

PREVALENCE OF ANXIETY DISORDERS AMONG PEOPLE LIVING WITH HIV (PLWHIV) and EXPERIENCING NEUROPATHIC PAIN WHO ATTEND CLINICS IN NKOMAZI SUB-DISTRICT

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Dissertation presented for the degree of Master of Philosophy (MPhil)
in Palliative Medicine

School of Public Health and Family Medicine

University of Cape Town

27th AUG 2017

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PLAGIARISM Declaration

I, Walter Obal OCHAN, do hereby declare that the work, on which this thesis is based is original (except where acknowledgements indicate otherwise). I also do declare that the whole work, or any part of it, is not to be and has not been submitted for a degree at this or any other university (or institution of higher learning).

Signature:

Signed by candidate

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Date: 28th MARCH 2017

ACKNOWLEDGEMENTS

This project would not have been possible without the unwavering support of my wife, H L Ochan and our children Siyanda and Siyabonga. Sometimes their biggest contribution was time away from them. This time away from them was never taken for granted.

My sincere appreciation goes to Dr Liz Gwyther, my supervisor, for being the unshakeable Centurion behind all this. Naomi and her electronic devices which were forever on; Gill Morgan and colleagues at the library all made significant contributions to the project. The input by Prof P Becker, Dr JJ Ongole and Dr S A Mabunda in biostatics helped make sense of the raw data. I would also like to thank Dr L Nkombua, Ann and Prof P Mathews (May his soul rest in peace) for laying the ground works in research methods earlier on. The contributions made and permission issued by the Mpumalanga Provincial department of Health and the clinic heads for allowing us to conduct the study in their facilities were the turning point. I would like to thank all the research assistants (the trained nurses) and the clinic nurses who made our work easy. There would have been no research without the informed consent of the study participants; they were the game changers in this study.

The academic resources from where the literature review came:

EBSCO, Google Scholar, Psych Info, Science direct, CINHALL, MEDLINE, PUBMED, JSTOR, Medscape and other medical text books that have been referenced accordingly.

Overall the Ultimate Being made it possible.

W O Ochan

ACRONYMS

ADNOS	Anxiety Not Otherwise Specified
AIDS	Acquired Immune Deficiency Syndrome
DoH	Department of Health
GAD	Generalised Anxiety Disorder
DSP	Distal Symmetrical Polyneuropathy
HAART	Highly Active Anti-Retroviral Therapy
HCP	Health Care Provider
HIV	Human Immune deficiency Virus
HREC	Human Research Ethics Committee
NeuP	Neuropathic Pain
NeuPSIG	Neuropathic Pain Special Interest Group
OCD	Obsessive Compulsive Disorder
PD	Panic Disorder
PLWHIV	People Living With HIV
PTSD	Post Traumatic Stress Disorder
SAD	Social Anxiety Disorder
SUD	Substance Use Disorder

ABSTRACT

Background: Clinical and research experience indicates that a high HIV prevalence setting will have a high occurrence of conditions that are associated with HIV. These conditions are not always infectious in nature. General physiological pain, neuropathic pain (NeuP) and anxiety disorders are conditions that have a high prevalence in people living with HIV (PLWHIV). There is however, a literature gap on the prevalence of these conditions in Nkomazi Sub-district in South Africa's Mpumalanga Province. This study therefore aimed to serve as a baseline study for the determination of the prevalence of anxiety disorders and neuropathic pain amongst PLWHIV who attended Highly Active Antiretroviral Therapy (HAART) clinics in Nkomazi Sub-district.

Aim of the study: To determine the prevalence of anxiety disorders among PLWHIV with neuropathic pain who attended HAART clinics in Nkomazi sub-district.

Objectives of the study: 1) To determine the prevalence of Neuropathic Pain among patients attending HIV clinics in Nkomazi Health District; 2) To determine the prevalence of Anxiety disorders among PLWHIV experiencing neuropathic pain who attended HIV clinics in Nkomazi sub-district. 3) To determine the Types of Anxiety Disorder among Nkomazi PLWHIV with NeuP who have one, or more anxiety disorders.

Methods: The objectives were achieved through a cross-sectional study using an interviewer-administered questionnaire. Three out of 34 facilities were sampled for the study and participants were recruited and interviewed for a month in April 2013. A total of 508 participants were recruited. The questionnaire was adapted from the Structured Clinical Interview DSM IV Axis I Disorders (Clinicians' Version) or SCID-CV and the DN4 interview tool for neuropathic pain. The questionnaire also sourced demographic data from all participants. Age is summarised using non-parametric statistics. Categorical variables are summarised using percentages and a bar graph. The Chi-squared and the Fisher's exact tests are used to compare binary categorical variables. The Prevalence Ratio is the relative measure of association used. The p-value is set at ≤ 0.05 for statistical significance. The 95% confidence interval (95 % CI) depicts the precision of estimates. Ethical and access approval were granted by the University of Cape Town Research Ethics Committee and the Mpumalanga Department of Health respectively.

Results: Participants were recruited at kaMhlushwa clinic (n = 203 or 39.96%; 95% CI: 35.67 – 44.37), Naas clinic (n = 126 or 24.80%) and Mangweni clinic. There were more females (77.56%; 95% CI: 73.68 – 81.12; n = 394) than males (22.44%; 95% CI: 18.88 – 26.32; n = 114). Pain prevalence was 46.06%; 95% CI: 41.66 – 50.51 (n = 234). The prevalence of neuropathic pain was 17.72%; 95% CI: 14.49 – 21.32 (n = 90) and that of anxiety disorders among those participants with Neuropathic pain was 80%; 95% CI: 70.25 – 87.69 (n = 72).

Conclusion: This study confirmed the high prevalence of a complex disease burden in a high HIV prevalent Primary Care setting. The community has high prevalence of pain, anxiety disorders and neuropathic pain amongst PLWHIV patients on HAART.

Keywords: *Pain, Neuropathic Pain, Anxiety disorders, Nkomazi*

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1. INTRODUCTION

Both neuropathic pain and anxiety disorders are prevalent among people living with the Human Immune deficiency Virus (PLWHIV). The introduction chapter sets the background for this study which looks at the prevalence of anxiety disorders among people living with Human Immune deficiency Virus (PLWHIV) and have neuropathic pain who attended clinics in Nkomazi sub-district, Mpumalanga Province of South Africa (2013).

1.1 Nkomazi sub district

Nkomazi is ranked third highest out of 17 sub-districts in Mpumalanga with ante-natal HIV prevalence of 47.3%, and 50% in the most affected sub-district in the province (2010). While other areas in the province had a decline in ante-natal HIV prevalence between 2006 and 2010, Nkomazi had an increase, 35.5% to 47.3%. Compared to the national prevalence (29.4%, 2010), Mpumalanga had 35.1%¹. This paints a picture of the gravity of HIV infection in Nkomazi.

1.2 Anxiety and Pain among PLWHIV

Anxiety and distress often accompany diagnosis, and living with HIV². Short-lived fear benefits all vertebrates³, but has negative effects when prolonged^{2,3}. Pain, stress and HIV symptoms produce a complex picture in PLWHIV⁴. Somatic symptoms of HIV provoke anxiety; eliciting pain and suffering⁵. Doctors often under-estimate the feelings, fears, anxiety, pain and suffering experienced by PLWHIV; focussing on the disease at the expense of patient-centeredness². Pain and anxiety are poorly recognized and sub-optimally treated^{2,4,5}; with up to 84% of pain untreated although widespread among PLWHIV⁶⁻⁸. Of all types of pain, neuropathic pain is the most difficult to diagnose and treat.

HIV infection predisposes to anxiety and anxiety predisposes to infection^{6,7,9}; with high anxiety levels increasing pain perception and pain increases anxiety^{6,7,9-11}. There is, thus, a bi-directional relationship between HIV and anxiety¹³. Poor educational status influences this relationship negatively^{12,13}. Traumatic events precede post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD) and panic disorder (PD), with or without HIV¹². Anxiety over-activates the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis (HPA), both linked to immune organs¹⁴⁻¹⁶.

Pre-morbid anxiety or anxiety sensitivity increase catastrophic thinking¹⁰ and AIDS in the spouse worsens anxiety¹⁴. However, in South Africa (RSA) there is little difference in levels of distress between PLWHIV and other chronic illnesses; and it seems the high prevalence of HIV in RSA give PLWHIV a sense of belonging¹⁵. Anxiety in PLWHIV exacerbate disease progression; and PLWHIV who have anxiety disorders also struggle with symptoms and psychological effects of HIV¹⁷⁻²². Anxiety disorders have notably escalated among PLWHIV while organic disorders like encephalitis and delirium have decreased^{12,13,23}.

1.3 Link between anxiety and pain

PLWHIV experience pain and anxiety more than the general population^{2,8,10,24}; with hyper-vigilance triggering panic attacks, the basic units of anxiety disorders^{2,4,8,24}. Anxiety disorders and pain in PLWHIV form a vicious loop with overlapping brain mechanisms^{5-7,9}. Caucasians are more likely to report pain, while black patients report less pain despite having higher pain intensity^{5,6} and poor socio-economic status increases prevalence and intensity of pain and anxiety⁵. Pain intensity and experience are maximal if PD and PTSD are co-morbid, with PD the greater predictor of pain. Pain and anxiety cause physiological arousal, with complex neuro-endocrine events releasing cytokines, which are counter-productive if prolonged^{12,13,22}.

Trauma increases sexual risk-taking; while anxiety plus mood disorders frequently co-occur in PLWHIV²⁵⁻²⁹. Child abuse is known to predispose victims to promiscuity, substance use and PTSD; with negative outcomes and pre-morbid anxiety being constant, or worsening in PLWHIV³⁰⁻³³. PLWHIV are likely to be of lower socio-economic status but those with obsessive compulsive disorder (OCD) may have higher educational levels^{32,34}. Worries about body image provoke anxiety among infected teens³⁵. Anxiety and pain in PLWHIV are independent of the bio-markers of the disease³⁶⁻³⁸.

1.4 Unique presentation of some Anxiety Disorders among PLWHIV.

Interestingly for social anxiety disorder (SAD), OCD and specific phobias, the prevalence between PLWHIV and the general population are similar²⁴. Adjustment disorders are now less prevalent since the availability of HAART among indigent patients²³. Efavirenz and tenofovir are part of HAART but cause psychiatric morbidity among some PLWHIV^{22,23}. Up to 2-4% of PLWHIV self-medicate with substances and are prone to substance use disorder, alcohol being dominant^{24,27}. Hyper-vigilance and rumination about pain and negative outcomes maintains PD and PTSD¹⁰.

1.5 Pain beyond the flesh

Living with HIV is a primal threat with inappropriate flight/fight response and chronic physiological arousal^{3,8,10}; resulting in psychological and physical symptoms in PLWHIV^{9,27}. Despite HAART the threat of mortality still persists², initiating and maintaining anxiety disorders^{24,27}; with “harmless” anxiety symptoms and pain disrupting all the spheres of health: physical, mental, social and spiritual^{2,26,38,39}. Dame Cicely Saunders described this concept of total pain where pain outweighs the structural, physiological or biochemical damage²⁶.

1.6 Neuropathic pain and anxiety in PLWHIV

Unlike the relationship between pain and depression in PLWHIV, less is known about the prevalence of anxiety disorders among PLWHIV with neuropathic pain. HIV has a predilection for neural tissue causing distal symmetrical neuropathy (DSP), post-herpetic neuralgia, pain of central origin and mono-neuritis multiplex in PLWHIV^{36,39,41,42}. Neuropathic pain is most difficult to diagnose, complex to treat and complicates both HIV and HAART^{6,42}. Life prolongation with HAART has increased symptom burden with neuropathic pain inducing negative neural changes centrally^{22,36,38,44-51}. When pain experienced by PLWHIV is neuropathic the anxiety that accompanies the pain is likely to be more florid.

2. LITERATURE REVIEW

The introduction chapter described the importance of pain and anxiety disorders among PLWHIV. The research focuses on the prevalence of anxiety among PLWHIV with neuropathic pain. This chapter critically appraises some work done on neuropathic pain and anxiety disorders among PLWHIV.

2.1 Sources of literature

A literature search was done in the following data bases: EBSCO, Google Scholar, Psych Info, Science direct, CINHAI, MEDLINE, PUBMED, JSTOR and Medscape. The following were the keywords used: anxiety disorders, neuropathic pain, co-morbidity and HIV/AIDS.

2.2 Anxiety disorders among PLWHIV

2.2.1 Introduction

The literature search targeted the anxiety disorders and pain, especially neuropathic pain, among people living with HIV/AIDS as a unique sub-population. Neuropathic pain was targeted since it is one of the most difficult and frustrating pain syndromes to treat. The anxiety disorders as a group of illnesses frequently co-occur with each other, other psychiatric disorders and other medical disorders including pain^{4,8-14,16,35}. Although Benton's work (2010) looked at children and adolescents only, the issue of co-morbidity is similar to that in the adult population³⁵. The literature search mainly concentrated on the co-occurrence of the anxiety disorders with pain in people living with HIV/AIDS, but more specifically the literature searched looked at both anxiety disorders and neuropathic pain in this sub-population.

As an introduction to the relevance of fear and anxiety among PLWHIV Casole et al (2011) and Baumann (2004) described these emotions in terms of their evolutionary values^{3,8}. Fear is an emotion that prepares man to fight, flee or freeze; irrespective of what elicits the fear. Such a description is important considering that being infected and living with HIV evokes many fears and uncertainties (Gonzales et al, 2010)⁵. Baumann reiterates the unpleasantness of anxiety, but also its importance, when it is acute⁸. The usefulness of anxiety disappears when it becomes chronic and established, and there is impairment of functioning; one may then diagnose an anxiety disorder^{8,24}. Tuncay (2007) described how HIV puts immense pressure on a patient's physique, psyche, sense of independence and sexuality².

At the time of doing this literature review and obtaining approval of the research proposal by the University Ethics Committee, the Diagnostic and Statistical Manual Fifth edition (DSM V) was still being developed; therefore in this research the DSM IV or DSM IV Text Revision (DSM IV TR) is referred to (First et al)²⁴. In the topic on anxiety disorders Baumann (2004) described six major types of anxiety disorders. These types were: panic disorder (PD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD) and specific phobias⁸. The Structured Clinical Interview for DSM IV Axis I disorders (SCID-I) (First et al, 1997)²⁴, however, goes on to list some more types of anxiety disorders besides the ones mentioned above: Anxiety disorders not otherwise specified (NOS), substance induced anxiety disorders, adjustment disorder, anxiety disorders due to generalized medical conditions and eating disorders are also included in the SCID-I²⁴. The DSM-IV TR also includes acute stress disorder (ASD) as another type of anxiety disorder⁸.

2.2.2 Epidemiology of anxiety disorders among PLWHIV

Tuncay (2007) in a review article highlighted how anxiety disorders are still prevalent among PLWHIV on HAART. The fact that the emotional pain of being infected with the virus is compounded by anxiety is also mentioned in the same article². In their study of the relationship between pain, panic disorder and post-traumatic stress disorder among PLWHIV by Tsao et al (2004) noted that although anxiety disorders were frequently co-morbid with each other this co-occurrence did not have a multiplicative effect on the level of pain that PLWHIV would have if they had pain, except where PTSD and PD co-occur. They noted that panic disorder was a stronger predictor of pain than post-traumatic stress disorder⁹.

Catastrophic thinking which is quite frequent in panic disorder escalates anxiety symptoms both in PLWHIV and people without HIV infection but who do have pain and/or anxiety⁹. Notably, anxiety sensitivity is also high among PLWHIV with panic disorder and helps to maintain anxiety disorders, especially panic disorder⁵. Interestingly pain in PLWHIV is both a trigger of panic disorder and pain is also a symptom of panic disorder. The robust literature review of systematic reviews and good case-control studies by Tsao et al (2004) noted that cognitive bias which is a strong feature of PTSD also increases pain intensity and experience. The fact that avoidance is prominent in PTSD is enhanced by pain, physical deconditioning frequently follows avoidance which, in turn, increases pain intensity. This partly points to how pain and anxiety are mutually maintained⁹.

2.2.3 Pathophysiology of anxiety disorders

In their work on neurobiological basis of anxiety disorders Tsao et al (2004) reviewed other seminal articles that emphasized the overlapping mechanisms for anxiety and pain⁹. Serchuck et al (2010) described the link among pain, stress, psychiatric disorders and reduced immune function; and immune dys-regulation is problematic in PLWHIV⁴. In anxiety disorders interoceptive perception is affected by interactions between brain regions in the cortex, the brain stem centres and the limbic system. The anterior cingulate cortex, the dorso-lateral and medial pre-frontal cortex are the cortical regions involved in this interaction^{3,9}. The periaqueductal grey (PAG) is a major brain stem region involved in the processing of pain and anxiety⁹.

Unlike depression PLWHIV anxiety disorders among the same subpopulation has not been widely studied^{9,10,12}. Roy-Byrne et al (2008) and Gonzalez et al (2009) also acknowledged this fact but also that the association between pain and anxiety disorders is stronger than that between depression and pain^{10,12}. The work done by these co-authors was based on pain and anxiety among patients with other chronic medical conditions, not HIV/AIDS, though. Although the co-workers are well published in this field, this article was an opinion of experts. Pre-morbid anxiety among PLWHIV, illness anxiety and anxiety sensitivity (AS) cause people to respond to their illness with catastrophic thinking^{5,10,38}. This same group of experts noted in their paper the adaptive value of acute pain; but this value is lost once the pain becomes chronic¹⁰. Based on their observation the contribution of anxiety and fear to the pain experience cannot be overemphasized^{9,10}. Campos et al also confirmed that prevalence of anxiety disorders among a Brazilian sub-population was higher than that for depression in the same group²⁰. They, however, did not use SCID-I as the tool for screening for anxiety disorders, instead they used HADS (Hospital Anxiety and Depression Scale) which is a rating scale as opposed to SCID-I which is a diagnostic tool. The amplification of pain by anxiety in chronic medical conditions is well known and described as the effect of the mind on the body, and effect of the body on the mind^{9,10}.

Serchuck et al (2010) and Brief et al (2004) reviewed articles of other experts on pain and anxiety; and described the possible potential pathways through which traumatic events negatively affected health outcomes leading to neurobiological changes^{4,30}. Traumatic exposure leads to increased risk-taking, neurochemical and physiological changes; and

negative psychological responses to trauma lead to immune suppression^{29,30}. The negative affect and negative emotions lead to neurochemical and physiological changes³⁰. Stressful events suppress immune cells and trauma suppresses immune function^{4,29,30}. PTSD and substance use disorder (SUD) are common in pre-morbid people who test negative for HIV but who do have the risk factors for HIV infection³⁰. Trauma increases psychological symptoms and somatization; and cumulative exposure to trauma eventually leads to poor self-care plus risk-taking. Brief and co-workers summarised their review in this way: trauma causes acute stress disorder, which progresses to PTSD in some patients, but not in all exposed to trauma. PTSD leads to risky sexual behaviour and HIV infection in some people. Negative life events and mal-adaptive coping skills are predictors of worse outcome of the anxiety in PLWHIV according to Olley et al (2006)³³.

A new struggle in life ensues for some people living with HIV and who are clinically doing well on HAART. For them their life-span is extended medically but this does not prepare them for the changes in relationship dynamics, work life and the retirement at the normal exit age according to Hinkin et al (2001)⁵¹. Indeed the anticipation of living to up old age becomes a challenge in some of the greying PLWHIV¹³. Hypothetically a pre-HAART patient might have come to terms with the possibility of premature death before initiation of HAART, but then initiation of treatment with HAART changes all this.

2.2.4 Consequences of anxiety disorders

Anxiety disorders among people living with HIV have their benefits and risks. Worrying about the progression of the disease may help improve treatment adherence in some patients; while concerns about physical symptoms and signs may decrease adherence, well-being and immune function. Worrying about toxicity of the drugs could also lead to reduced adherence to therapy. Reduction in functioning of the immune system when there is an anxiety disorder has already been mentioned, so chronic anxiety worsens the viral immune suppression and counteracts the effects of HAART. The basic characteristic of most anxiety disorders being the disruption and dys-regulation of the hypothalamus-pituitary-adrenal axis (HPA axis), the sympathetic and adrenal medullary system. This disruption increases the levels of stress hormones, adrenaline and cortisol. Disease progression follows persistently elevated levels of adrenaline and cortisol^{4,30}.

PTSD among PLWHIV has been extensively studied^{18-20,28,30-34}. Gonzalez et al reiterated the significant relationship between psychologically traumatic events and PTSD, GAD and panic psychopathology¹². The DSM-IV states that diagnosis with a life-threatening illness qualifies as a traumatic event with a possibility of resulting in PTSD. And PTSD that results from the diagnosis of HIV/AIDS ranges from 15% to 64% depending on the screening tool used. Negative emotions such as sadness, hopelessness, guilt, disappointment, blame, helplessness and despair make being diagnosed with HIV a psychologically distressing event. Difficulty in assessing and defining traumatic events makes diagnosis of PTSD difficult in PLWHIV¹⁸.

The complex life history of some, though not all, PLWHIV is discussed by Whetten et al (2008) in their review article¹⁹. Importantly psychological trauma was found to be more prevalent among PLWHIV than among the general population. Post-diagnosis abuse escalates in some PLWHIV and this increased the prevalence of anxiety and PTSD; stigma also increases risks of PTSD¹⁹. In a case-controlled study, which had the disadvantage of a small number of participants, Junqueira et al (2008) observed that most of the anxiety symptoms among the PLWHIV studied were provoked by uncertainties about the eventual outcome of the infection. Fear of pain, physical decline and premature death as a result of infection with HIV all evoke anxiety symptoms²⁶.

Adewuya et al (2007) cautioned about the need to differentiate between the established anxiety disorders and “sub-syndromal symptoms of anxiety” which may follow being diagnosed with HIV infection. Factors that contribute to psychiatric morbidity are: pre-existing psychiatric disorders, psychological reaction to a life-threatening illness, metabolic disturbances, side effects of medications and opportunistic infections²⁸.

A number of studies have observed that stigma is an underlying foundation for extreme emotional distress; and there is subsequent poor psychological functioning with resultant anxiety disorders in some patients^{12-14,,22,28,51}. Gonzalez et al (2009) observed that PLWHIV who had higher levels of mindfulness had significantly lower levels of anxiety and less catastrophic thinking. Their study did not use the SCID for screening for anxiety disorders¹². Nebhinani et al (2011) noted that stigmatization also enhances the bi-directional nature of the relationship between HIV and anxiety²⁷.

Some other aspects of social anxiety disorder (SAD) like shyness and lack of assertiveness compromise safe sexual behaviour and practice. PLWHA who have SAD and HIV-negative people with SAD are easily embarrassed about negotiating for safe sexual practice. Mental disorders as mentioned in the article of Whetten et al (2008) do worsen disease progression¹⁹. Anxiety and HIV are the legendary egg and chicken scenario^{29,51}. This is explained by anxiety disorders leading to infection with HIV and living with HIV also leads to anxiety disorders⁵¹. The chaotic lifestyles lead by people with psychiatric morbidities lead to their low probability of practising safe sex. Infection with HIV directly leads to some anxiety disorders and anxiety disorders predate infection with HIV in some people⁵¹. Treatment with efavirenz has negative psychological consequences, while the protease inhibitors seem to have a favourable profile⁵¹. In the article by Whetten et al (2008) it is mentioned that if dementia is excluded, older age is known to be generally protective against other neuro-psychiatric disorders until HIV enters the picture²⁵.

Benton (2010) discussed factors that threaten emotional health in HIV infection: coping with pain in the body, worry about health, the disruption of social life, isolation, fear of disclosure, anger and worry about self-image³⁵. In their French Guiana study Nacher et al (2010) observed that patients on HAART had a higher rate of GAD than the PLWHIV but not on HAART²². Their tentative explanation was similar to the transition points highlighted by Hinkin et al (2001)⁵⁴.

2.3 Neuropathic pain among PLWHIV

There is a strong intimacy between HIV and the nervous system; the brain is always infected and the peripheral nervous system is usually affected^{36,41}. Attas (2002) cited articles that deliberated on the fact that the neuro-psychiatric complications of HIV are not dependent on biological markers of the disease³⁶. However, the severity of the neurological complications is predictive of mortality³⁶.

Peripheral neuropathies, post-herpetic neuralgia (PHN) and pain of central origin are some of the types of neuropathic pain in PLWHIV². Up to 1/3 of PLWHIV have distal symmetrical polyneuropathy (DSP). In a review article authored by experts mainly from NeuroAIDS Research Programme Verma et al (2005) also noted that DSP was the most prevalent neuropathy among PLWHIV. Despite this high prevalence neuropathy among PLWHIV

remains a problem that is underdiagnosed and undertreated; and pain is the most devastating symptom of DSP³⁹.

2.3.1 Definition of neuropathic pain

The International Association for the Study of Pain (IASP) and the IASP special interest group (NeuPSIG) define neuropathic pain differently^{38,41-43}. The NeuPSIG defines neuropathic pain as “pain that arises as a consequence of a lesion or a disease affecting the somatosensory system” and by the time of doing the Nkomazi clinics study this was the most recent definition of neuropathic pain^{42,43}. Bouhassira elaborated on the new definition in depth in a review article “The Saga of the Clinical tool”⁴³. The older definition of neuropathic pain according to IASP was: “pain initiated or caused by a primary lesion or dysfunction of the nervous system”^{41,42,43}. Both definitions, unfortunately do not take the quality of neuropathic pain into consideration⁴³. Even with a new definition of neuropathic pain, agreement by experts on a single universal diagnostic tool is still lacking⁵²⁻⁵⁶. Work done by Kaki et al (2005) reviewed other articles which, in summary, warned clinicians about “over-simplifying a complex process” of dividing pain in to a purely neuropathic or nociceptive process. These two extremes are best looked at as co-existing parts of the same spectrum⁵⁷.

2.3.2 Epidemiology of neuropathic pain

According to an article by Verma et al (2005) up to 80% of pain in AIDS patients is undiagnosed³⁹. In an international Sub-Saharan, multi-centre study, Harding et al found that pain of all types among PLWHIV receiving HAART concurrently with palliative care up to 82.6% of the patients reported pain¹¹. The difference is that their study did not specifically look for neuropathic pain but sought pain of all types among their cohort of PLWHIV. And previous systematic review by Verma et al (2004) had found the prevalence of pain in PLWHIV to be as high as 84%^{39,40}. Little has changed in the prevalence of pain with advances in treatment of the disease. However, Hitchcock et al (2008) found a much lower prevalence (20.9%) of pain of predominantly neuropathic origin (POPNO) in pre-HAART patients in an urban academic setting in South Africa⁴¹. Anxiety disorders that are co-morbid with neuropathic pain in PLWHIV are even less studied; Brief et al (2004) in a review article noted that physical symptoms, including pain in PLWHIV tend to be severe if there is PTSD³⁰.

Neuropathic pain is underdiagnosed and even when diagnosed is usually undertreated according to two articles by Verma et al (2005)³⁹ and Verma et al (2004)⁴⁰. Of all the neuropathic pain in PLWHIV distal symmetrical polyneuropathy (DSP) is the commonest and pain is its most devastating symptom among others^{39,41}. Among PLWHA neuropathic pain is most common among those with low albumin levels, intra-venous drug users, stavudine and didanosine (d-drugs) as part of HAART (d-drugs), those with very low CD4 counts, those with very high viral counts and the female gender^{39,41,46}. Miaskowski et al (2011) also reported on the other characteristics of pain in PLWHIV other than intensity. They used Brief Pain Inventory and Pain Qualities Assessment Scale as the study instruments for holistic evaluation of pain in a longitudinal cohort of patients⁴⁵. Dorsey et al (2006) emphasized that the advantage of prolongation of life with HAART has added the burden of neuropathic pain⁴⁷.

2.3.3 Qualities of neuropathic pain

Sensory descriptors of neuropathic pain include words that have been found to be universal across cultures and nations; these include burning sensation, electric shock, numbness and tingling sensation among others⁵⁹. Unfortunately, despite the fact that there are many poorly understood pathophysiological mechanisms of neuropathic pain all the types of neuropathic pain are lumped together and treated uniformly⁶⁰.

In their review article Bouhassira et al (2011) described the unique characteristics of neuropathic pain having both positive and negative phenomena⁴³. The article by Hitchcock et al (2008) also mentioned that positive and negative phenomena have always been linked to neuropathic pain, but Hanpaa et al (2011) have mentioned that these phenomena also occur in non-neuropathic pain^{38,41,61}. Backonja & Krause (2003) described these phenomena on their work on the basis of diagnosis of neuropathic pain⁵⁸. Each type of neuropathic pain has a distinct, plausible anatomical explanation⁴³. A major problem experienced in managing neuropathic pain is the lack of universally accepted validated and operational diagnostic criteria. However, when allodynia, hypo-algesia, hypo-aesthesia and temporal summation occur in a patient with pain then these features are very discriminatory for neuropathic pain³⁸. Neuropathic pain has been described as part of a broader spectrum known as “pain of predominantly neuropathic origin” (POPNO)^{37,41}.

In a multi-national, multi-centre study Crawford et al (2008) analysed the sensory descriptors of neuropathic pain among different nations and cultures⁵⁹. The co-authors of Crawford (Bouhassira, Wong and Dukes) are all well published in the field of neuropathic pain. Their study confirmed the terms used by most patients with neuropathic pain: electric shocks, burning sensation, tingling sensation and numbness. The terms seemed universal across all the 6 countries studied. Interestingly all the Chinese participants with extreme pain related their pain to the heart. Numbness was explained as a term that may not describe pain but related to non-pain paraesthesia or dys-aesthesia. The qualitative nature of their study allowed the subjective characteristics of pain to come out in their sensory descriptors⁵⁹. Bennet et al (2007) and Bouhassira et al (2005) emphasized that verbal descriptors are vital in understanding patient's suffering^{58,61}. They also highlighted that paraesthesia and dys-aesthesia are fairly unique to neuropathic pain⁵⁸.

2.3.4 Measures of Anxiety Disorders

The anxiety sensitivity index (ASI), as a screening tool for anxiety disorders has a good internal consistency with an alpha co-efficient score of 0.79-0.90 according to work done by Gonzalez et al (2010)⁵. The Structural Clinical Interview (SCID) for Diagnostic and Statistical 4th edition (DSM –IV) axis I disorders (SCID-I) is the current gold standard used in the diagnosis of anxiety disorders (First et al)²⁴. The SCID clinician version (SCID-CV) was the diagnostic tool used for identifying anxiety disorders among PLWHIV who had neuropathic pain in this study. The ASI would only pick out PLWHIV with anxiety disorders but without identifying the underlying type of anxiety. SCID-CV on the other hand identifies people with anxiety disorders but also the type of anxiety disorder involved²⁴. The problem is that SCID-CV is long and tedious.

The other clinical or research instruments used in study of anxiety disorders have only been discussed briefly here because they are either purely screening tools, or are tools used for measuring severity of each type of anxiety disorders. With the exception of Anxiety Sensitivity Index (ASI) which is a useful instrument for screening for, and not for diagnosis of, anxiety disorders most of the other instruments are unique for evaluating each type of anxiety disorder⁵. Most of these tools are not helpful as diagnostic tools for all the anxiety disorders and, hence, some of which have been briefly critiqued herein under.

The ASI is a tool used for measuring anxiety sensitivity in patients. This refers to somatic sensations related to anxiety and fears that these sensations have harmful consequences. There is an accompanying fear of losing one's mind. This is different to trait anxiety which refers to fearful response to exogenous stressors, while anxiety sensitivity refers to fearful response to internal somatic sensations (endogenous sensations)⁵. ASI is very valuable in identifying people at risk of panic attacks/disorder because anxiety sensitivity is important in maintaining panic disorder. ASI has notably been found lacking in that sometimes it cannot differentiate between panic and non-panic anxiety disorder⁵. Although highly elevated among patients with PD, ASI is also elevated among patients with PTSD. It is slightly elevated among patients with SAD and those with major depressive disorder. As a screening tool it tells us whether, or not a patient has an anxiety disorder or depression. However, it is not a tool that we can use to diagnose a specific type of anxiety disorder⁵.

The Generalized Anxiety Disorder Severity Scale (GADSS), as the name suggests is a severity scale with good internal consistency and reliability but unfortunately this applies only to GAD. It is not useful, and not applicable in the diagnosis of other anxiety disorders. As a tool it has been found to be good in clinical trials involving GAD⁶². It is a stronger tool for evaluating GAD symptoms compared to the Penn State Worry Questionnaire (PSWQ) which does not directly assess DSM IV symptoms⁶². For assessing GAD symptoms the GADSS also compares favourably over the Hamilton Rating Scale for Anxiety (HAM-A) which dwells on a lot phobic symptoms, cardiorespiratory symptoms and gastrointestinal symptoms which are not related to the diagnostic symptoms of GAD⁶². Again these three tools are not as useful for diagnosing individual anxiety disorders as the SCID-CV.

The Spielberger State-Trait Anxiety Inventory (STAI) is an anxiety screening tool whose main purpose is for detecting cases. It affords us the ability to separate patients with, and those without mental disorders. It has good convergent validity and internal consistency, although unlike the SCID-CV it does not diagnose the different types of anxiety disorders. It has an advantage though, when assessing how study participants felt at that moment of the interview, in the recent past and how they are likely to feel in future hypothetical situations. It is a tool that has been found useful in senior citizens⁶³.

The Anxiety and Depression Detector (ADD) is a useful screening tool for anxiety and depression in primary care. This has been bench-marked against the computerised version of the Composite International Diagnostic Interview (CIDI-Auto); the interviewer administered version of CIDI is used. Like the SCID-CV the CIDI Auto is a structured interview whose responses are entered into a computer screen and automatically gives out a DSM IV diagnosis. The CIDI Auto is particularly useful especially for lay interviewers in studies where large numbers of participants are to be interviewed. As a screening tool ADD is good for picking out depression, PD, PTSD, GAD and SAD at the primary care level. Useful a tool as it may be, the ADD screens out the patients with the five disorders mentioned above without necessarily identifying each of the five diagnoses definitively. The ADD may not be useful for screening for the other anxiety disorders other than the five mentioned above⁶⁴.

Another tool for evaluating anxiety disorders is Overall Anxiety Severity and Impairment Scale (OASIS); and is a brief 5-item tool. It is useful in measuring severity and accompanying impairment across the board for all anxiety disorders, but is also not a diagnostic tool. It may be used even when anxiety disorders are comorbid and in patients with sub-syndromal distress⁶⁵. It unfortunately lacks the diagnostic capacity of the SCID-CV. For patients with panic disorder the Panic Disorder Severity Scale (PDSS) provides an easy to use tool but which diagnoses or assesses the severity of PD. Although it may not diagnose the other anxiety disorders it can differentiate between PD and other anxiety disorders with panic attacks⁶⁵. For the diagnosis and rating of severity of PTSD the Clinician Administered PTSD scale for DSM IV (CAPS) has been considered the gold standard, and is derived from the DSM IV. CAPS has been found to compare well with Short PTSD Rating Interview (SPRINT) with the later taking less time to administer. Unfortunately these tools are disorder specific, and not used for diagnosing all the other types of anxiety disorders.

If a rating scale, or a screening tool for panic disorder were used for this study it would not be helpful in diagnosing PTSD or the other types of anxiety disorders among PLWHIV who had neuropathic pain. The Rating Scales are useful instruments for assessing the severity of each anxiety disorder once a diagnosis has already been made with the help of a diagnostic tool such as the SCID-CV. A case in point is the Post Traumatic Stress Diagnostic Scale (PDS) which is helpful within the context of patients already confirmed to have PTSD⁶⁷. When it comes to diagnosing anxiety disorders the SCID-CV, despite its length and some other shortcomings is

still considered the gold standard. Unlike the other screening instruments mentioned above, the SCID-CV is not a screening tool but a diagnostic tool for anxiety disorders.

The SCID-CV is a semi-structured instrument that permits the evaluation of most mental health problems of DSM-IV Axis I disorders. Results of interview with SCID-I across countries and languages were similar for anxiety disorders, although our interviewers used mainly siSwati which is not one of the languages used for the evaluation of SCID-CV^{68,69,70}. Although not perfect SCID-CV serves as a gold standard against which other diagnostic instruments are measured⁷¹⁻⁷⁴. Allowing for clinical judgement, for modifying and supplementing SCID-CV questionnaires improves reliability of interviews^{70,71}.

The decision tree and the skip instructions make the SCID-CV clinician friendly^{68,70,71}. Unlike other structured instruments the SCID-CV allows for the use of the patient's vernacular to clarify some of the questions. SCID-I (SCID-CV) has been used in over a thousand studies besides its use as a gold standard for evaluating other diagnostic instruments^{71,72}.

2.3.5 Measures of neuropathic pain

Jensen's review article (2006) on measures of neuropathic pain describes pain as an "experience with multiple dimensions"⁵². Benson's editorial article on neuropathic pain also acknowledges the "different dimensions of pain"⁵³. By the year 2005 Benson had noted the lack of expert consensus on the diagnostic criteria of neuropathic pain. There has been a paucity of universally accepted scales for assessing the intensity of neuropathic pain. Despite its age and it being just an editorial this article still cited renowned experts in the field of pain management⁵³.

Irrespective of the multitude of diagnostic tools for neuropathic pain they all have a similar language; the sensory descriptors used in all of them are similar⁵³⁻⁵⁵. In the editorial Benson (2005) critically appraises the Neuropathic Pain Scale (NPS), the Neuropathic Pain Symptom Inventory (NPSI), the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Questionnaire (NPQ), the NPQ-short form (NPQ-SF) and the *Douleur Neuropathique 4* (French) or the Neuropathic Pain 4 questions (DN4) by looking at the pros and cons of each tool⁵³. Each of these tools has unique immense values in some specific area of clinical practice or research^{43,53}.

The basis of most of the diagnostic tools that are used for measuring neuropathic pain is subjective verbal descriptors with, or without bed side examination. As recent as the year 2012 there was still no gold standard instrument for the diagnosis of neuropathic pain despite this being a very old problem (Chetty et al, 2012)⁴². There is still a status quo as compared to a similar older report by Bennet et al (2007). The Leeds Assessment of Neuropathic Signs and Symptoms (LANSS) was the first instrument developed for the measurement of neuropathic pain with a sensitivity of 85% and specificity of 80%^{54,56}. LANSS includes both an interview and bed side examination. Bennet co-authored many articles on pain, especially neuropathic pain⁵⁶. The NPS stood out as a tool useful for evaluating therapeutic outcome measures and the advantage of the NPQ-SF is its brevity⁵³. The NPS assesses pain qualities such as intensity, unpleasantness and unique time characteristics⁵³.

The DN4 questionnaire stood out for its ease of administration with its YES/NO answer format. The DN4 scored highly on predictive value (85%) and sensitivity (82.9%) and specificity (89.9%). The characteristic sensory descriptors in the DN4 are: Burning sensation, cold sensation, electric shocks, tingling, pins & needles, numbness, itchiness, hypo-aesthesia to pin-prick, increased pain with brushing and hypo-aesthesia to touch^{53,54}.

Even without the examination component the 7 sensory descriptors have a high accuracy according to Bennet et al; and this is then called the DN4 interview⁵⁴. The DN4 was the screening tool used for diagnosing neuropathic among the PLWHA who took part in this study in Nkomazi district health clinics in South Africa. Other diagnostic instruments for neuropathic pain are the self-report version of LANSS (s-LANSS), Pain Quality Assessment Scale (PQAS) and Pain DETECT and ID-Pain⁵²⁻⁶¹. This is an internationally validated tool although not validated in RSA, and more specifically not validated in Nkomazi sub-district. The sensory descriptors of the DN4 Interview make a good tool for accurately diagnosing neuropathic pain⁵⁴.

Previous studies on anxiety disorders and/or pain in Nkomazi sub-district

It was not possible to identify any publications in respect of the above in the sites searched.

However, in an unpublished study (Ochan, 2010) among unselected private patients in 6 Nkomazi rural medical practices in 2010 the rate of anxiety disorders was as high as 74.67%,

with PTSD being the most prevalent (29.33%), followed by PD (24%), adjustment disorder (14.67%) and other anxiety disorders (13.3%)⁷⁵. This study has the weakness of having been conducted in the private medical setting only (and not among public sector patients), being a prevalence study and it had not stood the test of a published article.

Considering the work that has been reviewed above, there is a lot that has been done on the relationship between anxiety and pain in the general population and PLWHIV. However, there is a gap on the prevalence of anxiety disorders among PLWHIV who also experience neuropathic pain in Nkomazi sub district in Mpumalanga Province of South Africa.

The Problem Statement

The motivation to investigate the prevalence of anxiety disorders among PLWHIV with neuropathic pain in Nkomazi public health clinics in South Africa was that:

Anxiety disorders do make people prone to HIV infection and PLWHIV are also prone to developing anxiety disorders^{9,22,27,28,51}. Likewise screening for anxiety disorders in all PLWHIV reduces symptom burden in this subpopulation; and the anxiety disorders affect adherence to HIV/AIDS treatment^{19,20,25,28,30,31}. Nkomazi sub-district is in Mpumalanga province which has one of the highest rates of HIV infection in South Africa¹; and it is likely that pain and anxiety disorders among PLWHIV are under-diagnosed and under-treated.

Immense suffering accompanies neuropathic pain^{27,36,44-46} and central sensitization modifies pain modulation in the same neural pathways involved in processing anxiety^{47,48}. Anxiety disorders are more prevalent in people at risk of HIV infection even when uninfected^{43,50,51}. The intricate interplay between pain and anxiety disorders in PLWHIV was the basis for doing this study^{2,9-12,21}; and more so what the prevalence of anxiety disorders would be if the pain experienced by PLWHIV was neuropathic in nature.

3. AIM OF THE STUDY

To determine the prevalence of anxiety disorders among PLWHIV neuropathic pain who attended HAART clinics in Nkomazi sub-district.

Objectives of the study:

- 1 To determine the prevalence of Neuropathic Pain among patients attending HIV clinics in Nkomazi Health District.
- 2 To determine the prevalence of all Anxiety disorders among PLWHIV with neuropathic pain
- 3 To determine the types of anxiety disorders among Nkomazi PLWHIV who have NeuP.

4. METHODOLOGY

4.1 Study Design

To achieve the objectives an observational, cross-sectional study design with descriptive and analytical components was used. This study design was chosen because it is cheap and easy to conduct; and allowed for a snapshot view of the predictors of neuropathic pain and anxiety disorders amongst PLWHIV. This design also allowed for the determination of prevalence of both neuropathic pain and anxiety disorders in the study population.

4.2 Study Setting

The Study was conducted in Nkomazi Sub-district, which serves as one of five Sub-districts in the Ehlanzeni District in South Africa's Mpumalanga Province. This Sub-district has the 3rd largest population in the District having at least 23% of the District residents⁷⁶. This Sub-district was conveniently chosen because of its size and the fact that it shares borders with both Swaziland and Mozambique. Furthermore, this is one of the most deprived Sub-districts in the country⁷⁶. The Sub-district has 34 fixed Primary Care facilities, three of them were sampled for this study.

4.3 Study Population

This included all patients on HAART that attended nurse-run HAART clinics in Nkomazi sub-District between the 2nd of April 2013 and the 2nd of May 2013.

4.3.1 Patient Selection Criteria

Inclusion Criteria

-Adult Patients living with HIV

-Anxiety disorders were only diagnosed in those participants who had neuropathic pain, and all the other participants without neuropathic pain were then excluded from this component of the study.

-All those adult patients had to be on HAART.

- Patients who were fit to consent.

- Participants issued a voluntary consent before participating in the study.

Exclusion Criteria

-Patients younger than 18 years of age.

-Patients who were too weak or unwell to manage interview,

-Those with mental retardation and/or those with neurological or cognitive impairment.

-Patients waiting for initiation of HAART, or those who have stopped taking HAART, were not included in the study.

4.3.2 Sampling

4.3.2.1 Sample Size Calculation

The minimum sample size was calculated using the standard equation for a prevalence study⁷⁷.

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

Where;

n = minimum sample size; p = estimated prevalence of neuropathic pain or anxiety disorders; d = precision; Z= 1.96 (at the 5% significance level). Because there are two outcomes (anxiety disorders and neuropathic pain, two sample sizes were calculated).

1) With an estimated prevalence of neuropathic pain among PLWHA in RSA of 20.9%⁴¹, the expected sample size (n) is 254 with a precision of 5% around the 95% confidence interval (CI).

2) Globally the prevalence of Anxiety disorders among PLWHIV is 4-40%⁷⁸ and the sample size may be calculated using the following anticipated prevalence: (a) expected prevalence of anxiety disorders of 10.0%, n=384 with a precision of 3% around the 95% CI, (b) expected prevalence of anxiety disorders of 30.0%%, n=322 with a precision around 5% the 95% CI.

The sample size (n=384) with the smallest prevalence of 10% would give a reasonable estimate for both outcome measures. The sample size used in this study was 508, much higher than the calculated minimum of 384 participants.

4.3.2.2 Sampling Method

A convenient cluster sampling method was used to identify facilities. Participants were identified using a systematic random sampling method. The processes are described below:

Stage 1 was a convenience sampling of the 3 of the 34 nurse-run HIV treatment clinics. This was determined by looking at the monthly and annual figures of PLWHA that used all the 34 clinics of Nkomazi district. The reasons for using only 3 clinics were figures, costs and proximity of these centers to the medical practice of the researcher.

Stage 2 involved a systematic sampling of every 3rd patient attending each of the selected clinics until 508 participants had been interviewed. This resulted from an error that is explained later.

4.4 Instruments and Data Collection

Participant interviews were conducted in a private space which ensured confidentiality of respondents.

4.4.1 The variables measured were:

-The clinical features of neuropathic pain.

-The clinical features of the different anxiety disorders.

4.4.2 The data collection tools that were used in the study were:

i. **Socio-demographic data** were collected from all participants. These included: Gender, Age, Language, Educational status, Employment status and level of income. Race was not collected as the population is homogenous. The level of education does not necessarily mean attainment but rather means some contact with that level, e.g. someone who is listed as having a primary school level of education could for instance have only attended only 1-year or 7-years.

ii. The **Structured Clinical Interview DSM IV Axis I Disorders (Clinicians' Version), SCID-CV**, is a validated instrument although validation was not done in the sub-population studied in Nkomazi sub-district. We excluded the over-view part of the SCID-CV which would cover the socio-demographic data and past psychiatric/medical history of the patient⁶⁵; instead a shorter more concise socio-demographic questionnaire was used. The adopted questionnaire was translated to siSwati (the local language).

Module F of the SCID-I (clinician version, CV) of the DSM-IV was chosen for the diagnosis of anxiety disorders among PLWHA in Nkomazi. Our research assistants interviewed the majority of the participants in siSwati language with a few opting for xiTsonga, another language spoken in Nkomazi sub-district. The design of SCID-CV allowed us to extract all necessary information to help arrive at diagnostic decisions and also gave our interviewers room for flexibility to help clarify equivocal responses. Interviewers received satisfactory, however very brief training on the use of the SCID-CV.

iii. The **DN4 interview**.

The DN4 interview is a shorter version of the DN4 tool for identifying neuropathic pain in patients. Sensitivity is about 83% (82.9%) and specificity is about 90% (89.9%).

4.4.3 Data collection methods

The research assistants were nurses who were recruited, trained and tested on research ethics and the use of the DN4 Interview and SCID-CV questionnaires. Training of the research assistants involved going through the theories behind each of the tools. The assistants were then taught to administer the tools to the researcher in simulated interviews, and were observed while interviewing randomly picked patients from each of the 3 participating clinics.

Obtaining of the informed consent:

Trained research assistants explained the study to potential participants. There was detailed and complete disclosure of information regarding the study. To most of the patients this was explained in *si-Swati*, the language spoken by the majority in Nkomazi. A private space at each clinic was used for this purpose. Understanding of “whether the participants knew what they were getting themselves into” was assessed by requesting them to briefly repeat what the study entailed. The participants were advised that they could withdraw at any stage of the study and that they would continue to receive usual care. The patients agreed to take part in the study then signed the consent form.

The foundation of informed consent was the competence of the participant to understand and decide. All participants had to be mentally competent and not too sickly or weak. The participants were not coerced, voluntariness was respected as was explained to research assistants during their training. Whether, or not, patients participated in the study did not affect the way they were treated by each clinic. The only difference was a can of cold beverage and a pack of snacks was offered to each study participant after the interview; and the participants did not know about this prior to the interview. Refreshment was only offered after the interview.

Recruitment of participants:

Participants were recruited on clinic days dedicated for follow-up of patients on HAART. The 4 Research Assistants (RAs) did the recruitment of participants. A simple random sampling was used to select the first participant; thereafter systematic random sampling was used.

Diagnosis of Neuropathic Pain and Anxiety

Participants were asked if they had any nagging (significant) pain over the past month. The DN4-Interview was then administered to all patients who had pain for a month, or longer. All patients who scored at least 4 out of 7 on the DN4-Interview were diagnosed as having neuropathic pain. The SCID-CV was then administered to all the patients who were diagnosed with neuropathic pain. The SCID-CV was administered as a diagnostic tool for anxiety disorders amongst PLWHIV who had neuropathic pain. The SCID-CV, was preferred over an anxiety screening tool because the aim of the study was to identify any of the anxiety disorders in patients who had neuropathic pain.

The RAs kept all the questionnaires securely and handed them over to the principal investigator (PI) at the end of each clinic day.

4.4.4 Ethical considerations

The Research Proposal was approved by the University of Cape Town (UCT), Faculty of Health Sciences Human Ethics Research Committee (Ref 587/2012). The proposal was then submitted to the Mpumalanga Department of Health Provincial Human Research Ethics Committee which gave access approval. Ethical standards in keeping with the four principles of Autonomy, Beneficence, Non-maleficence and Justice were upheld. For instance; patient confidentiality was maintained and patients had the right to consent and withdraw at any stage of the study regardless of the reason. If a participant needed health care they were channeled to the sister-in-charge to manage further. The two heads of government clinics in the Nkomazi East and West gave written permission for the study to be conducted at the clinics in Nkomazi Sub-district.

4.4.5 Data Storage

A lockable case was provided for safe-keeping of the completed questionnaires. At the end of each clinic day the research assistants delivered the locked case with all the consent forms and completed questionnaires to the PI. The consent forms and questionnaires shall be kept locked and safe for not less than 5 years before they shall be safely disposed of.

This was the phase during which a tally of all incoming questionnaires should have been kept from day one; unfortunately this was not done. The calculated number of study participants (384) would not have been exceeded had a tally been initiated at the very beginning, instead of just eyeballing the incoming completed forms and relying on estimation. The PI underestimated the rate at which the interviews were conducted.

4.4.6 Data Analysis

All data collected were coded and entered in Microsoft excel 2010 (Microsoft corporation, Seattle, USA, USA) and exported into Stata 14.1 (STATA Corp LP, College station, Texas, USA) for analysis. The analyses report on three outcomes; that being general pain, neuropathic pain and anxiety disorders. Numerical variables were explored for normality using histogram, box-and-whisker plot and the Shapiro Wilk test. Age is reported on both as a numerical variable

and as an ordinal categorical variable. Age was not normally distributed, as a result it is summarized using the Interquartile Range (IQR) and median (non-parametric statistics). The Wilcoxon sum rank test is used to test the differences between two medians e.g. age differences in those with pain and those without pain, etc.

Univariate analysis of Categorical variables is summarized using proportions/percentages and a bar graph. The two sample test of proportions is used to compare the differences between two proportions. In a case where there are more than two categories, one of the categories is used as a reference category to allow for this binary comparison. Testing for an association between two categorical variables was conducted using the Chi-squared test or the Fisher's Exact test depending on the value of the expected frequencies. If <5 the Fisher's exact test was used. However, if the expected frequencies were <5 then the Fisher's exact test is used. Since this is a Cross-sectional study, the Prevalence Ratio (PR) is the relative measure of association used for reporting. The 95% Confidence Interval (95% CI) is used to show the precision of estimates. The level of significance was set at 5% (p-value ≤ 0.05).

5. RESULTS

A total number of 508 patients were included in the study. Participants were more likely to be interviewed at kaMhlushwa clinic (n = 203 or 39.96%; 95% CI: 35.67 – 44.37) than being interviewed at Naas clinic (n = 126 or 24.80%; 95% CI: 21.11 – 28.80). Similarly the proportion of participants interviewed at Mangweni clinic (n = 179 or 35.24%; 95% CI: 31.08 – 39.57) were more than those interviewed at Naas clinic (Table1).

Patient Demographics

Table 1 further shows the demographic characteristics of participants. There were more females (77.56%; 95% CI: 73.68 – 81.12; n = 394) than males (22.44%; 95% CI: 18.88 – 26.32; n = 114) in the sample. Furthermore, females were significantly more likely to be younger (median age = 36) than their male counterparts (median age = 39.50; p-value = 0.0001). Whilst 25% of all females were below the age of 30, only 25% of females were older than 43 years of age. In contrast to males where 25% of them were older than 48 years of age.

SiSwati was considered to be the home language for 77.56%; 95% CI: 73.68 – 81.12 (n = 394) of participants followed by xiTsonga (19.09%; 95% CI: 15.77 – 22.79; n = 97). Even though over half of the participants (51.97%; 95% CI: 47.52 – 56.39; n = 264) had some secondary education, 45.47%; 95% CI: 41.08 – 49.92 (n = 231) of the participants either had no education at all or had some primary education. Only 505 (99.41%; 95% CI: 98.28 – 99.88) participants responded on questions about employment status and their monthly income.

Most respondents (73.27%; 95% CI: 69.18 – 77.08; n = 370) were unemployed and most had no income at all (57.43%; 95% CI: 52.98 – 61.78; n = 290). Even though females comprised 68.89% (n =93; 95% CI: 60.36 – 76.57) of the employed respondents (n = 135), a significantly higher proportion of males was employed (n = 42 or 36.84%; 95% CI: 27.99 – 45.70) as opposed to females (n = 93 or 23.79%; 95% CI: 19.65 – 28.32).

Table 1: Patient Characteristics and Demographics (508 participants)

CLINIC	n (%; 95% Confidence interval)		p-value
Naas	126 (24.80; 21.05 – 28.56)		1
Mangweni	179 (35.24; 31.08 – 39.39)		0.0003
KaMhlushwa	203 (39.96; 35.70 – 44.22)		< 0.0001
Total	508 (100)		
SEX	n (%; 95% Confidence interval)		p-value
Female	394 (77.56; 73.93 – 81.19)		<0.0001
Male	114 (22.44; 18.81 – 26.07)		
Total	508 (100)		
AGE (Years)	n (%; 95% Confidence interval)		p-value
18 – 30	132 (25.98; 22.17 – 29.80)		1
31 – 40	194 (38.19; 33.96 – 42.41)		<0.0001
41 – 50	122 (24.02)		0.469
>50	60 (11.81)		<0.0001
Total	508 (100)		
AGE (Years) by SEX	Interquartile Range	Median	p-value
Female	30 – 43	36	0.0001
Male	33 – 48	39.50	
LANGUAGE	n (%; 95% Confidence interval)		p-value
siSwati	394 (77.56; 73.93 – 81.19)		1
xiTsonga	97 (19.09; 15.68 – 22.51)		<0.0001
Other	17 (3.35; 1.78 – 4.91)		<0.0001
Total	508 (100)		
RELIGION	n (%; 95% Confidence interval)		p-value
Christian	471 (92.72; 90.46 – 94.98)		1
Muslim	1 (0.20; -0.19 – 0.58)		<0.0001
African	16 (3.15; 1.63 – 4.67)		<0.0001
Other	20 (3.94; 2.25 – 5.63)		<0.0001
Total	508 (100)		
EDUCATION	n (%; 95% Confidence interval)		p-value
None	96 (18.90; 15.49 – 22.30)		1

Primary School	135 (26.57; 22.73 – 30.42)	0.004
Secondary	264 (51.97; 47.62 – 56.31)	<0.0001
Tertiary	13 (2.56; 1.19 – 3.93)	<0.0001
Total	508 (100)	
EMPLOYMENT	n (%; 95% Confidence interval)	p-value
Yes	135 (26.73; 22.87 – 30.59)	
No	370 (73.27; 6.94 – 77.13)	< 0.0001
Total	505 (100)	
Monthly Income (Rand)	n (%; 95% Confidence interval)	p-value
None	290 (57.43; 53.11 – 61.74)	1
< 1000	99 (19.60; 16.14 – 23.07)	<0.0001
1000 – 4 999	105 (20.79; 17.25 – 24.33)	<0.0001
≥5000	11 (2.18; 0.91 – 3.45)	<0.0001
Total	505 (100)	

When age and gender are used as a measure of demographic characteristics, Table 2 shows that participants had similar characteristics between the 3 facilities.

Table 2: Comparison of basic demographics by Facility

Gender	Naas: n (%)	Mangweni: n (%)	KaMhlushwa: n (%)	p-value
Female	96 (76.19)	145 (81.01)	153 (75.37)	0.384
Male	30 (23.81)	34 (18.99)	50 (24.63)	
Age Group (Years)	Naas: n (%)	Mangweni: n (%)	KaMhlushwa: n (%)	p-value
18 – 30	36 (28.57)	44 (24.58)	52 (25.62)	0.913
31 – 40	50 (39.68)	71 (39.66)	73 (35.96)	
41-50	27 (21.43)	44 (24.58)	51 (25.12)	
>50	13 (10.32)	20 (11.17)	27 (13.30)	

Univariate Analysis of Outcome variables

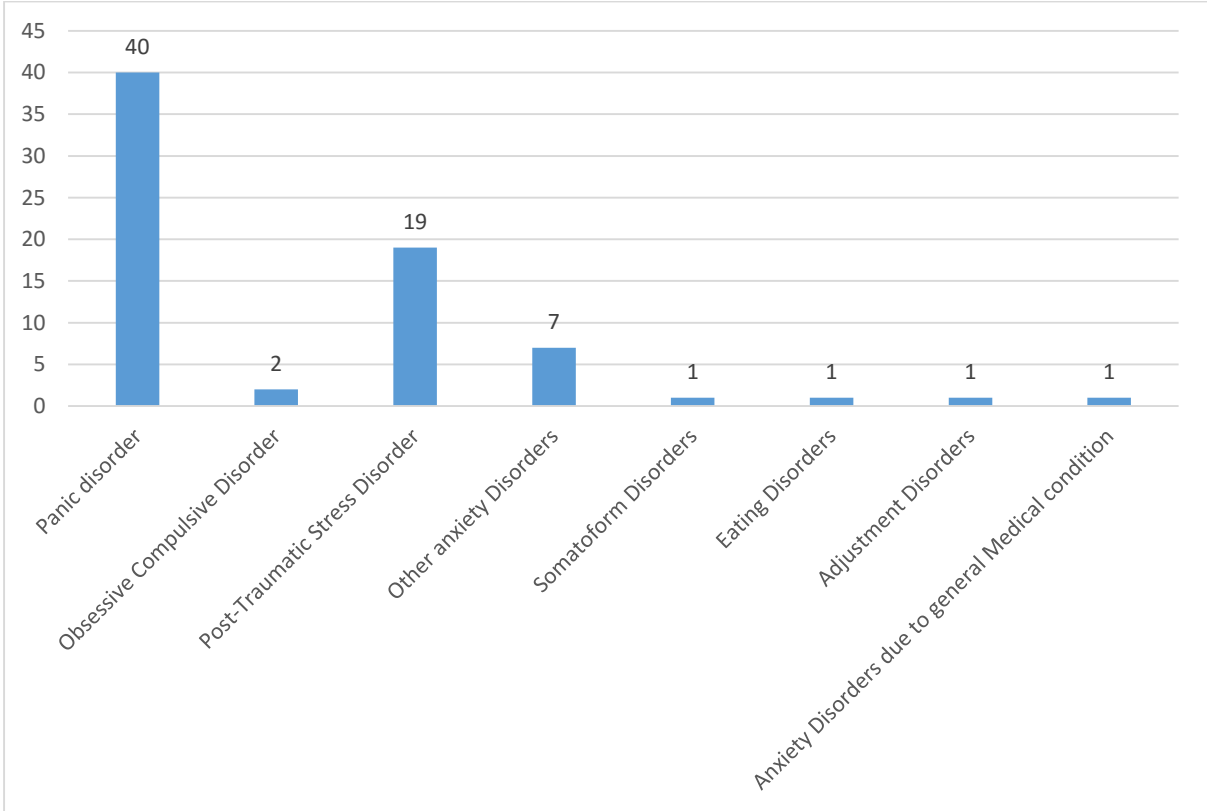
Table 3 is the most vital of all the tables in the results chapter, the corner stone of this study and is the answer to the aim of the study. Of all the participants, 46.06%; 95% CI: 41.66 – 50.51 (n = 234) described having at least some pain when screened. Similarly, there were individuals with neuropathic pain (17.72%; 95% CI: 14.49 – 21.32; n = 90) and the majority of those with pain had no neuropathic pain (82.28%; 95% CI: 78.68 – 85.51; n = 418). Table 3, also shows that 80%; 95% CI: 70.25 – 87.69 (n = 72) of respondents who had neuropathic pain (n = 90) had anxiety disorders. It has to however, be noted that anxiety disorders were only assessed in those patients with Neuropathic pain (n = 90).

A detailed analysis (Figure 1) showed that the majority of participants (n = 40; 55.56%; 95% CI: 43.36 – 67.28) who had an anxiety disorder had a panic disorder. Just over a quarter of anxiety disorders (26.39%; 95% CI: 16.70 – 38.10; n = 19) were due to Post-Traumatic Stress disorders (PTSD) followed by Other Anxiety disorders (n = 7) and Obsessive Compulsive Disorders (n = 2). Somatoform disorders, eating disorders, adjustment disorders and anxiety disorders due to general medical conditions each accounted for a single case of an anxiety disorder (n = 1).

Table 3: Univariate Analysis of Outcome Variables

PAIN	n (%; 95% Confidence interval)	p-value
Yes	234 (46.06; 41.73 – 50.40)	0.012
No	274 (53.94; 49.60 – 58.27)	
NEUROPATHIC PAIN	n (%; 95% Confidence interval)	p-value
Yes	90 (17.72; 14.40 – 21.04)	<0.0001
No	418 (82.28; 78.96 – 85.60)	
ANXIETY DISORDER	n (%; 95% Confidence interval)	p-value
Yes	72 (80; 71.74 – 88.26)	<0.0001
No	18 (20; 11.74 – 28.26)	

Figure 1: Types of Anxiety Disorders



Association of pain with demographic characteristics

Table 4: Association of Pain with Demographic Characteristics

Variable	Category	n (%)		PR (95% CI)	p-value
		Yes	No		
CLINIC	Naas	26(20.63)	100 (79.37)	1	1
	Mangweni	19 (10.61)	160 (89.39)	1.94 (1.13 – 3.36)	0.015
	KaMhlushwa	189 (80.77)	14 (6.90)	0.22 (0.16 – 0.31)	<0.0001
	Total	234 (46.06)	274 (53.94)		
SEX	Female	178 (45.18)	216 (54.82)	1	1
	Male	56 (49.12)	58 (50.88)	0.92 (0.74 – 1.14)	0.457
AGE (Years)	18 – 30	57 (43.18)	75 (56.82)	1	1
	31 – 40	77 (39.69)	117 (60.31)	1.09 (0.84 – 1.41)	0.529
	41 – 50	64 (52.46)	58 (47.54)	0.82 (0.64 – 1.07)	0.139
	>50	36 (60)	24 (40)	0.72 (0.54 – 0.96)	0.031
LANGUAGE	Siswati	172 (43.65)	222 (56.35)	1	1
	xiTsonga	51 (52.58)	46 (47.42)	0.83 (0.67 – 1.03)	0.114
	Other	11 (64.71)	6 (35.29)	0.67 (0.47 – 0.98)	0.087
RELIGION	Christian	213 (45.22)	258 (54.78)	1	1
	Muslim	0	1 (100)	N/A	0.549
	African	6 (37.50)	10 (62.50)	1.21 (0.64 – 2.29)	0.541
	Other	15 (75.00)	5 (25.00)	0.60 (0.46 – 0.79)	0.009
EDUCATION	None	56 (58.33)	40 (41.67)	1	1
	Primary School	54 (40)	81 (60)	1.46 (1.12 – 1.90)	0.006
	Secondary	117 (44.32)	147 (55.68)	1.32 (1.06 – 1.63)	0.019
	Tertiary	7 (53.85)	6 (46.15)	1.08 (0.64 – 1.84)	0.759
EMPLOYMENT	Yes	63 (46.67)	72 (53.33)	1	1
	No	171 (46.22)	199 (53.78)	1.01 (0.82 – 1.25)	0.928
MONTHLY INCOME (Rands)	None	94 (32.41)	196 (67.59)	1	1
	< 1000	80 (80.81)	19 (19.19)	0.40 (0.33 – 0.49)	<0.0001
	1000 – 4 999	55 (52.38)	50 (47.62)	0.62 (0.48 – 0.79)	0.0003
	≥5000	5 (45.45)	6 (54.55)	0.71 (0.37 – 1.39)	0.366
Age (Years)	Category	n (%)	IQR (Years)	Median (Years)	p-value
	Pain	234 (46.06)	31 – 48	38	0.005
	No pain	274 (53.94)	30 – 42	35.5	
	Total	508 (100)	30 – 45	37	

When clinics were compared, kaMhlushwa had the majority of patients with pain (Table 4). In fact, pain was prevalent in 80.77%; 95% CI: 75.13 – 85.61 (n = 189) of the participants from kaMhlushwa clinic. It was further found that patients from Naas clinic were 22% less likely to

report pain than patients from kaMhlushwa clinic and this was statistically significant (PR = 0.22; p-value <0.0001). When compared to participants from Mangweni clinic, those from Naas were 94% more likely to experience pain than those from Mangweni clinic, this association was also statistically significant (PR = 1.94; p-value = 0.015).

There was no statistical difference in the gender characteristics of patients who reported pain and those who did not (PR = 0.92; p-value = 0.457). Patients with pain were more likely to be older (median age of 38) compared to those without pain (median = 35.5) and this was statistically significant (p-value = 0.005). Furthermore, participants younger than 31 years of age were found to be 28% less likely to report pain than those older than 50, this was also statistically significant (PR = 0.72; p-value = 0.031).

Even though there was no statistical difference in pain experiences of those with tertiary education and those with no education at all (PR = 1.08; p-value = 0.759); those without education were 46% more likely to report pain than those with primary school education, this was statistically significant (PR = 1.46; p-value = 0.006). Similarly, having no education at all increased the likelihood of reporting pain by 32% (PR = 1.32; p-value = 0.019).

Neuropathic Pain

As mentioned under Univariate analysis of outcome variables and indicated in Table 5, neuropathic pain among all the study participants was prevalent in 17.72% (n =90; 95% CI: 14.49 – 21.32) of the participants. However, if only those with pain are considered (n = 234), the prevalence of neuropathic pain in this subgroup was 38.46% (95% CI = 32.20 – 45.02). Of all the clinics, neuropathic pain prevalence was highest in KaMhlushwa clinic (28.57%; 95% CI: 22.47 – 35.32; n = 58) this is 64.44% (95% CI: 53.65 – 74.26) of all the neuropathic pain cases (n = 90). Shown in Table 4 is that patients from Naas clinic were 53% less likely to have neuropathic pain compared to patients from KaMhlushwa clinic (PR = 0.47; p-value = 0.0002).

Table 5: Bivariate Analysis of Demographic Characteristics and Neuropathic pain

Variable	Category	n (%)		PR (95% CI)	p-value
		Yes	No		
CLINIC	Naas	17 (13.49)	109 (86.51)	1	1
	Mangweni	15 (8.38)	164 (91.62)	1.61 (0.84 – 3.10)	0.151
	KaMhlushwa	58 (28.57)	145 (71.43)	0.47 (0.29 – 0.77)	0.002
	Total	90 (17.72)	418 (82.28)		
SEX	Female	71 (18.02)	323 (81.98)	1	1
	Male	19 (16.67)	95 (83.33)	1.08 (0.68 – 1.72)	0.739
AGE (Years)	18 – 30	20 (15.15)	112 (84.85)	1	1
	31 – 40	26 (13.40)	168 (86.60)	1.13 (0.66 – 1.94)	0.656
	41 – 50	26 (21.31)	96 (78.69)	0.71 (0.42 – 1.21)	0.203
	>50	18 (30)	42 (70)	0.51 (0.29 – 0.88)	0.017
LANGUAGE	Siswati	70 (17.77)	324 (82.23)	1	1
	xiTsonga	17 (17.53)	80 (82.47)	1.01 (0.63 – 1.64)	0.956
	Other	3 (17.65)	14 (82.35)	1.01 (0.35 – 2.87)	0.644
RELIGION	Christian	85 (18.05%)	386 (81.95)	1	1
	Muslim	0	1 (100)	N/A	0.820
	African	2 (12.50)	14 (87.50)	1.44 (0.39 – 5.35)	0.433
	Other	3 (15)	18 (85)	1.20 (0.42 – 3.48)	0.504
EDUCATION	None	23 (23.96)	73 (76.04)	1	1
	Primary School	15 (11.11)	120 (88.89)	2.16 (1.19 – 3.91)	0.009
	Secondary	48 (18.18)	216 (81.82)	1.32 (0.85 – 2.04)	0.223
	Tertiary	4 (30.77)	9 (69.23)	0.78 (0.32 – 1.90)	0.593
EMPLOYMENT	Yes	27 (30)	63 (70)	1	1
	No	108 (26.02)	307 (73.98)	1.15 (0.81 – 1.64)	0.440
MONTHLY INCOME (Rand)	None	42 (14.48)	248 (85.52)	1	1
	< 1000	24 (24.24)	75 (75.76)	0.60 (0.38 – 0.93)	0.026
	1000 – 4 999	22 (20.95)	83 (79.05)	0.69 (0.43 – 1.10)	0.123
	≥5000	2 (18.18)	9 (81.82)	0.80 (0.22 – 2.88)	0.496
Age (Years)	Category	n (%)	IQR (Years)	Median (Years)	p-value
	Neuropathic Pain	90 (17.72)	32 – 50	39.5	0.017
	No Neuropathic pain	418 (82.28)	30 – 44	37	
	Total	508 (100)	30 – 45	37	

Once more there was no statistical difference in the prevalence of neuropathic pain in males and females (PR = 1.08; p-value = 0.739). However, the age pattern was similar to that of

general pain in that those with neuropathic pain were significantly older than those without neuropathic pain (p-value = 0.017). Further found was that those younger than 31 years of age were 49% less likely to have neuropathic pain than those older than 50 years of age (PR = 0.51; p-value = 0.017).

There was no statistically significant association between religion, language, or employment status with neuropathic pain (Table 5). Having no income at all, however, made it 40% less likely for participants to be diagnosed with neuropathic pain compared to those who had an income of < R1000 and this was statistically significant (PR = 0.60; p-value = 0.026). In addition, those without education were at least 2 times more likely to have neuropathic pain than those with some primary school education (PR= 2.16; p-value = 0.009). All the other level of education categories were not statistically significant.

Bivariate Analysis of Demographic characteristics and Anxiety Disorders

As previously highlighted, the prevalence of anxiety disorders was 80% (n = 72; 95% CI: 71.74 – 88.26) in the study sample who were diagnosed with neuropathic pain. Participants who were interviewed from kaMhlushwa clinic were $\pm 17\%$ more likely to be diagnosed with an anxiety disorder when compared to participants who were seen at Naas clinic (PR = 1.17; 95% CI: 0.84 – 1.63; p-value = 0.308). Even though a comparison of participants between the age of 18 to 31 and other age categories did not yield a statistically significant difference in their diagnoses of an anxiety disorder; participants with an anxiety disorder were slightly older but this was not statistically significant (median age of 41.5 years compared to 38) with a p-value of 0.984. Neither gender, language, education, religion, employment nor income were statistically associated with anxiety disorders. Table 6 shows a summary of the bivariate association of anxiety disorders and demographic characteristics.

Table 6: Bivariate Analysis of Demographic Characteristics and Anxiety Disorders

Variable	Category	n (%)		PR (95% CI)	p-value
		Yes	No		
CLINIC	Naas	12 (70.59)	5 (29.41)	1	1
	Mangweni	12 (80)	3 (20)	0.88 (0.59 – 1.31)	0.691
	KaMhlushwa	48 (82.76)	10 (17.24)	0.85 (0.61 – 1.18)	0.308
	Total	72 (80)	18 (20)		
SEX	Female	57 (80.28)	14 (19.72)	1	1
	Male	15 (78.95)	4 (21.05)	1.02 (0.78 – 1.32)	1.00
AGE (Years)	18 – 30	15 (75)	5 (25)	1	1
	31 – 40	20 (76.92)	6 (23.08)	0.98 (0.70 – 1.36)	1.00
	41 – 50	24 (92.31)	2 (7.69)	0.81 (0.62 – 1.07)	0.213
	>50	13 (72.22)	5 (27.78)	1.04 (0.71 – 1.52)	1.00
LANGUAGE	Siswati	53 (75.71)	17 (24.29)	1	1
	xiTsonga	16 (94.12)	1 (5.88)	0.80 (0.67 – 0.96)	0.178
	Other	3 (100)	0	N/A	N/A
RELIGION	Christian	68 (80)	17 (20)	1	1
	Muslim	0	0	N/A	N/A
	African	2 (100)	0	N/A	N/A
	Other	2 (66.67)	1 (33.33)	1.2 (0.54 – 2.69)	0.501
EDUCATION	None	18 (78.26)	5 (21.74)	1	1
	Primary School	11 (73.33)	4 (26.67)	1.07 (0.73 – 1.55)	1.00
	Secondary	39 (14.77)	9 (18.75)	0.96 (0.75 – 1.24)	0.759
	Tertiary	4 (100)	0	N/A	N/A
EMPLOYMENT	Yes	22 (81.48)	5 (18.52)	1	1
	No	50 (79.37)	13 (20.63)	1.03 (0.82 – 1.28)	0.818
MONTHLY INCOME (Rand)	None	35 (83.33)	7 (16.67)	1	1
	< 1000	18 (75)	6 (25)	1.11 (0.85 – 1.45)	0.523
	1000 – 4 999	18 (81.82)	4 (18.18)	1.02 (0.80 – 1.29)	1.00
	≥5000	1 (50)	1 (50)	1.67 (0.41 – 6.71)	0.334
Age (Years)	Category	n (%)	IQR (Years)	Median (Years)	p-value
	Anxiety Disorders	72 (80)	32 – 50	41.5	0.984
	No Anxiety Disorder	18 (20)	30 – 51	38	
	Total	90	30 – 50	39.5	

6. DISCUSSION

6.1 Introduction

There appears to be a gap in the literature with regards to studies that specifically research the prevalence of comorbid neuropathic pain and anxiety disorders among PLWHIV. This study was conducted in a high HIV prevalence setting in the Mpumalanga Province of South Africa, as the two conditions appeared to be highly prevalent in clinical practice and additional knowledge may be able to contribute to the literature and influence practice for better patient outcomes.

6.2 Pain Prevalence

Of note is the fact that patients at KaMhlushwa reported a high prevalence of pain whereas patients at the other two clinics reported a much lower prevalence of pain. The high prevalence of pain in kaMhlushwa clinic is consistent with literature that reported a pain prevalence of 84%^{32,39,40}. It is important to consider the possible reasons behind the difference in pain prevalence between the three clinics:

-It may be that pain was better assessed and managed at the Mangweni and Naas clinics than at kaMhlushwa clinic. There has recently been an increase in effort by national department of health to improve pain control primary health care facilities (anecdote).

-The other possible explanation is that of reporting bias in that pain was underreported at Mangweni and Naas clinics.

The KaMhlushwa figures are in keeping with the fact that several factors threaten emotional health in those diagnosed with HIV, including coping with physical pain, worry about health, disrupting social life, isolation, fear of disclosure, anger and worry about self-image²⁵ and this impacts on a patient's pain experience. A previous South African Primary Care morbidity profile that sampled facilities from 4 of the countries Provinces (Limpopo, North West and Mpumalanga) found pain to be the primary presenting complaint in $\pm 23.9\%$ of Primary Care presentations⁷⁹. Although that primary care study did not look only at PLWHIV but all patients irrespective of their HIV serological status.

6.3 Bio-Medical data from the Study

This study in Nkomazi sub-district found that the pain experience was not discriminatory by gender, employment status, language and/or religion of PLWHIV from Nkomazi. In the literature lack of employment and the subsequent low socio-economic status intensifies pain experience and increases the prevalence of pain⁵. However, patients with pain were more likely to be older compared to those without pain (p-value = 0.005). Clinical research indicates that pain is perceived, assessed, experienced and even treated differently depending on a person's gender, race or ethnicity and age⁸⁰. Age differences in pain experience are less consistent^{81,82}. Some studies indicate older adults to be more sensitive to experimental pain than young adults, whereas others suggest a decrease in sensitivity with age^{81,82}. Although the literature describes that^{32,35,42} women have been found to be more susceptible to neuropathic pain than males^{32,35,42}, there was no statistically significant difference in the prevalence of neuropathic pain by gender in this study.

6.4 Neuropathic Pain

Neuropathic pain among this Nkomazi cohort was 17.72% which is comparable to 20.9% in an earlier South African study in an academic setting which looked at the prevalence of PLWHIV but who had not yet initiated HAART unlike the patients in this study⁴¹; and it is recognised as being difficult to treat and needs focused attention. The Nkomazi study might have therefore given patients an opportunity to report their pain as questions pertaining to pain were directly asked to patients who would, ordinarily have only come to collect medications and perform routine investigations.

A previous study in an urban academic setting in South Africa estimated the prevalence pain of predominantly neuropathic origin (POPNO) in pre-HAART patients to be at $\pm 20.9\%$ ⁴¹. Even though the populations can be said to be different in terms of their geography and their HAART status, the neuropathic pain prevalence of 17.72% among the Nkomazi cohort of patients in this study is comparable. The fact that neuropathic pain was prevalent among 38.46% of the Nkomazi PLWHIV who reported pain of all types from this study demonstrates the seriousness of this problem in rural Nkomazi.

The high prevalence of neuropathic pain (28.57% compared to 17.72% among all the participants from all the clinics put together) in KaMhlushwa clinic cannot be ignored and needs more attention. This is much higher than that found among a Pretoria cohort as noted above⁴¹. The significantly different findings between the facilities could be a direct result of poor management of neuropathic pain at kaMhlushwa clinic and/or very good pain recognition and management at the other two clinics.

6.5 Relationship between pain and anxiety

Anxiety disorders were only assessed in patients who had neuropathic pain in this Nkomazi study. This therefore limited the analyses that could be performed. The relationship between Anxiety and HIV is bi-directional, thus making it difficult to determine temporality i.e. which came first^{16,52}. There was a high prevalence of anxiety disorders in this study which is consistent with the prevalence of psychological symptoms among PLWHIV in a multi-centre, Sub-Saharan Africa¹¹. This international sub-Saharan study used the terms worry and sadness in a survey designed for patient responses as being more accessible terms to describe anxiety and depression. Therefore, the high prevalence of anxiety disorders among the Nkomazi PLWHIV who experienced neuropathic pain still stands out. Interesting the 50% of the patients who took part in the international study were on HAART and receiving palliative care concomitantly but psychological symptoms were still prominent¹¹. It would have been thought that the widespread rollout of HAART, including palliative care, would result in a reduction in this prevalence of anxiety disorders since patients would be expected to worry less about the progression of the disease, however, this has not been the case^{11,38}. This could be due to the fact that disease progression is not the only source of anxiety for patients with a chronic illness but the stigma and the nature of medication also increases the vulnerability to anxiety disorders.

Our study focused on prevalence of anxiety disorders among PLWHIV who also had neuropathic pain, since there are more research focused on the association between depression and pain than there are between HIV and anxiety disorders despite the stronger association between HIV and anxiety¹⁰. It is also of interest that neuropathic pain and anxiety disorders were comorbid in 80% of patients with neuropathic pain and it would have been of greater value to have sought the prevalence of anxiety disorders among those PLWHIV with non-neuropathic pain in Nkomazi.

Even though participants from this study were recruited at varying stages since their initiation of HAART, it is documented that the prevalence of Post-Traumatic Stress Disorder (PTSD) and anxiety increases in some PLWHIV post-diagnosis often because of an escalation of abuse and being stigmatised^{24,28}. This was not however, explored in this study. In this Nkomazi study, Panic disorders had the highest prevalence (55.56%) of all anxiety disorders (n = 72) which was followed by PTSD (26.39%) and Other Anxiety Disorders (9.72%). In the literature reviewed the prevalence of PTSD was as high as 15-64%¹⁸. This is a contrast to the findings of a previous study that was conducted in private practices of Nkomazi among non-selected patients where PTSD was more prevalent (29.33%) followed by Panic Disorders (24%)⁷⁵.

Participants who were interviewed from kaMhlushwa clinic were ± 2.5 times more likely to be diagnosed with an anxiety disorder when compared to those who were seen at Naas clinic; and overall women in this Nkomazi study were 8% more likely to have an anxiety disorder than males but this was not statistically significant, a contrast to the findings by McLean et al⁸³. Literature according to their article has found anxiety disorders to not only be more prevalent but to also be more disabling in women than in men⁸³.

As confirmed in this study, participants with an anxiety disorder were slightly older (median age of 41.5 years) than those without (Median age = 37 years). Even though anxiety disorders are chronic, they are not necessarily lifelong. The median age of onset is often below the age of 12 years (if pre-existing)⁸⁴. The median age of onset for Panic Disorders is ± 24 years⁸⁴. Panic disorders accounted for more than 50% of the patients with anxiety disorders, the age would therefore be skewed by them. Given all this it would therefore be expected that anxiety disorders would be higher at an older age.

The finding in this study that those with no education at all were more than twice more likely to have had an anxiety disorder than those with some primary school education is in keeping with those in the literature that lower educational status tended to worsen the anxiety among PLWHIV^{12,21}. This could be due to several reasons such as; an inability to negotiate for safer sexual practice, economic dependence, lack of knowledge and a delay to seek healthcare.

6.6 Prevalence of Anxiety disorders among PLWHIV in Nkomazi sub-district who also experience Neuropathic Pain

Although this study did not look for anxiety disorders among non-HIV infected patients who attended the three clinics, it has been noted there is a strong link between anxiety and pain in the general population and among PLWHIV⁶⁻⁸. The high prevalence (80%) of anxiety disorders among those Nkomazi PLWHIV confirms the reasoning that if pain in general increases rates of anxiety disorders among general population and among PLWHIV, then the prevalence of anxiety disorders among PLWHIV with neuropathic pain would be much higher.

Panic disorders had the highest prevalence (n = 40 or 55.56%) of all anxiety disorders (n = 72) which was followed by PTSD (26.39% or n = 19) and Other Anxiety Disorders (n = 7 or 9.72%). Whether, or not, this was due to escalation of abuse post-diagnosis as was the case in another study was not tested for in this study^{24,28}. This is a contrast to the findings of a previous study that was conducted in private practices of Nkomazi where PTSD was more prevalent (29.33%) followed by Panic Disorders (24%)⁷⁵. The PTSD prevalence among the Nkomazi PLWHIV also is in the lower range of the prevalence of PTSD among PLWHIV found in the literature (15-64%)¹⁸.

6.7 Importance of Good Pain Assessment

Without any co-morbidities neuropathic pain is already a major problem on its own; this is true for the sufferer, the intimate contacts and the health care providers. It is worth noting how prevalent pain in general is among the Nkomazi cohort and that the prevalence of neuropathic pain among the PLWHIV who attended Nkomazi HIV treatment clinics is comparable to an urban setting in South Africa⁴¹.

Knowing the intimate relationship between pain and anxiety disorders and seeing how prevalent these disorders were among the Nkomazi PLWHIV who took part in the study; there is good reason that routine evaluation of pain among PLWHIV pays off in the long run. Anxiety is known to worsen immune-suppression and pain of any kind impacts negatively on anxiety; so by properly managing pain in PLWHIV one would indirectly be bolstering the immune system of a patient in need of a robust immune system^{4,11,30}.

6.8 Limitations of the study

Despite efforts being made to enhance the study's validity and reliability there were however limitations in the study. Findings cannot therefore be extrapolated outside the study setting (kaMhlushwa, Naas and Mangweni clinics). The study was a health facility survey that use an interviewer administered questionnaire:

1. Most important of all the limitations of this study was the fact that anxiety disorders were only assessed in patients who had neuropathic pain. This therefore limited the analyses that could be performed. For instance, anxiety disorders in patients without neuropathic pain could have been missed. As a result, the prevalence ratio of anxiety disorders amongst patients with neuropathic pain (a hypothesised exposure) and those with non-neuropathic pain (a hypothesized control group) could not be obtained. Furthermore, the prevalence of anxiety disorders cannot be generalised to all patients living with HIV in Nkomazi sub-district but only to those with neuropathic pain.
2. A healthy-worker effect bias could have been present as those who are non-symptomatic (absence of pain, neuropathy or anxiety disorders) could have been at work or in the community. This could have therefore resulted in over-sampling of the “unwell”, even if all those PLWHIV who were sampled were presumed to have come for routine tests and collection of medications.
3. The study design limited comparisons as participants all had HIV (no controls). This study therefore leaned towards a case-series.
4. The environment could have been intimidating for patients and they could have therefore given out “carefully thought out responses”. In addition, the facilities had limited space for interviews, participants could have overheard responses from other respondents. These factors could have therefore given rise to a social desirability bias and a diagnosis bias.
5. The study did not make use of a validated instrument for measuring pain of all types despite the fact that presence/absence of pain was the “entry point” in the search for neuropathic pain. Simply one question was asked and that was whether the patients had any nagging pain over the previous 4 weeks. There could therefore be a diagnostic bias due to this.
6. Even though the interviewers were nurses who received minimal training on the use of the tools, an interviewer bias could have occurred as they could have brought in their personalities

during the interviews. Such could have been the case when you compare the results of the pain prevalence of 80.77% in kaMhlushwa to those of Mangweni Clinic (10.61%).

7. SCID-CV the instrument that was used to diagnose anxiety disorders has not been validated and standardised for use in siSwati, the local dialect. This could have therefore affected the reliability of the questions and responses.

8. The training period was significantly short period of time to adequately train non-psychiatric nurses in the application of SCID-I (CV) for the purpose of research or in clinical use. This brevity of training and recruitment of non-psychiatric nurses might have adversely affected the quality of data collected by these research assistants.

9. The error of over-shooting the calculated sample size may not be seen as a limitation but a poor supervisory role of the PI with an added advantage of the larger sample size.

All these factors are however, balanced by the fact that all patients would have been assessed in the same way.

7. CONCLUSIONS AND RECOMMENDATIONS

South Africa's disease burden is complex and requires a systematic approach^{1,79}. This study aimed to determine the prevalence of common but often under-diagnosed conditions that are often comorbid with HIV. Nkomazi Sub-district is a deprived community with a high HIV prevalence. This study achieved its objectives by confirming a number of established findings such as the high prevalence of pain amongst Primary Care patients living with HIV; a high prevalence of neuropathic pain and a high prevalence of anxiety disorders among PLWHIV in the sub-district. In addition Neuropathic pain and anxiety disorders were found to be higher in older participants.

- 1) Co-occurrence of anxiety in patients with neuropathic pain was as high as 80% which strengthens the belief that Primary Care providers should be empowered on the management of pain, neuropathic disorders and anxiety disorders. Recognition of pain of all types, but especially neuropathic pain should be high on the priorities of health care workers who work with PLWHIV.
- 2) This study will serve as a baseline and yardstick for other future studies on pain in this population. Feedback will be given to stakeholders at various levels of the community and the Mpumalanga department of health to get their insights on some of the outliers found in the study.
- 3) Findings from this study will not only be shared with academics and policy makers but will also be used as a health promotion instrument. Community participation is one of the key principles of health promotion. The community need to therefore be made aware of the importance of de-stigmatising HIV; the reduction of new HIV infections; the presence and treatment of anxiety disorders and various types of pain including Neuropathic pain in PLWHIV. The other factors mentioned have already been part of programs of the national and provincial DoH, except looking at/for anxiety and pain (especially, neuropathic) in most patients at risk. In this way the systematic approach to the improvement of the disease burden will be ensured.
- 4) It would therefore be considered good clinical practice to screen for anxiety disorders in all patients with neuropathic and non-neuropathic pain and vice-versa. This is of course is dependent on time and skills level of the health care providers. This does not mean administering the long and tedious SCID-CV or DN4 in all patients at all times. Simply asking a follow up patient simple questions like: “are there any nagging pains, any other issues, worries and/or fears?”
- 5) Further evaluation of the possibility of poor pain control at KaMhlushwa clinic, or that of poor pain recognition at the other two clinics may result in additional training and a quality improvement programme at kaMhlushwa clinic to improve pain control or at the other two clinics to improve pain recognition.
- 6) This study could be an eye-opener that clinicians and nurses who manage HIV treatment centres need to have a high index of suspicion that the ‘pain’ they are treating could be neuropathic pain. Even without administering the DN4 interview in full, just asking a patient

to describe their pain as is they were telling a friend might elicit the unique sensory descriptors of NeuP. It is also important for health providers to routinely screen for pain more specifically in older patients, e.g. above the age of 50 as it might not always be reported⁸².

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9. APPENDICES

Appendix 1: Patient Information Sheet

Patient Information Sheet for:

The association between Neuropathic Pain and Anxiety Disorders among patients attending HIV treatment centres in Nkomazi District

1) INTRODUCTION

Thank you taking your time to hear about this study.

You are invited to volunteer for a study. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you fully understand what is involved. If you have any questions, which are not fully explained in this leaflet, do not hesitate to ask the investigator. You should not agree to take part unless you are completely happy about all the procedures involved.

2) THE NATURE AND PURPOSE OF THE STUDY

You are invited to take part in a study. The aim of this study is to evaluate the **Association between NEUROPATHIC PAIN (pain due to nerves in your body that are not working normally) and ANXIETY DISORDERS (medical conditions characterized by a feeling of dread accompanied by bodily symptoms and signs that cause distress, discomfort, interferes with our work/functioning and social life. They are not the same as fear which occurs in response to a known cause)**. By doing so we wish to learn more about **how common these medical conditions are among patients attending HIV treatment centres in Nkomazi district**. Some illnesses could be serious and if identified early should save you from having problems later on.

3) EXPLANATION OF THE PROCEDURES TO BE FOLLOWED

This study involves answering some questions with regards to your health. There will no be physical examination or any tests involved.

4) RISK AND DISCOMFORT INVOLVED

The only possible discomfort involved is sparing 25-35minutes of your time for the list of health related questions to be completed. There are no procedures involved. No experimental medicines or drugs shall be given.

5) POSSIBLE BENEFITS OF THIS STUDY. The Anxiety disorders and Neuropathic Pain are commonly under-diagnosed and many patients suffer for years before being diagnosed. Even when correctly diagnosed, many patients receive inadequate treatment for these medical conditions.

There is an arrangement with your clinic to refer you for further expert help in case you are found to have neuropathic pain with/without an Anxiety Disorder.

6) You should understand that if you do not want to participate in this study, you will still receive standard treatment for your illness.

7) You may withdraw at any time from this study.

8) HAS THE STUDY RECEIVED ETHICAL APPROVAL?

This Protocol was submitted to the Faculty of Health Sciences Research Ethics Committee, University of Cape Town and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last update: October2000), which deals with recommendations guiding doctors in biomedical research involving human subjects. A copy of the Declaration may be obtained from the investigator should you wish to review it.

Contact person at UCT Faculty of Health Sciences Human Research Committee:

Mrs Lamees Emjedi

Human Research Ethics Committee

E52 Room24, Old Main Building, Groote Schuur Hospital, OBSERVATORY

TEL: 021 406 6338

9) INFORMATION. If you may have any questions about this study you should contact:

Dr W O Ochan Tel: 013 780 0331 Cell: 082 437 6840

10) CONFIDENTIALITY

All records obtained whilst in this study will be regarded as confidential. Results will be published or presented in such a fashion that patients remain unidentifiable.

Appendix 2: Consent form

CONSENT FORM FOR:

A study of the “Association between Neuropathic pain and Anxiety disorders among patients attending HIV treatment centres in Nkomazi district”.

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

I have received a signed copy of this informed consent agreement.

Patient:..... Date:.....

Person obtaining informed consent:.....Date:.....

Witness:..... Date:.....

VERBAL PATIENT INFORMED CONSENT

(Applicable when patient cannot read or write)

I, the undersigned, have read and have explained fully to the patient, named..... and his/her relative, the patient information sheet, which has indicated the nature of the 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 and the alternative treatments available for his/her illness. The patient has indicated that he/she understands that he/she will be free to withdraw from the study at any time for any reason and without jeopardizing his/her treatment.

I hereby certify that the patient has agreed to participate in this study.

Patient's Name:

Interviewer's Name:

Interviewer's Signature:..... Date:...../...../2013

Witness's Name:

Witness's Signature:..... Date:...../...../2013

Appendix 3: Data Collection Tools

3.1 Demographic Data

Instructions on how to carry to administer the Questionnaire

->For gender identification circle F for female gender and M for the male gender.

->Gender considered is that which is denoted on the South African barcoded green identity document (card) or passport.

->In the absence of the above documents the gender considered is that which the patient shall report. The appearance of the patients and their dress code shall not be used for identifying their gender.

->For tribal grouping tick (1) for a **Swazi**, (2) for a **Tsonga** and (3) for **other tribal or race groups**.

->Age shall be rounded off in years with no fractions or decimal points. Eg, a participant who is 18years and 4months shall be deemed to 18years old. One who is 18years and seven to eleven months shall be deemed to be 19years old. This shall be written next to **Age.....**

->Religious affiliation shall be ticked off as (1) for **Christian**, (2) for **Moslem**, (3) **Traditional Practitioners** or (4) for **others**.

->For employment status tick (1) for '**Employed**' or (2) for '**Not Employed**'.

->Tick (1), (2), (3) or (4) for no education, primary education, secondary education and tertiary education respectively.

->For Income Levels tick (1) for no income, (2) for less than R1000, (3) for R1000-4999 or (4) for R5000 and over.

Gender: F M

Age:.....

Tribal Group: Swazi (1), Tsonga (2), Other (3)

(Nkomazi is predominantly populated by the Swazi tribal group and the Tsonga, a minority)

Religious affiliation: (Christian (1), Moslem (2), Traditional practitioner (3), others (4))

Employed? Yes (1), No (2).

Highest Educational Achievement: None (1), Primary (2), Secondary (3), Tertiary (4)

Income: None (1), Less than R1000/month (2), R1000-4999 (3), R5000 and above (3)

3.2 DN4 Interview (the sensory descriptors only)

Instructions to Interviewer

>Question 1 has three parts; for each of three points give one point if the symptom is present.

Each point adds up to a maximum of three points from this question.

>Question 2 has four parts; a point is to be given for each symptom that is present up to a maximum of four points for this question.

>The points shall be tallied out of a maximum total of 7 points, eg, 2/7 score for a patient means that only two symptoms were found in that particular patient.

Question 1: Does the pain have any of the following characteristics?

1.1 Burning?

1.2 Painful sensation of cold?

1.3 Electric shocks?

Question 2: Is the pain associated with any of the following symptoms in the same area?

2.1 Tingling?

2.2 Pins and needles?

2.3 Numbness?

2.4 Itching?

Tally of symptoms present:/7

Eg, 3/7 means that 3 sensory descriptors of Neuropathic Pain were present.

2/7 means that 2 sensory descriptors of Neuropathic Pain were present.

3.3 SCID-CV Questionnaire

The interview shall be clinician-administered.

Instruction to Clinician:

>For each of the anxiety disorders there shall be a list of questions and for each there shall be three options to choose from.

? Tick first box if information provided by the patient is not adequate/sufficient to come to a conclusion.

- Tick second box if symptom sought is absent or not prominent enough.

+ Tick box third box (+) if symptom sought is present.

>If the (?) and (-) boxes are ticked skip the rest of the subsequent questions and proceed to the next number.

>If the (+) box is go then proceed step wise to the next item.

>For each anxiety disorder once the interview is completed for that section tally the number of symptoms to see if meets, or fails to meet, the minimum number of symptoms to make a diagnosis is attained.

SCID-I Score-sheet: ANXIETY/OTHER DISORDERS

Ratings:

? = Information not adequate.

- = Absent (or sub-threshold).

+ = Present.

PANIC DISORDER CRITERIA

F1 (A) Recurrent unexpected panic attacks

? - +

If go to F25.

F2 (A) At least one of the following:

(a) worry about the implications of the attack.

?	-	+
---	---	---

(b) concern about having additional attacks

?	-	+
---	---	---

(c) a significant change in behaviour

?	-	+
---	---	---

SCORE.....

If go to F25.

F3 Four (or more) of the following panic attack symptoms developed abruptly and developed a peak within 10 minutes.

?	-	+
---	---	---

F4 (1) palpitations

?	-	+
---	---	---

F5 (2) sweating

?	-	+
---	---	---

F6 (3) trembling or shaking

?	-	+
---	---	---

F7 (4) shortness of breath

?	-	+
---	---	---

F8 (5) choking

?	-	+
---	---	---

F9 (6) chest pain

?	-	+
---	---	---

F10 (7) nausea or abdominal distress

?	-	+
---	---	---

F11 (8) feeling dizzy

?	-	+
---	---	---

F12 (9) derealisation or depersonalization

?	-	+
---	---	---

F13 (10) fear of losing control or going crazy

?	-	+
---	---	---

F14 (11) fear of dying

?	-	+
---	---	---

F15 (12) Paraesthesia's (numbness, pins & needles)

?	-	+
---	---	---

F16 (13) chills or hot flushes

?	-	+
---	---	---

F17 4/13 or more are (+)

?	-	+
---	---	---

SCORE.....

If - go to F25

F18 (C) Not due to a substance or medical condition

?	-	+
---	---	---

If there is substance abuse: go to F25.

F19 (D) not better accounted for by another mental disorder

?	-	+
---	---	---

If there is another mental disorder go to F25

If no other medical condition or mental disorder responsible + in F17 diagnosis = PANIC DISORDER.

If - go to F25.

F20 (B) (1) presence of agoraphobia.

?	-	+
---	---	---

If - go to F24

F21 (B) (2) agoraphobic situations are avoided, endured with marked distress or with anxiety, or requires a companion

?	-	+
---	---	---

If - go to F24

F22 (B) (3) the anxiety or phobic avoidance is not better accounted for by another mental disorder.

?	-	+
---	---	---

If - go to F24

F23 AGORAPHOBIA IS PRESENT

?	-	+
---	---	---

[] tick box if + on the last month...

Diagnosis = PANIC DISORDER WITH AGORAPHOBIA if F23 is ticked

F24 AGORAPHOBIA IS ABSENT

Go to F25

OBSESSIVE-COMPULSIVE DISORDER CRITERIA

?

F25 Obsessions

(1) Recurrent and persistent thoughts, impulses, or images

? - +

If - go to F30

Notes:

F26 (2) excessive worries about real-life problems

? - +

Notes:

If - go to F30

F27 (3) the person attempts to ignore or suppress or neutralize such thoughts

? - +

Notes:

If - go F30

F28 (4) the person recognizes that the thoughts are a product of his/her own mind

? - +

Notes:

If - go to F30

F29 OBSESSIONS if (1), (2), (3) and (4) are +

F30 Compulsions

(1) Repetitive behaviour or mental acts

? - +

Notes:

If - go to F33

F31 (2) the behaviour or mental acts are aimed at reducing distress

? - +

SCORE.....

Notes:

If - go to F33

F32 COMPULSIONS (1) & (2) ARE (+) (?)

F33 EITHER F29 IS + OR F32 IS + (i.e., either obsessions or compulsions) ? - +

If - go F39

F34 B. The person has recognized that the obsession/compulsions are excessive or unreasonable.

? - +

Notes:

If - go to F39

F35 C. The obsessions or compulsions are clinically significant ? - +

Notes:

If - go to F39

F36 D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it.

? - +

Notes:

If - go to F39

F37. E. Not due to a substance or general medical condition. ? - +

Tick box [] if criteria met in the past month.

If all above not due substance or medical condition DIAGNOSIS = OBSESSIVE COMPULSIVE DISORDER.

F38 Diagnosis of OBSESSIVE-COMPULSIVE DISORDER if criteria A, B, C, D & E are + have been met in the past month.

SCORE.....

POST-TRAUMATIC STRESS DISORDER CRITERIA

F39 TRAUMATIC EVENTS LIST

Brief Description	Date	Age
-		
-		
-		
-		

-
-
-
-
-

A) The person has been exposed to a traumatic event in which both of the following were present:

F40 (1) the person experienced, witnessed, or was confronted with an event that involved death, serious injury, or a threat to the physical integrity of self or others. ? - +

Note:

If - go to F65

F41 (2) the response involved intense fear, helplessness, or horror ? - +

Notes;

B, The traumatic event is persistently experienced in one (or more) of the following ways:

F42: (1) distressing recollection of the event ? - +

Notes:

F43: (2) dream of the event ? - +

Note:

F44: (3) acting or feeling as if the traumatic event were recurring ? - +

F45: (4) intense psychological distress at exposure to internal or external cues ? - +

Notes:

F46: (5) physiological reactivity on exposure to internal or external cues ? - +

SCORE.....

F47 AT LEAST ONE 'B' SYMPTOM IS +

If - go to F65

C Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness as indicated by three (or more) of the following:

F48 (1) effort to avoid thoughts, feeling, or conversations related to the trauma ? - +

Notes:

F49 (2) effort to avoid activities, places, or people that arouse recollections of the trauma ? - +

Notes:

F50 (3) inability to recall an important to aspect of the trauma ? - +

F51 (4) markedly diminished interest or participation in significant activities ? - +

Notes:

F52 (5) feeling of detachment or estrangement from others ? - +

Notes:

F53 (6) restricted range of affect (e.g., not able to have loving feelings) ? - +

Notes:

F54 (7) sense of foreshortened future ? - +

SCORE.....

F55 THREE OR MORE OF THE 'C' SYMPTOMS ARE +

If - go to F65

D Persistent symptoms of increased arousal as indicated by 2 or more of the following:

F56 (1) difficulty falling asleep/staying asleep ? - +

F57 (2) irritability or angry outbursts

? - +

F58 (3) difficulty concentrating

? - +

F59 (4) hyper-vigilance

? - +

F60 (5) exaggerated startle response

? - +

SCORE.....

F61 TWO OR MORE 'D' SYMPTOMS ARE +

If - go to F65

F62 E. Duration of disturbance is more than 1month

? - +

If - go to F65

F63 F. Clinically significant distress or impairment

? - +

If - go to F65

F64 IF CRITERIA A, B, C, D, E & F ARE (+) DIAGNOSIS IS PTSD. +

Tick box [] if criteria have been met in past month

OTHER ANXIETY DISORDERS

F65 300.22 Agoraphobia without history of Panic Disorder

? - +

Tick box [] if present in the past month

F66 300.23 Social Phobia

? - +

Tick box [] if present in the past month

F67 300.29 Specific phobia

? - +

Tick box [] if present in the past month

F68 300.02 Generalised Anxiety Disorder

? - +

Tick box [] if present in the past month

ANXIETY DISORDERS NOT OTHERWISE SPECIFIED

? - +

F69 Clinically significant anxiety or phobic avoidance

(?)

Notes:

If go to F72

F70 Not due a substance or a general medical condition

If there is substance abuse or medical condition tick

If go to F72

If then DIAGNOSIS IS ANXIETY DISORDER NOT OTHERWISE SPECIFIED.

F71 Tick box if present in the past month

SOMATOFORM DISORDERS

F72 300.81 Somatization Disorder OR

300.82 Undifferentiated somatoform Disorder

Notes:

Tick box if present in the past month

F73 300.7 Hypochondriasis

Notes:

Tick box if present in the last month

F74 300.7 Body Dysmorphic Disorder

Notes:

Tick box if present in the past month

EATING DISORDERS

F75 307.1 Anorexia Nervosa

Notes:

Tick box if present in the past month

F76 307.51 Bulimia Nervosa

(?)

Notes:

Tick box [] if present in the past month

ADJUSTMENT DISORDERS CRITERIA

F77 A. The development of emotional or behavioural symptoms in response to an identifiable stressor(s)

? - +

If - end the interview.

Notes:

F78 B. These symptoms or behaviour are clinically significant

? - +

Notes:

F79 C. Does not meet criteria for another specific Axis I disorder and is not an exacerbation of a pre-existing Axis I or Axis II disorder

? - +

Notes:

F80 D. The symptoms do not represent Bereavement

? - +

If bereavement tick -

If - or there is bereavement stop the interview

Notes:

F81 E. Once the stressor has terminated, the symptoms do not persist for more than extra 6months

? - +

Notes:

If - go to D17 on the SCID-I

If + DIAGNOSIS = ADJUSTMENT DISORDER

F82 Make diagnosis of Adjustment Disorder based on predominant symptoms:

Tick one:

309.0 Adjustment Disorder with Depressed Mood

? - +

309.24 Adjustment disorder with Anxiety

? - +

309.28 Adjustment Disorder with Mixed Anxiety and Depressed Mood

? - +

? - +

309.3 Adjustment Disorder with Disturbance of Conduct (?)

309.4 Adjustment Disorder with Mixed Disturbance of Emotions and Conduct

? - +

309.9 Unspecified Adjustment Disorder

? - +

End interview if F81 is +

ANXIETY DISORDER DUE TO A GENERAL MEDICAL CONDITION

F83 A. Prominent anxiety, panic attacks, obsessions, or compulsions

? - +

Notes:

F84 B/C. The disturbance is the direct physiological consequence of a general medical condition, and the disturbance is not better accounted for by another mental disorder

? - +

Notes:

If - go to F87

F85 E. The symptoms cause clinically significant distress or impairment

? - +

Notes:

F86 CRITERIA A, B/C, AND E ARE +

? - +

Notes:

If - go to F18, F37, F70

F91 CRITERIA A, B, C & E ARE + Diagnosis = SUBSTANCE-INDUCED ANXIETY DISORDER (292.89)

? - +

[] 291.89 for Alcohol

[] 292.89 for other substances

Specify the substance.....

Indicate type of anxiety symptoms:

[] With Generalized Anxiety

[] With Panic Attacks

[] with Obsessive-Compulsive Symptoms

With Phobic Symptoms

Tick box if criteria have been present in the past month

Specify the causative general medical condition:

Indicate type of anxiety symptoms:

With Generalized Anxiety

With Panic Attacks

With Obsessive-Compulsive Symptoms

Tick box if criteria has been met in the past month

If - go to F18, F37, F70

If F86 is + DIAGNOSIS IS ANXIETY DISORDER DUE TO A GENERAL MEDICAL CONDITION

SUBSTANCE-INDUCED ANXIETY DISORDER

F87 A. Prominent anxiety, panic attacks, obsessions or compulsions ? - +

Notes:

If - go to F18, F37, F70

F88 B. Either:

(1) Symptoms in A developed during/within 1 month of substance intoxication or withdrawal, or

(2) Medication use is aetiologically related to the disturbance ? - +

Notes:

If - go to F18, F37, F70

F89 C. The disturbance is not better accounted for by an Anxiety Disorder that is not substance induced

? - +

Appendix 4: Permission from Clinic Heads

4.1 Clinic 1

The Clinic Manager

Date.2013/03/14

Dear Facility Head;

(1)Mrs N D Ndahse

(2)Mr Victor Gwebu

RE: **ASSOCIATION BETWEEN NEUROPATHIC PAIN AND ANXIETY DISORDERS AMONG PATIENTS ATTENDING HIV TREATMENT CENTRES IN NKOMAZI DISTRICT**

I am writing to invite your clinic to join us as a research site in this study.

Neuropathic pain and anxiety disorders are two independent illnesses that cause untold suffering among people living with HIV/AIDS (PLWHA).

These two illnesses are under-diagnosed and undertreated by doctors across the world.

This problem of under-recognition and under-treatment by doctors is compounded by under-reporting by PLWHA.

This study is a cross-sectional study and there shall NOT be any experimentation with new procedures or medicines.

The study instruments that shall be used during the interviews are: Demographic data, the DN4-Interview and the SCID-CV.

The study shall not commence until the university and Provincial Health department has given ethical approval for the study.

We shall introduce to you the research assistant, who shall have been trained in the use of the study instruments.

The following are some basic pieces of the study information:

1) Who is to be recruited for the study?

Only consenting patients on anti-retroviral therapy (ART) who are 18years, or older, shall be requested to participate in the study. Two other clinics in Nkomazi district shall be approached to participate. Between the 3 clinics a total of 384 patients shall be interviewed, approximately 126 patients form each clinic.

2) How will patients be approached to ask them if they would like to take part in the study?

Every 3rd patient shall be randomly approached, asked if they are interested, the study explained to them and recruited to participate if they give consent.

3) How will data collection happen?

The research assistant will then interview the patient once consent has been given. The data collected shall be kept in a safe case in a locked storage place. Patients' names and identifying characteristics shall not be recorded. The questionnaires shall only have a number which is not unique to the patient.

4) What is a patient becomes distressed?

Every participant has the opportunity to stop the interview at any time and may be given time at end of interview to talk without any data being recorded. The clinic sisters shall also be informed of such a patient as well.

5) Responsibilities of the study site (the clinic) are the following:

- Introducing the research assistant to the patients.
- Introduction of the other clinic personnel to the research assistant, and vice-versa.
- Ensuring patients that shall participate in the study not miss out laboratory tests and medication supplies.

6) Study feedback.

The research assistant shall give frequent progress report about study. When the study is concluded a copy of the results in lay terminology shall be displayed at the clinic.

We look forward to working with your clinic and clients.

For more information do not hesitate to contact us as, and when, the need arises.

Sincerely yours;

Dr Walter O Ochan

mwochan@mweb.co.za

painmed.ochan@gmail.com

ochanwo@gmail.com

Cell: 082 437 6840

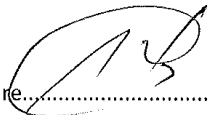
Tel: 013 780 0331

Fax: 086 67 2159

Stand B380 Main Road, Tonga

Kwa-Lugedlane, 1341

I, Victor Gwebu (name), do give permission for the above study to be conducted at Naas and Mangweni Clinics.

Signature.....

Date.....14/3/2013

Place.....Mauve Sub-district Free

4.2 Clinic 2

The Clinic Manager

Date.2013/03/14

Dear Facility Head;

(1)Mrs N D Ndahse

(2)Mr Victor Gwebu

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The research assistant shall give frequent progress report about study. When the study is concluded a copy of the results in lay terminology shall be displayed at the clinic.

We look forward to working with your clinic and clients.

For more information do not hesitate to contact us as, and when, the need arises.

Sincerely yours;

Dr Walter O Ochan

mwochan@mweb.co.za

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Cell: 082 437 6840

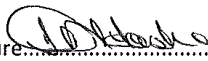
Tel: 013 780 0331

Fax: 086 67 2159

Stand B380 Main Road, Tonga

Kwa-Lugedlane, 1341

I, N.S. NDASHI.....(name), do give permission for the above study to be conducted at **Ka-Mhlushwa Clinic**.

Signature.....

Date.....14.09.2013

Place.....Nkomazi sub-district

Appendix 5: University of Cape Town HREC Approval



UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: sumayah.riefdien@uct.ac.za

21 November 2012

HREC REF: 587/2012

Dr W Ochan
c/o Dr L Gwyther
Palliative Medicine
School of Public Health & Family Medicine
FHS

Dear Dr Ochan

PROJECT TITLE: TO INVESTIGATE THE ASSOCIATION BETWEEN NEUROPATHIC PAIN AND ANXIETY DISORDERS AMONG PATIENTS ATTENDING HIV TREATMENT CENTRES IN NKOMAZI DISTRICT, MPUMALANGA

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** your collaboration in the above mentioned study.

Approval is granted for one year till the 28 November 2013.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

A handwritten signature in black ink, appearing to be 'M Blockman', written over a horizontal line.

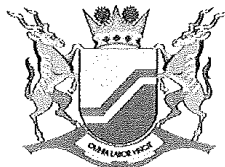
PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
sAriefdien

Appendix 5: Mpumalanga Provincial Ethics Approval

MPUMALANGA PROVINCIAL GOVERNMENT

Building No.3
No. 7 Government Boulevard
Riverside Park Extension 2
Nelspruit
1200
Republic of South Africa



Private Bag X 11285
Nelspruit, 1200
Tel: 013 766 3429
int: +27 13 766 3429
Fax: 013 766 3458
int: +27 13 766 3458

Department of Health

Litiko Lecomphilo

Umyango WezaMaphilo

Departement van Gesondheid

Enquiries: Themba Mulungo (013) 766 3511

28 February 2013

Dr W O Ochan
PO Box 412
MALELANE
4320

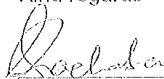
Dear Dr W.O Ochan

APPLICATION FOR RESEARCH & ETHICS APPROVAL: TO INVESTIGATE THE ASSOCIATION BETWEEN NEUROPATHIC PAIN AND ANXIETY DISORDERS AMONG PATIENTS ATTENDING HIV TREATMENT CENTRES IN NKOMAZI DISTRICT, MPUMALANGA

The Provincial Research and Ethics Committee has approved your research proposal in the latest format that you sent.

Kindly ensure that you provide us with the soft and hard copies of the report once your research project has been completed.

Kind regards


Mr. Molefe Machaba
Research and Epidemiology

28/02/2013
Date

