PROJECT TITLE: The Morbidity associated with Painful Neuropathy in HIV-infected subjects on Anti-Retroviral Therapies: An assessment of self-management strategies.

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DECLARATION

Degree: Masters in Family Medicine

Dissertation title: The Morbidity associated with Painful Neuropathy in HIV-infected subjects on Anti-Retroviral Therapies: An assessment of self-management strategies.

I, Majedah Ismail (ISMMAJ001) declare that the work I have submitted is my own and where the work of others has been used (whether quoted verbatim, paraphrased or referred to) it has been attributed and acknowledged.

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Date: February 2010

ABSTRACT

Objective: To establish the frequency of anti-retroviral treatment (ART)-related distal sensory polyneuropathy in a community-based clinic. To identify the self-management strategies these subjects are using to cope with their pain, and the possible impact on therapeutic management.

Methods: A cross-sectional analysis was done of the patients attending the ART clinic at Woodstock Community Health Centre (CHC). During the three-month study period, 123 patients on anti-retroviral therapy were asked to answer the questionnaire and those who had painful feet, were then asked to complete questions about health- seeking behaviors. All participants were asked to complete questions about their health status and all were assessed with the Brief Peripheral Neuropathy Screen (BPNS). Based on the finding of the BPNS, subjects were divided into those with symptomatic distal sensory polyneuropathy (SDSP) and those without. SDSP was defined as the presence of any of the neuropathic symptoms in addition to one of the following; either reduced or absent ankle reflexes or abnormal vibration sense of ≤10 seconds at the great toes. Further data was obtained from patients by asking them to answer questions with regard to quality of life (QOL) as well depression.

Results: Almost one third of patients were diagnosed with SDSP. Of those affected, 73% had significant pain ranging from moderate to severe intensity. Many of these patients were using self-management strategies, such as paracetamol (68%), while close to a third of patients were also using activities such as massaging feet, soaking or elevating feet. A significant proportion of patients with symptomatic neuropathy experienced a negative impact on the following QOL categories; mobility, usual activities, pain or discomfort and anxiety or depression. Further, those with SDSP were also more likely to be unemployed.

Conclusions: Our results show that SDSP is a significant problem affecting patients' QOL and that those patients are not adequately treated for pain, hence seeking alternative management strategies. These strategies do not seem to adequately relieve pain and hence better pain management strategies need to be explored in primary care facilities.

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CHAPTER 1: INTRODUCTION

Distal symmetrical polyneuropathy (DSP) is the most frequent neurological complication associated with HIV infection, either as a result of the effects of the virus or from the toxicity of anti-retroviral therapy (ART) (Verma et al., 2005). DSP refers to a small fibre neuropathy that starts in the feet symmetrically, and can be painful; the latter is referred to as symptomatic DSP although it may also include patient experiencing "numbness" without painful neuropathic symptoms. Although HIV-infected patients may develop neuropathies other than a predominantly, small fibre painful neuropathy, these are uncommon in a community-based population (Treihaft, 2002). DSP occurs in over one-third of HIV-infected patients (HIV-DSP) from developed countries (Verma et al., 2005). In a South African community-based cohort the overall DSP frequency was noted to be 49%, whilst 39% of the study population was diagnosed with symptomatic DSP (SDSP). Of this group, 70% reported the pain or paresthesiae to be moderately severe (Maritz et al., 2010).

DSP occurs mainly in patients with advanced immunosuppression and may also be secondary to the neurotoxicity of several antiretroviral agents (Wulff et al., 2000). The nucleoside reverse transcriptase inhibitor (NRTI) class of ART is thought to play a prominent causative role in the development of anti-retroviral associated neuropathy (ATN) (Verma et al., 2005). The most toxic drugs of the NRTI class with respect to the development of ATN are the di-deoxynucleosides (d-drugs) such as zalcitabine, didanosine and stavudine (Cornblath & Hoke, 2006). Currently these d-drug NRTI agents make up the backbone of first-line ART in the developing world and are likely to remain as such due to its low cost coupled with the burden of HIV disease in sub-Saharan Africa.

Pain is generally often a neglected or poorly managed symptom by the health care profession. Standard treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen have no proven efficacy in neuropathic pain, whereas other drug classes, such as anti-epileptics and antidepressants, are more likely to be effective in neuropathic pain than in nociceptive pain (Haanpaa et al., 2009). Further, drugs such as

gabapentin or pregabalin, which have proved beneficial in other painful neuropathies such as that associated with diabetes mellitus, are expensive and unavailable to state-sponsored HIV clinics. Some of the ARTs, such as the non-nucleoside reverse transcriptase inhibitors (NNRTIs) act as inducers of the cytochrome P450, whilst the protease inhibitors (PIs) act as inhibitors of the cytochrome P450 and hence may not be effectively combined with the anti-epileptics which utilize the same metabolizing enzyme system. Patients with painful HIV-DSP, receiving treatment in a public-sector health care facility have limited options for pain relief. We propose that the above factors may drive patients to seek alternative methods of pain relief such as alternative medicines, recreational drugs or even interrupting their ART that they may perceive as the offending agents. All these factors could be impacting on adherence to ART programs with the potential of initiating HIV resistance.

In addition, in the Western Cape Province, alcohol and marijuana overuse and abuse is substantial (Schneider et al., 2007) and these strategies may be used as pain relief by these HIV patients with painful neuropathy. This could result in a negative impact on adherence to ART and may even contribute to ART-induced neuropathy.

With this study, the aim was to establish health seeking behaviors to cope with pain in a community-based health care facility. We were interested in the strategies used by subjects with painful neuropathy to relieve their symptoms and whether these were likely to impact on an ART program and adherence to the program. Further, as a family physician it is important to understand how the symptoms of painful neuropathy impacts on the lives of HIV-infected subjects.

In order to establish the pain management strategies of our patients we designed a questionnaire, which were given to all subjects to complete. The questionnaire obtained demographic details and then a question dividing the participants into those with and without pain. Those with pain were asked to complete questions about their pain management behaviors. The questions were based on work previously done in a multi-centered study conducted by Nicholas et al. (2008). This study analyzed health seeking behavior for painful neuropathy amongst HIV-infected patients from north and central

America, Norway and Taiwan and found that patients frequently used self-care measures such as walking, elevating the feet, rubbing the feet with cream, hot baths and massage. It also looked at measures such as smoking cigarettes and alcohol use to control the pain. Other pain management strategies included using over-the-counter medications (unspecified), while some used prescribed medications such as analgesics and anti-epileptics. In addition to these questions, we included focused questions regarding the use of recreational drugs, alcohol, as well as traditional medication, as these may play a role in our setting.

As an objective measure of PN, we used the Brief Peripheral Neuropathy Score (BPNS) (Cherry et al., 2005), which is a validated clinical tool for diagnosing DSP. A more detailed description of the BPNS will follow in the methods section.

CHAPTER 2: METHODS

Study population:

The study questionnaire was presented to a cross-section of subjects attending the ART-clinic at the Woodstock community health centre (CHC) over a 3-month time period from July to August 2009. All the subjects were over the age of 18 years and on anti-retroviral (ART) therapy.

Questionnaire & Procedure:

Every morning the clinic sister in charge of the ART clinic addressed the patients as they were waiting in the waiting room. She explained the purpose and procedure of the study and asked who might be interested. Those who agreed to participate and who signed the consent document were issued with a questionnaire to assess 1) whether they have symptoms of painful neuropathy and 2) their quality of life (QOL) (The Euroquol group, 1990) and 3) their general mood as assessed by the hospital and anxiety scale (Zigmond et al., 1983). (See appendix for questionnaire). All patients who participated, irrespective of the presence of pain, were asked to complete the QOL questionnaire and the mood scale.

Those subjects, who responded positively to the presence of painful feet, were then asked to complete further questions regarding their self management strategies to cope with their pain. The questions were derived from previous studies which looked at self-management strategies. In addition to being asked about specific self-management strategies, patients were also asked to rate the frequency of using the strategies as either daily or weekly.

As an objective measurement of clinical neuropathy status, the investigator (MI) examined the patients using the measurements of the Brief Peripheral Neuropathy Scale (BPNS) (Cherry et al., 2005) which was developed to specifically score clinical elements to quantify painful HIV-neuropathy.

Instruments:

EuroQuol (The Euroquol group, 1990); (Appendix- page 30) – The Euroqol is an instrument that assesses five areas of an individual's health status with respect to daily living: - mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each area was assessed on a three-level ordinal scale; normal, moderately abnormal and severely abnormal. For the data analysis these were grouped into a nominal scale according to normal and abnormal (moderately abnormal and severely abnormal). The five areas of the Euroquol are independent areas and a score can not be cumulatively summated. All five areas are therefore to be correlated independently with the patient's reported health status on the day of the interview.

The Hospital Anxiety and Depression Scale (Zigmond et al., 1983); (Appendix- page 33) - In this section seven questions were asked to assess depression. We excluded the questions related to anxiety and only concentrated on depression in order to see if those had an impact on pain. Again, this instrument used an ordinal scale from normal (0), mildly abnormal (1), moderately abnormal (2) to severely abnormal (3). The total score was summated and if greater than ten, the subjects were considered to be depressed (Zigmond et al., 1983).

The Brief Peripheral Neuropathy Score (BPNS) (Cherry et al., 2005); (Appendix- page 36) - This section was performed by the PI (MI). The patients were asked about three neuropathic symptoms namely; pain, pins and needles, and numbness and these were assessed according to the subjective severity on a visual analogue scale (VAS) which rated each symptom from absent (0), mild (1) to severe (10). Each neuropathic symptom was scored independently as a category. Of the three categories, the single highest severity score was obtained and graded on a scale as:
grade 0 refers to VAS= 0 or no pain;
grade 1 refers to VAS= 1-3 or mild pain;
grade 2 refers to VAS= 4 –6 or mild to moderate pain;
grade 3 refers to VAS= 7-8 moderate to severe pain;
grade 4 refers to VAS= 9-10 or severe pain.

The next part of the BPNS assessed the examination of vibration sense and deep tendon ankle reflexes of the patient. The patient was asked to sit on an examination couch with their legs hanging freely. Vibration perception was assessed using a 128Hz tuning fork. The two ends of the tuning fork were pressed together and released suddenly, then placed on the patient's forehead, so they could recognize the vibration or buzzing of the tuning fork. This was immediately repeated and the tuning fork was placed over the interphalangeal bone of the great toe and immediately the seconds were counted until the vibration stops. The same was repeated on the other foot and the highest score recorded but both the right and left sides had to be abnormal. This score was then graded according to:

grade 0 refers to vibration felt for >10secs (normal);
grade 1 refers to vibration felt for 6-10secs (mild loss),
grade 2 refers to vibration felt for 5secs or less (moderate loss);
grade 3 refers to no feeling of vibration (severe loss).

Ankle reflexes were evaluated at the achilles tendon with the patient seated as described. The examiner would use one hand to press upward on the ball of the foot, dorsiflexing the patient's ankle to 90 degrees. Using a reflex hammer (long-handled), the examiner strikes the achilles tendon. This was done on both feet and the highest score recorded although both right and left had to be abnormal. This score was recorded as:

grade 0 refers to clonus;
grade 1 refers to hyperactive deep tendon reflexes;
grade 2 refers to normal deep tendon reflexes;
grade 3 refers to reduced reflexes;
grade 4 refers to absent reflexes.

The reflexes were scored differently from the way it is usually scored in clinical practice, as an increasing score of 'abnormality' had to be obtained. The highest score was recorded as abnormal and hence the category of no reflexes would fall into this category.

Definitions:

Symptomatic distal sensory polyneuropathy (SDSP) was defined as the presence of any of the neuropathic symptoms in addition to one of the following signs; either reduced or absent ankle reflexes or abnormal vibration sense of ≤10 seconds at the great toes (Wright et al., 2008).

Data manipulation and statistical analyses:

For this study, we based our sample size on the 50% frequency of SDSP found in a previous Cape Town cohort of HIV-infected subjects on ART (Maritz et al., 2010). Taking this into account, we estimated that a sample size of at least 100 patients would give us an adequate sample of subjects with DSP with symptoms.

Questionnaires were coded thematically for easy entry into an excel sheet. The major separation of data was the division of the patient cohort into those with SDSP and those without symptoms. Categorical data such as these was analyzed using the Pearson Chi-Square test.

Continuous data such as age, CD4 count, viral load and duration on treatment was analyzed using non-parametric methods. This method was used as it makes no assumptions about the normality of the underlying distribution of study population data. The data was represented as median values with the respective interquartile range (IQR). A p-value (2-sided) of <0.05 was set to be the level of significance. All statistical analysis was assisted and supervised by Dr. Motasssim Badri, statistician from the Department of Medicine, UCT, as well as by Henri Carrara, MPH, Biostatistician from the Faculty of Health Sciences.

Ethics:

Permission to perform the study was obtained from the University of Cape Town Research Ethics committee (REC REF: 465/2008) and all participants provided written, informed consent.

CHAPTER 3: RESULTS

Description of the study population:

All the patients who were approached with the questionnaire agreed to participate in the study. Seventy-five (61%) of the study population were females, whilst 48 (39%) were males. Of the 123 patients interviewed, 21(17%) had co-morbid illnesses with hypertension (7%) as the most frequent additional illness. Four patients were receiving therapy for pulmonary tuberculosis (PTB) and 11 (9%) had received therapy for PTB in the preceding year.

Table 3.1: Additional illnesses amongst 123 HIV-positive subjects

Co-morbid illness	**Number of patients (% of Total)**
Current Pulmonary Tuberculosis	4 (3%)
Asthma	4 (3%)
Hypertension	9 (7%)
Kaposi Sarcoma	1 (1%)
Diabetes Mellitus	1 (1%)
Lymphoma	1 (1%)
Chronic Obstructive Airways Disease and Cancer#	1 (1%)

Type of cancer not specified in questionnaire or in folder

Neuropathic Pain as a symptom of neuropathy:

As the main aim of the study was to assess self-management strategies of patients who have painful feet, the discriminative question on the questionnaire was the presence of subjective pain. Of the 123 subjects, 38 (31%) were experiencing painful feet whereas 85 (69%) had no pain. However, one patient was subsequently excluded as his results were inconsistent; he answered "yes" to experiencing painful feet but then scored all the neuropathic symptoms as zero (absence of symptoms) on the BPNS questions. Thus, from here on a total of 37 (30%) subjects were recorded as responding positively to the presence of neuropathic pain.

The median ages of subjects with neuropathic pain symptoms (41 years; IQR = 35; 49) were not statistically different from the median ages of those without pain (39 years; IQR= 33; 44) (p= 0.065). More females were interviewed as a greater proportion of the patients attending our clinic are female, however the proportion of males (26%) and females (33%) affected with SDSP, were similar (Table 3.2; p= 0.36).

Table 3.2: Comparison of gender

	SDSP (n=37)	No SDSP (n=85)
MALE (n= 47)	12 (26%)	35 (74%)
FEMALES (n= 75)	25 (33%)	50 (67%)

p-value = 0.36

Clinical characteristics

In order to quantify the severity of neuropathic symptoms and to examine certain clinical aspects of the peripheral nervous system, the BPNS was performed. This assessed three neuropathic symptoms on the VAS, followed by an examination for ankle reflexes and vibration sense.

Table 3.3 shows the results of the qualitative subjective assessment of neuropathic symptoms by the patients as measured on the VAS. Burning pain was the most frequent neuropathic symptom experienced of the triad of symptoms, with all 37 patients experiencing this aching or burning feeling in the feet or legs. Most patients (43%) experienced the intensity as moderately severe (Figure 3.1) but more important clinically, almost a third of the subjects had pain intensity levels reaching moderately-severe to severe levels of pain (grade 3 and 4 combined).

More than two-thirds of subjects with pain also had pins and needles or paresthesiae. Of these 43 % perceived this symptom as of moderate intensity. Numbness was perceived by 49% of the subjects with SDSP. Of these almost half also experienced a moderate grade of numbness (Table 3.3).

Table 3.3: Proportion of patients with painful feet experiencing the different neuropathic symptoms as measured by the VAS component of the BPNS

Neuropathic symptom	TOTAL N (%)	Mild N (%)	Moderate N (%)	Moderately severe N (%)	Severe N (%)
Burning Pain	37 (100)	10 (27)	16 (**43**)	6 (16)	5 (14)
Pins & needles	28 (76)	8 (29)	12 (**43**)	4 (14)	4 (14)
Numbness	18 (49)	3 (17)	8 (**44**)	2 (11)	5 (28)

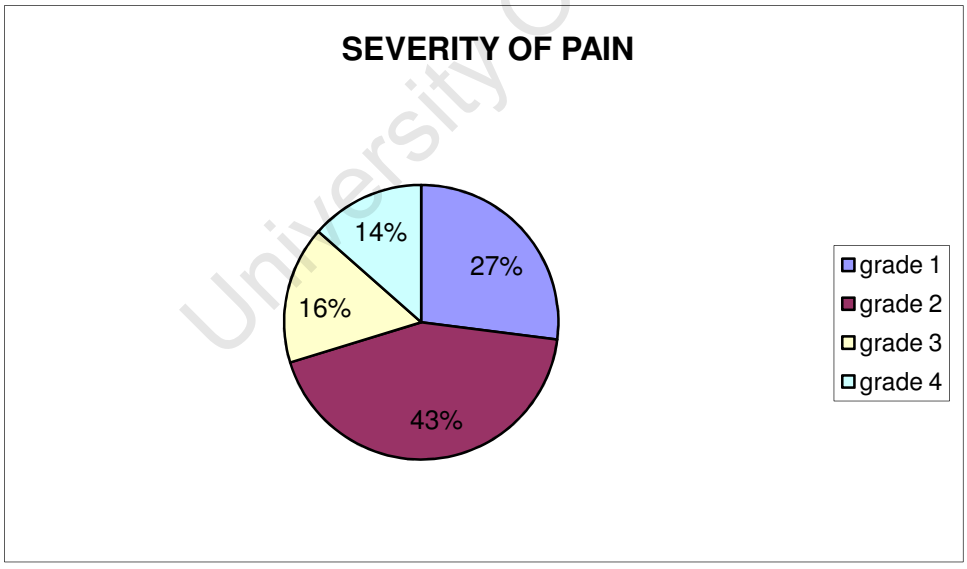
grade 1 refers to a VAS =1-3 (mild)

grade 2 refers to a VAS=4-6 (moderate)

grade 3 refers to a VAS= 7-8 (moderately severe)

grade 4 refers to a VAS= 9-10 (severe)

Figure 3.1: Grading of the most frequent neuropathic symptoms according to VAS



grade 1= mild

grade 2= moderate

grade 3= moderately severe

grade 4= severe

The clinical examination component of the BPNS is summarized in Table 3.4. Abnormal reflexes (reduced ankle jerks) were only found in one of the 37 subjects with neuropathic pain, whereas all 37 subjects had impaired vibration sense. Of the subjects without symptoms of neuropathic pain, one had hypo-reflexia but 83% also had abnormal vibration sense. A comparison of the vibration scores of the BPNS showed that almost half of the patients with SDSP had mild vibration sense loss and half had moderate vibration loss (Table 3.5). Of the patients with no SDSP, half had mild vibration loss and less than a third had moderate vibration loss (Table 3.5).

Table 3.4: Comparison of examination findings of the BPNS

	SDSP (n=37)	No SDSP (n=85)
Hypo-/areflexia	1 (3%)	1 (1%)
Vibration loss	37 (100%)	71 (83%)

Table 3.5: Comparison of vibration scores

	SDSP (n=37)	No SDSP (n=85)
Normal vibration	0	15 (18%)
Mild vibration loss	17 (46%)	43 (50%)
Moderate vibration loss	19 (51%)	26 (31%)
Severe vibration loss	1 (3%)	1 (1%)

normal vibration= 0

mild vibration loss= 1

moderate vibration loss= 2

severe vibration loss= 3

Clinical and Laboratory factors:

Subjects who had SDSP, were found to be exposed to ARTs for a period of 16 months (IQR 11; 42) compared to those without SDSP for 24 months (IQR 12; 42; p= 0.32). The two groups showed similar characteristics with regards to their most recent CD4 count and their latest viral load, both taken within the last six months (Table 3.6). The table shows that both groups were virologically suppressed which probably indicates that they were adherent on their medication.

Table 3.6: Comparison of laboratory characteristics

	SDSP (n= 37)	no SDSP (n= 85)	p- value
CD4 count, median (IQR)	282 (176-371)	283 (191-392)	0.68
Viral load, median	0 (0-0)	0 (0-0)	0.96

IQR -Interquartile Range

Viral load of 0 = Lower than detectable limit.

Self-management strategies for pain and their frequencies:

The categories of self-care strategies are tabulated below (Table 3.7). Most subjects (68%) used analgesics such as paracetamol, whilst only 3% used other agents such as amitriptyline to manage their painful symptoms. Similarly, many patients were also using activities such as soaking feet, massaging feet and elevating feet, at least on a daily basis. Interestingly, very few patients admitted to smoking cigarettes (5%) and recreational drugs (3%) as a source of pain relief. None of the patients admitted to using alcohol, traditional medication or stopping ARTs. An open category was available for subjects to complete, in which only one patient admitted to using amitriptyline, but no further information on self-management behavior in this group, was added.

Table 3.7: Health- seeking behaviors and the frequency with which they are used in patients with painful feet

Self-care strategy:	Number of patients (n= 37)	Daily (at least once per day)	Weekly (at least once per week)
1. Analgesics-paracetamol	25 (68%)	12 (48%)	13 (52%)
-amitriptyline	1 (3%)	1 (100%)	0
2. Activities-massaging feet	21 (57%)	14 (67%)	7 (33%)
-soaking feet	25 (68%)	13 (52%)	11 (48%)
-elevating feet	17 (46%)	12 (71%)	5 (29%)
3. Substance use-cigarettes	2 (5%)	1 (50%)	1 (50%)
-alcohol	0	0	0
-recreational drugs (dagga)	1 (3%)	0	1 (100%)
4. Alternate treatment-traditional meds	0	0	0
5. Stopping ARVs	0	0	0

Quality Of Life (QOL) measures:

The QOL assessed five basic themes: mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Level one indicated no problem; level two indicated moderate symptoms, whilst level three indicated severe problems. Most patients complained of moderate symptoms. No patients had severe symptoms in the categories of mobility and self-care. In the category of pain or discomfort, three patients with no SDSP had severe symptoms compared to six with SDSP. The patients in the group without SDSP did not have neuropathic pain, but had other pain or discomfort symptoms. With regard to usual activities, one patient without SDSP had severe symptoms. In the category of anxiety or depression, there were two patients in the SDSP and two patients in the group without SDSP, who had severe symptoms.

Since only a small proportion of our patients subjectively experienced severe symptoms, we present the combined level two and three data as abnormal in each category of the QOL. Therefore the results of the QOL are presented as normal vs. abnormal when comparing those with neuropathic symptoms and signs (SDSP) to no SDSP; only those with abnormal ratings i.e. level two and three, are presented as proportions in Table 3.8.

When comparing the individual categories of QOL, the proportions of abnormal results in all the groups except self- care, were significantly higher amongst those categorized as SDSP. Approximately one third of the patients, with SDSP were negatively impacted in the categories of mobility, usual activities and anxiety or depression while more than two thirds admitted to symptoms of pain or discomfort. In the group with no SDSP, i.e. no neuropathic symptoms or signs, 18% complained of pain and 20% also had symptoms of anxiety or depression. This suggests that other forms of pain could be prominent in HIV/AIDS and may contribute to the relatively high anxiety or depression rate in these individuals.

Table 3.8: Comparison of proportions of individuals with abnormal symptoms in each of the categories of the EQ- 5D, according to the presence of neuropathic symptoms (SDSP)

	SDSP (n= 37)	No SDSP (n= 85)	p-value
Mobility	13 (35%)	7 (8%)	<0.001
Self care	1 (3%)	1 (1%)	0.54
Usual activities	12 (32%)	6 (7%)	<0.001
Pain/ Discomfort	23 (62%)	15 (18%)	<0.001
Anxiety/ Depression	14 (38%)	17 (20%)	0.038
EQ- 5D Health today VAS	80 (70- 99)	90 (80- 100)	0.007

Table 3.9 shows that more patients with SDSP (8%) showed positive symptoms of depression as opposed to 1% amongst those without SDSP as measured by the Hospital Anxiety and Depression Scale (Zigmond et al., 1983). This tool asked seven questions

related to symptoms of depression. A score was then achieved and if greater than ten, the patient was categorized as depressed. Proportionately fewer patients tested positive for depression on this tool as opposed to the QOL, which only asked one question about depression and anxiety as a combined question. A reason for the difference could be that in the QOL, patients may have ticked the category of "anxiety or depression" when they only felt anxious at the time. However, when more specific questions about depression were asked, these patients did not score more than 10 on the scale as defined for depression. Both tools showed that depression in the hospital anxiety and depression scale, and depression in the QOL was significant.

Table 3.9: Proportions of patients with depression as measured by the hospital anxiety and depression scale

	SDSP (n=37)	no SDSP (n=85)
depression	3 (8%)	1 (1%)
no depression	34 (92%)	84 (99%)

p-value= 0.052

Additional Factors associated with SDSP:

People with SDSP were less likely to be employed (32%) than those who did not have SDSP (55%) (p= 0.02) (Table 3.10).

There was no association with subjects currently taking D-drugs and the presence of SDSP (Table 3.10; p=0.33); only 58% of those with symptomatic neuropathy were taking D-drugs compared to 67% of those without symptomatic neuropathy.

Less than 16% of subjects were either currently taking TB drugs or had been exposed to a TB regimen in the previous year and there was no association with the presence of symptomatic neuropathy (p= 0.42).

Table 3.10: A comparison of additional factors in subjects with SDSP vs. no SDSP

	SDSP (n=37)	no SDSP (n=85)	p-value
Employment	12 (32%)	47 (55%)	0.02
D-Drugs	22 (58%)	57 (67%)	0.33
TB treatment (current or in the last year)	6 (16%)	9 (11%)	0.42

CHAPTER 4: DISCUSSION

Data from this study confirms that DSP is a common problem amongst HIV-infected patients who are on ART. The frequency of SDSP in this Woodstock community-based cohort on ART is 30%. This is in keeping with studies that were done in developing countries elsewhere (Verma et al., 2005). A recent cross-sectional study in a South African community-based cohort showed the frequency of SDSP in subjects on ART to be higher, at 50% (Maritz et al., 2010).

To diagnose SDSP we used the criteria of having symptoms with either abnormal reflexes or abnormal vibration sense. Currently there seems to be some confusion in the literature as to which definition to use for a neuropathy diagnosis in the primary care clinic-setting, probably due to the difficulties of obtaining nerve biopsy which is likely the gold standard test at present. Some consider "definite symptomatic DSP" as the presence of neuropathic symptoms plus abnormal (absent or reduced) ankle reflexes and vibration sense of ≤10 seconds at the great toes (Wright et al., 2008; reviewed in Maritz et al., 2010). Others have defined SDSP as the presence of neuropathic symptoms together with one additional sign only, which could be either absent or reduced ankle reflexes or vibration sense of ≤10 seconds at the great toes (Affandi et al., 2008). We have used the latter definition for SDSP as only two of our patients had abnormal reflexes and thus, most of the symptomatic patients only had one additional sign which was vibration sense loss. This is an important observation for general practice. HIV-associated DSP is a small fiber neuropathy which will predominantly affect the unmyelinated pain fibers. Different neuropathic symptoms may be experienced, and they can range from mild, vague complaints of discomfort to more severe burning pain, which is usually worse at night. Examination often reveals allodynia (perception of non-painful stimuli as being painful), hyperalgesia (perception of painful stimuli as being more painful than expected), or reduced pinprick and thermal sensation in the affected area. Vibratory sensation can be mildly reduced at the toes. Motor strength, tendon reflexes, and proprioception, however, are preserved because they are functions of large myelinated nerve fibers (Tavee et.al,

2009). It is therefore not surprising that reflexes were found to be intact in most of our patients.

As the main aim of this study was to look at self-management strategies, we compared these strategies and the frequency with which they were used. The use of analgesia, especially paracetamol, was high (68%) and frequently used daily, whilst activities such as massaging feet (57%), soaking feet (68%) and elevating feet (46%) were also commonly used on a daily basis. These findings were similar to those observed by Nicholas et al. (2008) analyzing health seeking behavior for painful neuropathy amongst HIV-infected patients from north and central America, Norway and Taiwan. None of our patients admitted to using alcohol, traditional medication or stopping ART to cope with their pain. This may have been under-reported as we know that alcohol and marijuana use is a problem in the Western Cape (Schneider et al., 2007). Even though the questionnaires were confidential, patients may have felt that since the PI (MI) and their treating doctor was the same person, they may have chosen not to disclose this information. However, the viral loads were suppressed in both groups strongly suggesting that the patients were adherent to their treatment plan.

A study done by Toth et al. (2008) found that oral based pharmaco-therapies, such as gabapentinoids, tricyclic antidepressants, anti-epileptics and cannabinoids provided approximately similar levels of pain relief in neuropathic pain. Topical therapies, such as lidocaine and capsaicin proved to be less effective (Toth et al., 2008). In our study population, only one patient, with SDSP volunteered to using tricyclic antidepressants but the questionnaire was not designed to obtain this specific information. It is however, standard practice in our clinic to prescribe tricyclic antidepressants to patients who complain of painful neuropathy. Patients may not have volunteered this information as they might not see it as an analgesic agent or that it may not be effective in the treatment of neuropathic pain.

SDSP affects the quality of life on four of the five themes of the Euroqol assessment. It seems that the pain is significant enough to affect basic functions of daily activities, such as mobility, usual activities, pain or discomfort as well as and anxiety or depression. Only

one patient with SDSP and one without SDSP showed abnormal symptoms with regard to self care. We found that most patients with SDSP had significant subjective levels of pain; less than one third (27%) had mild symptoms, while the rest all had moderate to severe symptoms, and that their QOL was adversely affected compared to those without SDSP. This was similar to findings in a recent study by O'Connor et al. (2009).

In an overview of treatment guidelines for neuropathic pain by O'Connor et al. (2009) involving first-line (anti-depressants, calcium channel ligands and topical lidocaine) and second-line (opiod receptor agonists) medications generally used to alleviate neuropathic pain in various conditions, showed that several agents are consistently useful in subjects with neuropathic pain. However, the results only looked at two agents in the treatment of symptomatic HIV-DSP. Both agents used in the trials, tricyclic antidepressants and gabapentin, did not show benefit in relieving pain in HIV-DSP, compared to placebo. Both these agents have proven very useful in diabetic painful neuropathy suggesting perhaps a different pain causing mechanism in HIV-DSP. With this in mind, adequate analgesic strategies need to be sought as it also indicates that despite all the self-management strategies patients are using, it is not enough to control the pain in order to be functioning at their full potential. At the same time, conventional analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), are prescribed frequently for patients with neuropathic pain despite potential risks and limited efficacy. Inappropriate or delayed treatment is a serious concern because it may worsen the patient's condition (Haanpaa et al., 2009).

We noted an association between unemployment and having SDSP. Most of the subjects with SDSP had at least a moderate level of perceived pain. This could mean that the pain is debilitating enough to prevent them from seeking employment. A recent review suggests that chronic pain is both the source of severe patient suffering and a major cause of work absenteeism (Haanpaa et al., 2009). In our patients, unemployment could contribute to depression, even though proportionately few patients achieved scores suggestive of depression on the hospital depression and anxiety screen.

Irrespective of the presence of SDSP or not, the two groups shared similar characteristics in terms of CD4 count and viral load. There is no association with SDSP on CD4 and viral load. This however does not take into account the CD4 nadir at the start of treatment.

Surprisingly, we did not find a significant association with SDSP and the use of D-drugs, or with current or recent TB treatment as was found in a recent South African study (Maritz et al., 2010). Many studies have found a strong association with DSP and D-drugs. ART-DSP is associated with the use of the nucleoside analog reverse transcriptase inhibitors, didanosine (ddI), zalcitarabine (ddC), and stavudine (d4T) (Gonzalez-Duarte, et al., 2008). The reason our findings were not consistent with other studies may be due to the fact that a large number of our patient were referred from a tertiary hospital, where they were started on d4T (40mg twice daily at the time), and if they suffered from peripheral neuropathy were then changed to the lower dose (d4T 30mg twice daily) and subsequently to zidovudine (AZT). By the time our clinic was established many of the patients who had been initiated on ART elsewhere, and had symptoms suggestive of peripheral neuropathy had already been changed to AZT.

Many of the patients without SDSP (83%) were found to have vibration abnormalities but no symptoms. The reason for this observation might be that it is still relatively early in the evolution of neuropathy and that they may have asymptomatic DSP which will at some later stage still evolve into symptomatic DSP. This is one of the shortcomings of a cross sectional study in that the patient cohort is not followed up over time and one is not aware of what happens in the future. In a previous South African community-based cohort, 40% of the subjects with DSP on ART had no symptoms, although they were more stringently defined as having two signs present, abnormal vibration sense and ankle jerks (Maritz et al., 2009). Another possible explanation is the presence of falsely abnormal vibration sense due to a temperature effect. It is well known that nerve impulses, particularly fast conducting impulses using myelinated fibers, are influenced by temperature; cooling slows down the conduction velocity whereas higher body temperature allows efficient fast conduction (Dyck et el., 1984). For example, the

conduction velocity increases almost linearly, by 2.4m/s or approximately 5%/degree, as the temperature measured near the nerve increases from 29 to 38°C (Dyck et el., 1984). Interestingly, most of the subjects were tested during the colder seasons and in a clinic that was not always optimally warmed. Theoretically, colder temperatures may have resulted in altered vibration sensibility which is transmitted via myelinated fast conducting nerves. It is unclear whether this is a reason for our spurious results and how much the room temperature would impact on bedside vibration assessment. A study assessing the effect of room temperature on normal control vibration sensibility is planned.

It must be noted that this study does have several shortcomings. Our cohort was only a small sample and may not have been an accurate reflection of the bigger, representative population. Secondly, problems arose with the definition of SDSP and we opted to use one which only incorporated one clinical sign rather than two, although many researchers do accept this definition. This might bear significance to primary level care practitioners in that it would mean that the presence or absence of reflexes may not be useful as supportive features of HIV-DSP with symptoms. However, without a gold standard test to definitely categorize patients with DSP or not, it is difficult to determine the predictive value or lack thereof, of a clinical assessment.

The BPNS has been validated and is regarded as having sufficient sensitivity and specificity as a tool which should be incorporated into clinical general practice where patients complain of pain. The Neurologic Aids Research Consortium (NARC), a sub-study in Adult Longitudinal Linked Randomized Trials looked at the sensitivity and specificity of a BPNS carried out by a nurse coordinator and how these correlated with a total neuropathy screen (TNS) performed by neurologists. The frequency of neuropathy diagnosed using the BPNS was 20% vs. 32% using a TNS in the same population. This gives the BPNS a sensitivity of 46% and a specifity of 91%. The investigators conclude that the BPNS provides a quick, simple and low-cost screening tool with acceptable diagnostic efficiency (Blanchard, 2004).

A study assessing different clinical tests in the diagnosis of diabetic neuropathy found that the 128- Hz tuning fork was both a valid and reliable test for screening purpose in clinical practice, albeit in diabetic patients (Meijer et al., 2005). Although the aim was to screen for diabetic neuropathy it does shows similar results to the findings in this report in that vibration testing may be a more sensitive clinical assessment than the presence or absence of ankle jerks. Furthermore, the calibrated Rydel-Seiffer tuning fork compared to the 128-Hz qualitative tuning fork, did not increase the sensitivity of vibration assessment in patients with electrophysiologically diagnosed polyneuropathy. This implies that the standard 128- Hz tuning fork is still adequate to test vibration sensibility (Pestronk et al., 2004). Interestingly, Simpson et al. found that the performance of the BPNS provided different results depending on whether the examiner was a nonphysician clinician or neurologist. For example, nonphysician clinicians examined only ankle reflexes (as required), whereas study neurologists performed all the tendon reflexes. The comparison of ankle with knee reflexes provides a more reliable assessment of relative depression of ankle reflexes (Simpson et al., 2006). Unfortunately, I did not always assess both ankle and knee reflexes during the study. This may be an important point for general practitioners – if one is unsure whether the ankle jerks are abnormally reduced, it would be useful to compare with the knee and other upper limb jerks.

Our patients use self-management strategies to deal with pain; however, this does not necessarily adequately alleviate the problem. Pain is a huge and challenging problem in HIV infection. Eighty-four percent of ambulatory patients' with AIDS have been found to be receiving inadequate analgesia according to the WHO criteria compared to 42% of patients with cancer (Blanchard, 2004). It is therefore important that as general practitioners, we equip ourselves with the skills to adequately diagnose painful neuropathy, which would mean the use of tools such as the BPNS, which includes testing ankle reflexes and vibration abnormalities. Once SDSP has been identified, and treatable co-morbid factors such as diabetes, alcohol abuse, vitamin B12 deficiency or d-drug NRTI have been excluded, the next step would be to provide sufficient treatment to control the symptoms so that patients are able to function at optimal health. Management should start by addressing psychological aspects of pain and its impact on the patients'

quality of life, in addition to pharmacological management which could be based on the WHO pain management algorithm. The latter would include paracetamol and tricyclic antidepressants and possibly gabapentin or pregabalin. However, preliminary trials of both pregabalin and gabapentin have not showed superiority compared to placebo specifically in painful HIV-DSP subjects (Finnerup et al., 2005). With limited resources and effective therapies for HIV-DSP, general practitioners should try all that is available to support these patients and if all else fails; referral to the next level of care may be indicated.

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APPENDICES

SECTION 1: PERIPHERAL NEUROPATHY QUESTIONNAIRE:

Following are a few questions we would like to ask you in order to find out whether you have any problems with your feet and how you cope with the problem. We would like you to be as honest as possible and assure you that the information you share with us will remain confidential.

Study number:				P1
Age:				P2
Date:				P3
CD4 count- last 6 months:				P4
Viral Load- last 6 months:				P5
Employed?	Yes -1	No -0		P6
Which month & year was HIV diagnosed?	Month? Year?			P7 P8
When did you start taking ARV treatment?	Month? Year?			P9 P10
Which ARVs are you taking?	Stavudine (d4T) yes-1 or no-0			P11
	Didanosine (ddI) yes-1 or no-0			P12
	AZT /Lamivudine (3TC) yes-1 or no-0			P13
	Efavirenz or Nevirapine yes-1 or no-0			P14
	Kaletra / Aluvia yes-1 or no-0			P15
Are you on TB treatment?	Currently-1	In the last year-2	In the last 5 years -3	P16
Do you take any other treatments?				P17
-vitamins	Yes -1	No -2		
-herbal medication	Yes -1	No -2		P18
-traditional medication	Yes --1	No -2		P19
How often do you take these other treatments?	Daily-1	At least once a week-2		P20
Do you suffer from any other illness?	Yes -1	No -2		P21
If yes, what? • Diabetes (high sugar)-1 Any other _____				

• Thyroid disease- 2				P22
Do you have painful feet?	Yes-1	No -2		P23
If the last question is NO then go to section 2 on the next page.				
Did the pain in your feet start before taking ARVs?	Yes-1	No-2	Don't know -3	P24
Did the pain in your feet start within 2 to 4 months of starting ARVs?	Yes-1	No-2	Don't know -3	P25
Does the pain affect your day to day activities?	Yes -1	No-2		P26
What do you do to manage your pain?				P27
Do you elevate your feet for the pain? Do you soak feet in hot water for the pain?	Yes-1 Yes-1	No-2 No-2		P28 P29
How often?	Daily-1	At least once a week-2		P30
Do you ever massage your feet? How often?	Yes-1 Daily-1	No -2 At least once a week-2		P31 P32
Do you ever take pain medication? How often?	Yes -1 Daily-1	No -2 At least once a week-2		P33 P34
Do you ever smoke to relieve the pain? How often?	Yes-1 Daily-1	No -2 At least once a week-2		P35 P36
Do you drink alcohol to relieve the pain? How often?	Yes-1 Daily-1	No -2 At least once a week-2		P37 P38
Do you take recreational drugs for the pain?	Yes-1	No-2		P39
Dagga?	Daily-1	At least once a week-2		P40 P41
Tik?	Daily-1	At least once a week-2		P42
Heroine?	Daily-1	At least once a week-2		P43
Cocaine?	Daily-1	At least once a week-2		
Do you take traditional medication for pain? How often?	Yes -1 Daily-1	No -2 At least once a week-2		P44 P45
Do you ever stop your ARVs to control the pain? How often?	Yes -1 Daily-1	No -2 At least once a week-2		P46 P47

SECTION 2: QOL (English version for SA):

By placing a tick in one box in each group below, please indicate which statements best describe your own state of health TODAY.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

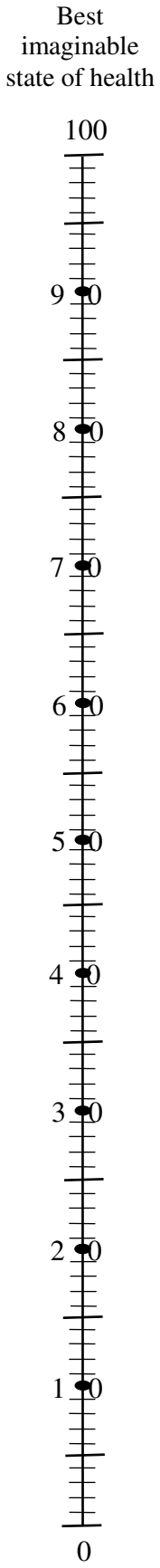
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

Your own state of health today

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale, in your opinion, how good or bad your own health is today. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.



SECTION 3: MOOD SCALE:

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more. This questionnaire is designed to help your doctor to know how you feel. Ignore the numbers printed on the left of the questionnaire. Read each item and underline the reply which comes closest to how you have been feeling in the past week.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

D1 I still enjoy the things I used to enjoy:

0 Definitely as much

1 Not quite so much

2 Only a little

3 Hardly at all

D2 I can laugh and see the funny side of things:

0 As much as I always could

1 Not quite so much now

2 Definitely not so much now

3 Not at all

D3	I feel cheerful:	
3		Not at all
2		Not often
1		Sometimes
0		Most of the time
D4	I feel as if I am slowed down:	
3		Nearly all the time
2		Very often
1		Sometimes
0		Not at all
D5	I have lost interest in my appearance:	
3		Definitely
2		I don't take so much care as I should
1		I may not take quite as much care

0 I take just as much care as ever

D6 I look forward with enjoyment to thing:

0 As much as ever I did

1 Rather less than I used to

2 Definitely less than I used to

3 Hardly at all

D7 I can enjoy a good book or radio or TV programme:

0 Often

1 Sometimes

2 Not often

3 Very seldom

FOR CLINIC USE ONLY **(D>10) Total D8_____**

Section 4: BPNS Neuropathy screen (performed by clinician): *We are going to ask you a few questions about sensation in your legs. We will also briefly examine the nerves in your arms and legs.*

BPNS: INSTRUCTIONS FOR RECORDING SYMPTOM SCORE: *Ask subject to rate the severity of each symptom in 1a to 1c on a scale of 0 (absent) to 10 (most severe) for right and left feet, legs- worst in last week.*

1a. Pain, aching, burning in feet or legs.

Normal	Mild	→	→	→	→	→	→	→	→	Severe
0	1	2	3	4	5	6	7	8	9	10

Nn1
Score 1a

1b. "Pins-and-Needles" in feet or legs.

Normal	Mild	→	→	→	→	→	→	→	→	Severe
0	1	2	3	4	5	6	7	8	9	**10**

Nn2 score 1b	

1c. Numbness (lack of feeling) in feet or legs

Normal	Mild	→	→	→	→	→	→	→	→	Severe
0	1	2	3	4	5	6	7	8	9	**10**

Nn3 Score 1c	

TOTAL SENSORY PRESENCE/SEVERITY SCORE: Obtain the single highest severity score from 1-10 in 1(a - c) above: 0 = Grade 0 1-3 = Grade 1

4- 6 = Grade 2 7-8 = Grade 3

9-10= Grade 4 **Total sensory severity GRADE** ___/4 nn4

If a symptom was present in the past, but not now i.e "Currently Absent" Yes (1) N/A (0) nn5

Has anything helped for the pain (medicine or other)?_____ Yes (1) No (0) nn7

Do you think the ARV treatment helped your symptoms? Yes (1) No (0) Unknown (2) nn8

Did the sensory symptoms in your feet start or get worse within 2-4 months of starting ARV Rx?

Yes (1) No (0) Unknown (2) nn9

Did the sensory symptoms in your feet start or get worse within 2-4 months of changing the dose of ARV Rx? Yes (1) No (0) Unknown (2) nn10

2. INSTRUCTIONS FOR PERCEPTION OF VIBRATION:

Press the 2 ends together of a 128 Hz tuning fork, and release suddenly; place the vibrating tuning fork on the subject's clavicle; can they recognise the vibration or "buzzing" of the tuning fork? Repeat and immediately place the vibrating tuning fork firmly on the interphalangeal bone (not nail) of one great toe and begin counting the seconds. Subject to tell you when the "buzzing" stops. Repeat on the other side. (Take highest score but both R & L must be abnormal)

Vibration Perception 0- Vibration felt for >10 seconds (normal)
1- Vibration felt for 6-10 seconds (mild loss)
2- Vibration felt for 5 seconds or less (moderate loss)
3- No feeling of vibration (severe loss)

Great toe interphalangeal bone right____ Left____ usehighest value_____/3 nn11

3. EVALUATING DEEP TENDON REFLEXES: With subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subject's ankle to 90 degrees. Using a reflex hammer (long-handled), the examiner strikes the Achilles tendon. (Take highest score but both R & L must be abnormal)

Ankle Reflexes : 4- Absent 3- Reduced (difficult to elicit)
2- Normal deep tendon reflexes 1- Hyperactive deep tendon reflexes
0- Clonus

Tendon Reflex score right____ Left____ use highest value_____/3
nn12

Final score for BPNS (1+2+3) ____/11