express pain-related interference.

The six domains of daily functioning may be classified into physical functioning (walking, sleeping), emotional functioning (mood, enjoyment of life) and role and social functioning (ability to work, relations with other people). A similar classification was used in a review of Jensen et al, 2007, which examined the impact of neuropathic pain on health-related quality of life.

The severity of pain of predominantly neuropathic origin was significantly associated with greater interference in each of the domains of daily functioning ($P<0.001$ for all, except relations with others). Relations with other people, however, correlated the least with pain severity ($P=0.01$). This confirms the findings of several previous studies, where increasing pain intensity was significantly associated with greater impairment in functional ability in several domains of daily living (Breitbart et al, 1996a & Gore et al, 2005). In a review of the impact of neuropathic pain on quality of life, by Jensen et al, 2007, patients reported less impact on social relationships than on other domains of functioning. It is possible that these patients, who are generally more dependent on other people due to their respective diseases, avoid contemplating the possibility that their pain might negatively influence these valuable relationships. Alternatively, the disability caused by the pain, may, in many cases, evoke greater caring by other people, leading to improved relationships between the patient and their social support persons.

Symptoms and signs of POPNO

Burning pain (82%), pins and needles paresthesia (78%), itching (69%) and numbness (68%) were the commonest symptoms experienced by patients identified, by the DN4, as having POPNO.

A Swedish study by Martin et al, 2003 of peripheral neuropathy in HIV-infected patients had similar findings, with numbness (75%), pins and needles (70%) and burning pain (65%) being the commonest symptoms in patients with painful peripheral neuropathy.

These findings concur with much of the literature, where burning pain, pins and needles paresthesia and numbness are the commonest symptoms of peripheral neuropathy (Bouhassira et al, 1999 & Verma at al, 2005).

A focused neurological examination revealed that the majority of POPNO patients had a minimum of three neurological abnormalities. However, 8.1% of POPNO patients had no objective neurological abnormality. This indicates that, while most patients with neuropathic pain can be expected to have some evidence of this on neurological examination, a small percentage have symptoms, but no signs of this condition. This is confirmed by the work of Backonja et al, 1998, who state that, "the lack of physical findings does not rule out the presence of neuropathic pain".

Abnormal pinprick sensation (73.0%) and tactile sensation (68.9%), both in which the sensation was more frequently decreased, were the commonest findings on the neurological examination. This was followed by decreased or absent vibration sense in 62.1% of POPNO patients. Findings of other studies of peripheral neuropathy or DSP, demonstrated impaired tactile and pinprick sensation in between 71% and 100% of patients (Tagliati et al, 1999 & Martin et al, 2003). Other researchers, including those from a Kenyan study by Mbuya et al, 1996, found vibration sense diminished or absent in 60-65% of cases of peripheral neuropathy. One of these studies demonstrated reduced or absent ankle reflexes in 66% (Tagliati et al, 1999). The present study found diminished ankle reflexes in fewer cases (39.4%). This might relate to technical difficulty in eliciting this sign, because patients with substantial pain found the testing for distal reflexes very uncomfortable.

Clinical descriptions of HIV related peripheral neuropathy in the literature frequently allude to evoked pain, such as when touching bed sheets, wearing shoes and walking (Polydefkis, 2002). It would therefore be expected that allodynia would be a common finding in these patients with POPNO, largely due to peripheral neuropathy. In this study, while static mechanical allodynia (evoked by a pressure stimulus) occurred quite frequently, in 47.3%, dynamic mechanical allodynia (evoked by a moving stimulus) was present in only 18.9%. This concurs with a French study of HIV related peripheral neuropathy by Bouhassira et al, 1999, where static mechanical allodynia was common, while dynamic allodynia was elicited in only 20%. It has been suggested in the literature that the static and dynamic sub-types of mechanical allodynia involve different neural mechanisms (small versus large afferent fibres and peripheral versus central sensitisation, respectively) (Tagliati et al, 1999). This may have implications regarding treatment of HIV related POPNO, which could be mechanism-based.

Strengths and limitations of the study

The demographic characteristics of the sample were compared with those of the general patients attending the Kalafong HIV clinic. Their similarity indicated that there were unlikely to be any important sampling biases amongst the patients who attended the clinic.

Representation in this sample was limited to patients with AIDS, who were both willing and able to attend this particular public health facility for ARV therapy. It therefore excluded those who do not wish to use ARV therapy, or who were unable to attend the facility due to physical disabilities and/or socio-economic factors. This could have resulted in a disproportionate number of patients who are most impacted upon by AIDS, being excluded from the sample. Furthermore, the sample was restricted to patients who are reliant on public health care and those patients not yet using antiretroviral therapy. Further research should be done, involving more varied populations and patients on ARV therapy, to determine the influence of antiretroviral therapy on the prevalence of neuropathic pain in patients with AIDS. The widely-used NRTI's, such as didanosine and stavudine are well known to sometimes cause a painful sensory neuropathy (Brinley et al, 2001).

Certain participants found it difficult to distinguish between functional interference by the POPNO and that due to other pain or physical impairments. In these cases, scoring of certain of the interference items was omitted.

A further limitation could be that the study relied, to a large extent, on self-report data, at a single point in time. It is, however, unlikely that patients would have purposefully exaggerated their pain or pain-related interference, since no additional treatment was offered in connection with the study, other than expediting a referral to the HIV clinic doctor in the case of acute problems. Furthermore, the researcher-administered questionnaire enabled respondents to motivate their replies, indicating their understanding of the instruction and thus improving the validity of the results.

Summary of discussion

- A prevalence of 20.9% was found for POPNO, in patients with AIDS, in this study.
- POPNO was significantly more likely in male patients, patients with a lower CD4 cell count and a higher viral load and those using treatment for tuberculosis.
- The majority of POPNO patients (79.7%) experienced substantial pain (worst pain severity rating ≥5 out of 10) and even average pain was reported as moderate or severe in 25% of patients.
- POPNO severity in the present study concurred with that in other studies of neuropathic pain syndromes.
- There is limited evidence, from this and other studies, that POPNO is experienced as more severe than other AIDS-related pain and even cancer pain.
- Aspects of daily living most impacted upon by POPNO are enjoyment of life, mood and the ability to work.
- Pain-related interference is significantly correlated with the severity of POPNO for all aspects of daily living.
- While the severity of POPNO in the present study was as severe as that in other neuropathic pain or POPNO studies, the overall pain-related interference score was lower than that in other neuropathic pain studies.
- This and other studies of neuropathic pain, indicate that burning pain, pins and needles and numbness are generally the most frequent symptoms of neuropathic pain.
- While most patients with POPNO exhibit several neurological abnormalities in the area of their pain, a small group of POPNO patients show no objective neurological findings.
- Abnormalities in tactile and pinprick sensation and vibration sense are the most frequent examination findings in this and other studies of peripheral neuropathy.

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

This study demonstrates a substantial patient burden, relating to pain of predominantly neuropathic origin, in patients with AIDS, prior to the use of ARV therapy.

The presence, but not the severity, of the pain of predominantly neuropathic origin, is associated with male patients, lower CD4 cell count levels, higher viral load levels and patients using treatment for tuberculosis.

In the light of this, clinicians treating patients with AIDS should actively screen for symptoms of neuropathic pain. Typical symptoms of neuropathic pain, as found in this study, include burning pain, pins and needles paresthesia, numbness, or itching in the area of pain. A brief neurological examination may help to verify the diagnosis, however, positive neurological signs may not be found in every case of neuropathic pain. Clinicians are often faced with limited consultation time. In this situation, the neurological examination may be restricted to testing for impairment of tactile or pinprick sense and vibration sense, since these aspects are the most likely to yield positive results.

The majority of patients with neuropathic pain, in this study, experienced substantial pain (worst pain severity ≥ 5 out of 10). This substantial pain not only leads to significant patient suffering, but also affects their quality of life, in particular, their mood, enjoyment of life and ability to work. A strong correlation between the severity of the pain and interference with aspects of daily living was demonstrated.

The results of this study indicate the need for meticulous pain assessment and management in patients with AIDS, which in turn, should lead to improved quality of life for patients and keeping them economically active. In this regard, clinicians need to be optimally informed regarding the current guidelines for the management of neuropathic pain. This can be achieved by making short seminars or training courses on pain available to doctors. These training sessions should cover subjects such as the identification, assessment and appropriate management of neuropathic pain. The results of this study will also be submitted for publication, with the objective of informing clinicians about neuropathic pain in patients with AIDS.

Unlike nociceptive pain, neuropathic pain requires a different approach, with particular emphasis on adjuvant drugs, in addition to non-opioid and opioid analgesics. The effectiveness of tricyclic antidepressants (TCA's), anticonvulsants, in particular the $\alpha 2$-δ ligands, such as gabapentin and pregabalin and the serotonin and noradrenaline reuptake

2007). Both the primary care physician and palliative care clinicians, have a vital role to play in this regard.

REFERENCES

1. Attal N, Bouhassira D 2004, 'Can pain be more or less neuropathic?', *Pain,* vol.110, pp. 510-511.
2. Backonja MM, Galer BS 1998, 'Pain assessment and evaluation of patients who have neuropathic pain', *Neurology Clinics,* vol.16, no.4, pp. 775-790.
3. Bateman C 2007, '"Opi-phobia" among doctors leads to unnecessary suffering.', *South African Medical Journal, vol.* 97, no.6, pp. 399-404.
4. Belgrade MJ 1999, 'Following the clues to neuropathic pain: distribution and other leads reveal the cause and the treatment approach', *Postgraduate Medicine, vol.* 106, no.6, pp. 127-140.
5. Bennet M 2001, 'The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs', *Pain, vol.* 92, pp. 147-157.
6. Bennett MI, Smith BH, Torrance N, Potter J 2005, 'The S-LANSS Score for identifying Pain of predominantly neuropathic origin: Validation for use in clinical and postal research', *The Journal of Pain, vol.* 6, no.3, pp. 149-158.
7. Berger AR, Arezzo JC, Schaumburg HH, Skowron G, Merigan T, Bozette S 1993, '2',3'-dideoxycytidine (ddc) toxic neuropathy: a study of 52 patients', *Neurology, vol.* 43, pp. 358-362.
8. Bouhassira D, Attal N, Willer JC, Brasseur L 1999, 'Painful and painless peripheral sensory neuropathies due to HIV infection: A comparison using quantitative sensory evaluation', *Pain, vol.* 80, pp. 265-272.
9. Bouhassira D, Attal N, Alchaar H, et al 2005, 'Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)', *Pain,* vol.114, pp. 29-36.
10. Breitbart W, Rosenfeld BD, Passik SD, McDonald MV, Thaler H, Portenoy RK 1996b, 'The under treatment of pain in ambulatory AIDS patients', *Pain, vol.* 65, pp. 243-249.
11. Breitbart W, McDonald MV, Rosenfeld BD, et al 1996a, 'Pain in ambulatory AIDS patients. I Pain characteristics and medical correlates', *Pain, vol.* 68, no. 2-3, pp. 315-321.
12. Breitbart W, Passik S, McDonald MV et al 1998, 'Patient-related barriers to pain management in ambulatory AIDS patients', *Pain, vol.* 76, pp. 9-16.
13. Breitbart W, Kaim M, Rosenfeld B 1999, 'Clinicians' Perceptions of Barriers to Pain Management in AIDS', *Journal of Pain and Symptom Management, vol.* 18, no. 3, pp. 203-212.
14. Brinley FJ, Pardo CA, Verma A 2001, 'Human Immunodeficiency Virus and the Peripheral Nervous System Workshop', *Archives of Neurology, vol.* 58, pp. 1561-1566.

15. Brunton S 2004, 'Approach to the assessment and diagnosis of chronic pain', *Journal of Family Practice, vol.* 53, no.10 suppl, pp. 3-10.
16. Centers for Disease Control 1992, '1993 Revised classification system for HIV infection and Expanded Surveillance Case Definition for AIDS among adolescents and adults', *MMWR (Morbidity and mortality weekly report), vol.* 41, no. RR17, pp. 1-19.
17. Cherry CL, Wesselingh SL, Luxshimi L, McArthur JC 2005, 'Evaluation of a clinical screening tool for HIV-associated sensory neuropathies', *Neurology, vol.* 65, no.11, pp. 1778-1781.
18. Cleeland CS, Gonin R, Hatfield AK et al 1994, 'Pain and its treatment in outpatients with metastatic cancer' *New England Journal of Medicine, vol.* 330, pp. 592-596.
19. Cole JW, Pinto AM, Hebel JR et al 2004, 'Acquired immunodeficiency syndrome and the risk of stroke', *Stroke, vol.* 35, no.1, pp. 51-56.
20. Cruccu G, Anand P, Attal N, et al 2004, 'EFNS guidelines on neuropathic pain assessment', *European Journal of Neurology, vol.* 11, pp.153-162.
21. Daut RL, Cleeland CS, Flanery RC 1983, 'Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases', *Pain, vol.* 17, pp. 197-210.
22. Dworkin RH, Backonja M, Rowbotham MC et al 2003, 'Advances in neuropathic pain', *Archives of Neurology, vol.* 60, pp. 1524-1534.
23. Dworkin RH, O'Connor AB, Backonja B et al 2007, 'Pharmacologic management of neuropathic pain: evidence-based recommendations', *Pain, vol.* 132, pp. 237-251.
24. Estanislao L 2003, 'Abstracts of the 5th International symposium of Neurovirology, Molecular and Clinical Neuroscience Workshop', Baltimore, *Journal of Neurovirology, vol.* 9, no. 3 Suppl, pp. 1-149.
25. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH 2005, 'Algorithm for neuropathic pain treatment: An evidence based proposal', *Pain, vol.* 118, pp. 289-305.
26. Fischoff DK, Sirois DA, Raphael KG, Marbach JJ, Kloser P 1995, 'Orofacial neuropathic pain in patients with HIV infection', *Oral surgery, oral medicine, oral pathology, oral radiology and endodontics, vol.* 87, no. 4, pp. 458-459.
27. Galer BS, Jensen MP 1997, 'Development and preliminary validation of a pain measure specific to neuropathic pain: The neuropathic Pain Scale', *Neurology, vol.* 48, no.2, pp. 332-338.
28. Galer BS, Gianas A, Jensen MP 2000, 'Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life', *Diabetic Research Clinical Practice, vol.* 47, pp. 123-128.

29. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B 2005, 'Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep', *Journal of Pain and Symptom management, vol.* 30 no. 4, pp. 374-385.
30. Hewitt DJ, McDonald M, Portenoy RK, Rosenfeld B, Passik S, Breitbart W 1997, 'Pain syndromes and aetiologies in ambulatory AIDS patients', *Pain, vol.* 70, no. 2-3, pp. 117-123.
31. Holdcroft A, Jaggar S (Editors) 2005, 'Nerve damage and its relationship to neuropathic pain', *Core Topics in Pain,* Cambridge University Press, pp. 43-47 and 71-77.
32. IASP task force on taxonomy 1994, '*Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms',* second edition, Mersky H, Bogduk N (Editors), Seattle, IASP Press, pp. 209-214.
33. Jensen MP 2005, 'Using pain quality assessment measures for selecting analgesic agents', *Clinical Journal of Pain, vol.* 22, pp. S9-S13.
34. Jensen MP, Chodroff MJ, Dworkin RH 2007, 'The impact of neuropathic pain on health-related quality of life', *Neurology, vol.* 68, pp. 1178-1182.
35. Katz N 2000, 'Neuropathic pain in AIDS and cancer', *The Clinical Journal of Pain, vol.* 16, no. 2 suppl, pp. 41-48.
36. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS 2004, 'Validity of the Brief Pain inventory for use in documenting the outcomes of patients with non-cancer pain', *The Clinical Journal of Pain, vol.* 20, no. 5, pp. 309-318.
37. Keswani SC, Pardo CA, Cherry CL, Hoke A, McArthur JC 2002, 'HIV-associated sensory neuropathies', *AIDS, vol.* 16, no.16, pp. 2105-2117.
38. Krause SJ, Backonja MM 2003, 'Development of a Neuropathic Questionnaire', *The Clinical Journal of Pain, vol.* 19, no. 5, pp. 306-314.
39. Larue F, Fontaine A, Colleau SM 1997, 'Underestimation and under treatment of pain in HIV disease: multicentre study', *British Medical Journal, vol.* 314, pp. 23-28.
40. Lebovits AH, Lefkowitz M, McCarthy D et al 1989, 'The prevalence and management of pain in patients with AIDS: a review of 134 cases', *The Clinical Journal of Pain*; vol. 5, pp. 245-8.
41. Martin C, Solders G, Sonnerborg A, Hansson P 2003, 'Painful and non-painful neuropathy in HIV-infected patients: an analysis of somatosensory function', *European Journal of Pain, vol.* 7, no.1, pp. 23-31.
42. Mbuya SO, Kwasa TO, Amayo EO, Kioy PG, Bhatt SM 1996, 'Peripheral neuropathy in AIDS patients at Kenyatta National Hospital', *East African Medical Journal, vol.* 73, no. 8, pp. 538-540.

43. McDermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM 2006, 'The burden of neuropathic pain: results from a cross-sectional survey', *European Journal of Pain, vol.* 10, no. 2, pp. 127-135.
44. Meyer HP 2007, 'Pain management in primary care- current perspectives', *South African Family Practice, vol.* 49, no. 7, pp. 20-25.
45. Morgello S, Estanislao L, Simpson D, Geraci A, DiRocco A, Gerits P, et al 2004, 'HIV-associated distal sensory polyneuropathy in the era of Highly Active Antiretroviral Therapy', *Archives of Neurology, vol.* 61, pp. 546-551.
46. Nakasujja N, Musisi S. Robertson K, Wong M, Saktor N, Ronald A 2005, 'Human immunodeficiency virus neurological complications: An overview of the Ugandan experience', *Journal of Neurovirology, vol.* 11, no. 3 Suppl, pp. 26-29.
47. Norval DA 2004, 'Symptoms and sites of pain experienced by AIDS patients', *South African Medical Journal, vol.* 94, pp. 450-454.
48. O'Neill WM, Sherrard JS 1993, 'Pain in human immunodeficiency virus disease: a review', *Pain, vol.* 54, pp. 3-14.
49. Ong KS, Seymour RA 2004, 'Pain measurement in humans', *Journal of the Royal College of Surgeons of Edinburgh and Ireland, vol.* 2, no.1, pp. 15-27.
50. Oster G, Harding G, Dukes E, Edelsberg J, Cleary PD 2005, 'Pain, medication use, and health-related quality of life in older persons with post-herpetic neuralgia: results from a population-based survey', *The Journal of Pain, vol.* 6, no. 6, pp. 356-363.
51. Polydefkis MJ, 'The Hopkins HIV Report: Peripheral neuropathy and HIV', http://www.hopkins-aids.edu/publications/report/july02_4.html
52. Portenoy RK 1996, 'Opioid therapy for chronic nonmalignant pain: clinicians' perspective', *Journal of Law, Medicine and Ethics, vol.* 24, pp. 296-309.
53. Poundja J, Fikretoglu D, Guay S, Brunet A 2007, 'Validation of the French version of the Brief Pain Inventory in Canadian veterans suffering from traumatic stress', *Journal of Pain and Symptom Management, vol.* 33, no. 6, pp. 720-726.
54. Prins M, Robertson JR, Brettle RP et al 1999, 'Do gender differences in CD4 cell counts matter?', *AIDS, vol.* 13, no.17, pp. 2361-2364.
55. Rehle T, Shisana O, Pillay V, Zuma K, Puren A, Parker W 2007, 'National HIV incidence measures- new insights into the South African epidemic', *South African Medical Journal, vol.* 97, no. 3, pp. 194-199.
56. Schiffito G, McDermont MP, McArthur JC et al 2002, 'Incidence of and risk factors for HIV associated distal sensory polyneuropathy', *Neurology, vol.* 58, pp. 1764-1768.
57. Schofferman J, Brody R 1990, 'Pain in far advanced AIDS', *Advances in Pain Research and Therapy, vol.* 16, pp. 379-386.
58. Simpson DM, Haidich AB, Schifitto G et al 2002, 'Severity of HIV-associated

neuropathy is associated with plasma HIV-1 RNA levels', *AIDS, vol.* 16, pp. 407-412.

59. Simpson DM, McArthur JC ,Olney R et al 2003, 'Lamotrigine for HIV associated painful sensory neuropathies. A placebo-controlled trial', *Neurology, vol.* 60, pp. 1508-1514.
60. Singer EJ, Zorilla C, Fahy-Chandon B, Chi S, Syndulko K, Tourtellotte WW 1993, 'Painful symptoms reported by ambulatory HIV-infected men in a longitudinal study', *Pain, vol.* 54, pp. 15-19.
61. Smith BH, Torrance N, Bennett MI, Lee AJ 2007, 'Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community', *Clinical Journal of Pain, vol.* 23, no. 2, pp. 143-149.
62. So YT, Holtzman DM, Abrams DI, Olney RK 1988, 'Peripheral neuropathy associated with acquired immunodeficiency syndrome. Prevalence and clinical features from a population-based survey', *Archives of Neurology, vol.* 45, no. 9, pp. 945-948.
63. Stephenson J 1996, 'Experts say AIDS pain "dramatically undertreated" ', *JAMA, vol.* 276, no.17, pp. 1369-1370.
64. Tagliati M, Grinell J, Godbold J, Simpson DM 1999, 'Peripheral nerve function in HIV infection: clinical, electrophysiologic and laboratory findings', *Archives of Neurology, vol.* 56, pp. 84-89.
65. Tölle T, Dukes E, Sadosky A 2006, 'Patient burden of trigeminal neuralgia: results of a cross-sectional survey of health state impairment and treatment patterns in six European countries', *Pain Practice, vol.* 6, no. 3, pp. 153-160.
66. Torrance N, Smith BH, Bennett MI, Lee AJ 2006, 'The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey', *The Journal of Pain, vol.* 7, no. 4, pp. 281-288.
67. Turk DC, Melzack R (Editors) 1992, *Handbook of Pain Assessment,* Guildford Press, New York, pp. 3-14 and 111-168
68. Verma S, Estanislao L, Simpson D 2005, 'HIV-associated Neuropathic Pain', *CNS Drugs, vol.* 19, no. 4, pp. 325-334.
69. Watters MR, Poff PW, Shiramizu BT et al 2004, 'Symptomatic distal sensory polyneuropathy in HIV after age 50', *Neurology, vol.* 62, pp. 1378-1383.
70. White S 2004, 'Assessment of chronic pain and the use of pain tools', *British Journal of Nursing, vol.* 13, no. 7, pp. 372-378.
71. Wilson D, Naidoo S, Bekker LG, Cotton M, Maartens G, (Editors) 2002, *Handbook of HIV Medicine,* Oxford University Press, Southern Africa, pp. 140-156 and 174-187.
72. World Health Organisation 1986, '*Cancer Pain Relief',* 1st Ed, Geneva, World Health Organisation.

73. Zelman DC, Gore M, Dukes E, Tai KS, Brandenburg N 2005, 'Validation of a modified version of the Brief Pain Inventory for painful diabetic peripheral neuropathy', *Journal of Pain and Symptom Management, vol.* 29, no. 4, pp. 401-409.

APPENDIX 1

Patient Information Document

Research study of physical problems in patients requiring ARVs

Dear Sir/Madam

1. *Dr Sonia Hitchcock is a family physician who works in the Kalafong Family Medicine Clinic and the Kalafong Immunology Clinic (ARV Clinic). She is presently doing research as part of a master's degree in palliative medicine. You are invited to be part of this research study.*

2. *Nature and purpose of the study:*

   This research involves certain physical problems in patients requiring antiretroviral medication (ARV's). It is anticipated that by knowing more about these physical problems, doctors will be able to diagnose and treat these problems more effectively.

3. *Procedures to be followed:*

   This study involves answering a standard set of questions regarding certain of your physical problems. Depending on your physical problem(s), you may have to have a short examination of the feeling (sensation) and movement of your limbs. The questioning and the examination will be done by the researcher (Dr Sonia Hitchcock), with the help of a translator, where necessary. It will take between 5 and 20 minutes.

   Your CD4 cell count which appears on your referral letter for this clinic, will be recorded. The result of one other blood test, your viral load, which is routinely tested before you start to use ARV medication, will be recorded later on. This will be obtained from you hospital file once the result is available.

   You will be asked, at the end of the interview/ examination, whether the problem that you indicated should be documented by the researcher in your hospital file, so that the Immunology Clinic doctor can attend to it.

4. *Risk and discomfort involved:*

   The only discomfort involved is for certain participants whose skin sensation will be tested using mild pinpricks.

5. *Voluntary participation:*

   Participation in this study is entirely voluntary and your willingness to participate or not will have no influence on the treatment you receive in this clinic.

6. *Confidentiality:*

   All information obtained from you for this study will be regarded as confidential. No patient's name will be used in any presentation or publication of the results of the research.

7. *Once the results of this research have been collected and analysed, it may be written up in the form of a scientific article and published in a scientific or medical journal.*

8. *Information:*

   If you have any questions concerning this study, please contact Dr Sonia Hitchcock at
   Tel: 012 318 6814

   Cell: 082 579 5057

Should you be willing to take part in this research, please sign the consent form on the following page or ask the research assistant, who handed you this form, for assistance.

APPENDIX 2

Authorisation to Participate in a Research Project

Title of study:

Research study of physical problems in patients requiring ARVs

1. ***Nature and purpose of the study***

   I understand that I am being asked to take part in a research study. The aim of the study is to evaluate certain physical problems in patients requiring antiretroviral medication (ARV's). By doing so we hope to learn more about these physical problems, so that doctors will be able to diagnose and treat these problems more effectively.

2. ***Explanation of procedures to be followed***

   This study involves answering a standard set of questions regarding certain of your physical problems. Depending on your particular physical problem(s), you may have to have a short examination of the feeling (sensation) and movement of your limbs. The questioning and the examination will be done by the researcher (Dr Sonia Hitchcock), with the help of a translator, where necessary. It will take between 5 and 20 minutes.

   Your CD4 cell count which appears on your referral letter for this clinic, will be recorded.

   You will be asked, at the end of the interview/ examination, whether the problem you indicated should be documented, by the researcher, in your hospital file, so that the HIV Clinic doctor can attend to it.

3. ***Risk and discomfort involved***

   The only discomfort involved is for certain participants where the feeling (sensation) in the skin will be tested using mild pinpricks.

4. ***I understand that if I do not want to partake in this study, I will still receive standard treatment for my illness.***

5. ***Confidentiality***

   All information obtained from you, for this study, will be regarded as confidential. Results will be presented or published in such a fashion that patients remain unidentifiable.

6. ***Information***

If you have any questions concerning this study, please contact Dr Sonia Hitchcock at
Tel: 012 318 6814

Cell: 082 579 5057

7. ***Consent to participate in this study***

I have read or had read to me, in a language that I understand, the above information, before signing this consent form. The content and meaning of the information was explained to me. I have been given the opportunity to ask questions and am satisfied that these have been answered satisfactorily. I understand that if I do not participate, it will not alter my management in any way. I hereby volunteer to take part in this study:

---------- ----------

Patient *Date*

---------- ----------

Person obtaining informed consent *Date*

---------- ----------

Witness *Date*

Verbal patient informed consent (where patients are unable to read or write)

I, the undersigned, Dr _____, have read and have explained fully to the patient, named _____ and/or his/her relative, the patient information leaflet, which has indicated the nature and purpose of the research study, in which I have asked the patient to participate. The explanation I have given has mentioned both the possible risks and benefits of the study. The patient indicated that he/she understands that he/she will be free to withdraw from the study at any time, for any reason.

I hereby certify that the patient has agreed to participate in this trial:

Patient's name _____

Investigator's name _____

Investigator's signature _____

Witness's name _____ Date _____

Witness's signature _____ Date _____

APPENDIX 3

Questionnaire

SECTION A: QUESTIONNAIRE INFORMATION

Questionnaire number:		/record
File number		/file

SECTION B: DEMOGRAPHIC INFORMATION OF PATIENT

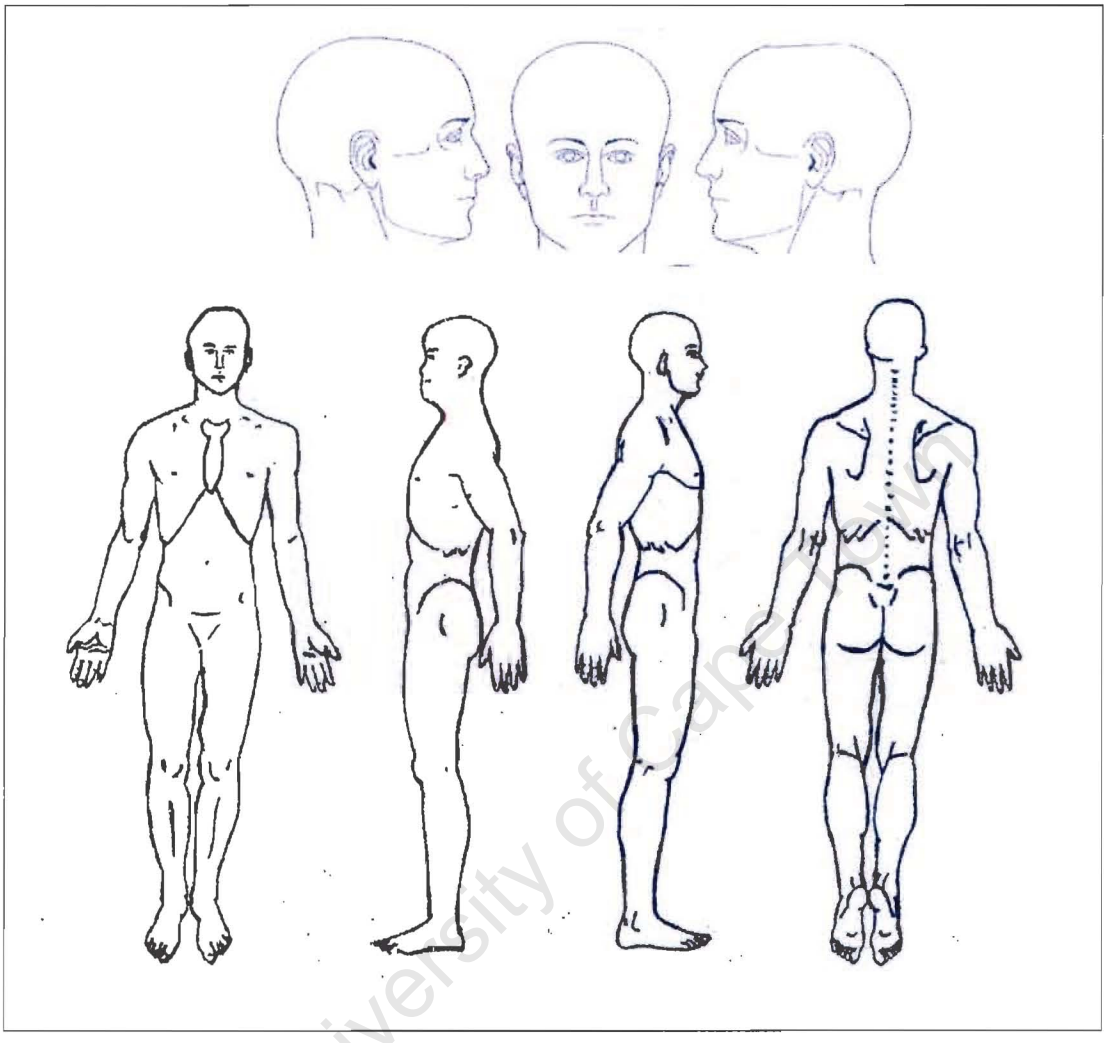
1. Gender:	Male	1	
	Female	2	/1
2. Age:			/2
3. CD4 cell count:			/3
4. Viral load			/4
5. Have you used any treatment for tuberculosis in the past two weeks?	Yes	1	
	No	2	/5

SECTION C: PAIN PREVALENCE

6. During the past two weeks, have you experienced any pain that has troubled you a lot?	Yes, I have a problem with pain	1	
	No, I do not have a problem with pain	2	/6

SECTION D: DISTRIBUTION AND TYPE OF PAIN

7. In the diagram, please shade in the areas where you feel pain. Put an X on the area that hurts the most.



Head- scalp	1
Headache ★	2
Face, eye,ear	3
Mouth ★	4
Neck	5
Odynophagia ★	6
Chest	7
Back- spinal	8
Back- muscle	9

Abdomen	10
Perineal	11
Perianal	12
Upper limb- joint ★	13
Upper limb- other	14
Lower limb- joint ★	15
Lower limb- other	16
Feet	17

SECTION E: DN4 QUESTIONS

		Yes	No	
9(a) Do any of your pains feel like any of the following descriptions?	i) Burning	1	0	/8.1
	ii) Painful cold	1	0	/8.2
	iii) Electric shocks	1	0	/8.3
9(b) Do you feel any of the following sensations in the painful area?	i) Tingling	1	0	/8.4
	ii) Pins and needles	1	0	/8.5
	iii) Numbness	1	0	/8.6
	iv) Itching	1	0	/8.7
9(c) Examination:	i) Hypoesthesia to touch (using cotton wool)	1	0	/8.8
	ii) Hypoesthesia to prick (using cocktail stick)	1	0	/8.9
	iii) Dynamic allodynia (brushing with cotton wool)	1	0	/8.10
	Total score			/8

Scoring:

All positive answers ('Yes') score 1, while negative answers ('No') score 0.

A total score of 4 or more out of 10 indicates pain which is predominantly neuropathic in origin.

The remainder of the questionnaire will be completed only by patients with a DN4 score of 4 or more.

Patients with more than one source of pain will be reminded that the questions that follow refer only to the pain that has been identified as the "neuropathic" pain.

SECTION F: FOCUSED NEUROLOGICAL EXAMINATION

All stimuli are to be applied first to an adjacent or contra lateral, non-painful area, and then to the painful area.

10. Tactile sense (using a cotton wool swab)	Same	1	/9
	Less intense	2	
	More intense	3	

11. Pinprick sense (using a cocktail stick)	Same	1	/10
	Less intense	2	
	More intense	3	

12. Vibration sense*:	Present	1	/11
	Decreased or absent	2	
	Non-applicable	3	

* Using a 128Hz tuning fork applied to the base of the big toe and medial malleolus and lateral wrist. Where the lower limbs are painful, big toe and medial malleolus vibration sense is compared with vibration sense in the upper limbs and vice versa.

13. Mechanical allodynia: Static*	No	1	/12
	Yes	2	

* Using blunt pressure with a finger tip that does not provoke pain in the normal area.

14. Mechanical allodynia: Dynamic*	No	1	/13
	Yes	2	

* Using a cotton wool swab brushed across the skin.

15. Thermal allodynia: (Using a tuning fork heated in water of 40°C)	Same	1	/14
	Less intense	2	
	More intense	3	

16. Thermal allodynia: (using a tuning fork cooled in water of 15°C)	Same	1	
	Less intense	2	
	More intense	3	/15

17. Distal muscle strength*	Normal	1	
	Distal muscles of painful area weaker	2	
	Non-applicable	3	/16

* Where the lower limbs are painful, the strength of big toe and ankle dorsiflexion is compared with finger spread, and vice versa).

18. Deep tendon reflexes	Same	1	
	Wrist or ankle reflex ↓	2	
	Non-applicable	3	/17

* Assess for a diminished or absent ankle or supinator reflex as compared to the knee or biceps brachii reflexes respectively).

SECTION G: TIMING OF THE PAIN

19. Would you describe your pain as continuous or intermittent?	Continuous	1	
	Intermittent	2	/18

20. How long have you had this pain?	Days	1	
	Weeks	2	
	Months	3	
	Years	4	/19

21(a) Was any medication prescribed for your pain in the past month (by your doctor, clinic or hospital)?	Yes	1	
	No	2	/20a
21(b) What medication?			/20b

22(a) What time of the day do you experience this pain?	Day only	1	
	Night only	2	
	Both day and night	3	/21a
22b) If both day and night:	Worse in the day	1	
	Worse at night	2	/21b

SECTION H: INTENSITY OF PAIN

23. Think about how bad your pain has been during the last week.

On a scale of 0 to 10 where 0 is "no pain" and 10 is "worst possible pain", where would you rate your pain:

a) **Pain at its worst**:

0--------1--------2--------3--------4--------5--------6-------7--------8--------9--------10 /22a

No pain Mild Distressing Severe Unbearable

b) **Pain on average**:

0--------1--------2--------3--------4--------5--------6-------7--------8--------9--------10 /22b

No pain Mild Distressing Severe Unbearable

SECTION H: IMPACT OF THE PAIN

(Adapted from the Brief Pain Inventory)

24. Think about how the pain has interfered with your life during the past week.

Using a scale of 0 to 10 where 0 is "does not interfere at all" and 10 is "interferes completely", please choose the number that best describes how much the pain has interfered with your:

a) **Walking ability**:

0--------1--------2--------3--------4--------5--------6-------7--------8--------9--------10 /23a

b) **Ability to work** (this includes housework and work outside the home):

0--------1--------2--------3--------4--------5--------6-------7--------8--------9--------10 /23b

c) **Sleep**:

0--------1--------2--------3--------4--------5--------6-------7--------8--------9--------10 /23c

d) **Relations with other people**:

0--------1--------2--------3--------4--------5--------6-------7--------8--------9--------10 /23d

e) **Mood** (e.g. how much sadness, anger, frustration or worry is caused by the pain):

0--------1--------2--------3--------4--------5--------6-------7--------8--------9--------10 /23e

f) **Enjoyment of life**:

0--------1--------2--------3--------4--------5--------6-------7--------8--------9--------10 /23f