

https://dspace.org/

Pain in South African HIV-positive patients

Mphahlele, Noko Reshoketswe

2014-01-10
http://hdl.handle.net10539/13428

Downloaded from a DSpace repository. https://dspace.org/

PAIN IN SOUTH AFRICAN HIV-POSITIVE PATIENTS

Noko Reshoketswe Mphahlele

A thesis submitted to the Faculty of Science, University of the Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg, 2013

DECLARATION

This thesis is submitted in the optional format, approved by the Faculty, of published work encompassing introduction and conclusion.

I declare that this thesis is my own work, with all assistance acknowledged. This thesis is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

.....

(NOKO RESHOKETSWE MPHAHLELE)

..... day of 2013

I certify that the procedures used in this thesis were approved by the Human Ethics Screening Committee of the University of the Witwatersrand (HESC number: M041112).

TABLE OF CONTENTS

DECLARATION ..... **i**

TABLE OF CONTENTS ..... **ii**

ABSTRACT ..... **vi**

ACKNOWLEDGEMENTS ..... **viii**

LIST OF FIGURES ..... **ix**

LIST OF TABLES ..... **xi**

LIST OF ABBREVIATIONS ..... **xiii**

RESEARCH OUTPUTS ..... **xiv**

Published papers xiv

Submitted paper xiv

International conference presentations xv

Local conference presentations xv

AUTHORS' CONTRIBUTIONS ..... **xvii**

INTRODUCTION **1**

1.1. Pain in HIV, an overview 2

1.1.1. Pre-highly active antiretroviral therapy (HAART) era 6

1.1.2. HAART era 11

1.1.3. Risk factors or predictors for developing pain in HIV 15

1.1.4. Longitudinal studies 16

1.2. Pain interference on the quality of life in HIV-infected patients 21

1.3. Pain management in HIV/AIDS 27

1.3.1. Pharmacological treatment of HIV-related pain 28

1.4. Under-treatment of pain in HIV 32

1.5. Aims of the thesis 48

VALIDATION OF THE WISCONSIN BRIEF PAIN QUESTIONNAIRE IN A MULTILINGUAL SOUTH AFRICAN POPULATION 52

2.1. Abstract 53

2.2. Introduction 54

2.3. Methods 58

2.3.1. Participants 58

2.3.2. Study Instrument and Procedure 58

2.3.3. Statistical Procedure 60

2.4. Results 62

2.4.1. Descriptive Statistics for the WBPQ 62

2.4.2. Reliability and Validity of the English Version of the WBPQ When Completed by Second Language English Speakers 63

2.4.3. Reliability and Validity of the WBPQ Translated into Three Indigenous African Languages 65

2.4.3.1. IsiZulu. 65

2.4.3.2. Setswana 65

2.4.3.3. Xitsonga 66

2.4.4. Construct Validity 66

2.5. Discussion 69

2.6. Acknowledgments 74

PAIN IN AMBULATORY HIV-POSITIVE SOUTH AFRICANS 75

3.1. Abstract 76

3.2. Introduction 77
3.3. Materials and Methods 79
3.3.1. Participants 79
3.3.2. Ethics 80
3.4. Study Instruments and procedures 81
3.4.1. Wisconsin Brief Pain Questionnaire (WBPQ) 81
3.4.2. Karnofsky Performance Scale (KPS) 82
3.5. Data analysis 83
3.6. Results 86
3.6.1. Demographics 86
3.6.2. Pain prevalence 88
3.6.3. Pain intensity 88
3.6.4. Pain sites 89
3.6.5. Functional interference 92
3.6.7. Risk factors for pain 99
3.7. Discussion 102
3.7.1. Pain in HIV-positive individuals 102
3.7.2. Study limitations 104
3.7.3. Pain prevalence 105
3.7.4. Pain under-treatment 109
3.7.5. Recapitulation 111
3.8. Acknowledgements 112

PAIN IN SOUTH AFRICAN HIV-POSITIVE AMBULATORY PATIENTS: A LONGITUDINAL STUDY 113

4.1. Abstract 114

4.2. Introduction 115

4.3. Materials and Methods 116

4.3.1. Participants 116

4.3.2. Study procedure 117

4.3.3. Statistical analysis 118

4.4. Results 119

4.4.1. Patients sampling 119

4.4.2. Changes in pain intensity between visit 1 and visit 2 121

4.4.3. Pain sites 121

4.4.4. Highly active antiretroviral therapy (HAART) and pain 124

4.4.5. Pain interference 125

4.4.6. Pain treatment 125

4.5. Discussion 130

4.6. Acknowledgements 138

CONCLUSION 139

APPENDICES 157

REFERENCES 197

ABSTRACT

Pain is one of the most frequent and debilitating symptoms in human immunodeficiency virus (HIV) infected individuals. With Southern Africa being the region with the highest population of HIV-infected individuals, I set out to determine whether the pain intensity, prevalence and management strategies that have been reported in other, non-African, countries are similar to that in South African patients. South Africa has eleven official languages, with nine of those being native languages. Also, there is a high level of illiterate people in the country, thus, for better assessment of the pain I translated the Wisconsin Brief Pain Questionnaire into five frequently spoken local languages. Using the translated questionnaires I investigated the prevalence, intensity and management of pain in ambulatory HIV-positive outpatients attending a metropolitan (n = 396) or rural (n = 125) clinic. I also assessed whether this pain changes over time in a subset of 92 metropolitan patients.

Seventy-two percent of rural participants and 56% of metropolitan participants had pain at the time of the interview, and this pain was moderate to severe in intensity in 60% of affected rural participants and 59% of affected metropolitan participants. In the rural cohort, use of antiretroviral therapy was independently associated with the reduced risk of pain [prevalence ratio (95% CI): 0.7 (0.5-0.9)] while in the metropolitan cohort increasing age was weakly, but independently associated with

having pain [prevalence ratio (95% CI): 1.01 (1.005-1.012)]. Pharmacological management of pain was poor, with 29% of rural participants and 55% of metropolitan participants with pain not receiving any treatment. Of those receiving treatment, no participants were receiving strong opioids, and only 3% of metropolitan participants were receiving a weak opioid. On a positive side, the pain that South African HIV-infected individuals endure decreases over time. Seventy-eight patients out of the subsample cohort consisting of 92 patients reported pain at the time of the first interview. Of the 78 patients who were in pain at visit 1, 48 were still in pain six months later with 36 of those not prescribed any form of analgesics. Thus I found a decrease in moderate and severe intensity pain to mild and moderate pain, respectively, from visit 1 to visit 2. Of the 78 patients that were in pain at visit 1, only 5% received some form of analgesic therapy. Forty-eight of the 78 patients were still in pain six months later, and of those, 25% were being prescribed some form of analgesics at visit 2. There were no changes in the pain-related interference over a six month period in patients who were in pain at visit 1 and visit 2. Therefore, as it has been reported previously for other developed and developing countries, pain in HIV-positive South Africans is common and is under-treated. Also, there are decreases in the pain intensity, pain prevalence, the number of pain sites over a period of six months. These decreases were evident in patients who were on HAART for the duration of six months as compared to those who were not on HAART for six month.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisors, A/Prof. Peter Kamerman and Prof. Duncan Mitchell, for their unlimited guidance, support and motivation, which helped me through this thesis. I also would like to thank A/Prof. Andrea Fuller for her input during the beginning stages of my PhD and data analysis, and for her support. Also, I would like to thank the interviewers; Edith Paledi, Zanele Msomi, the late Thulile Makafola, Busi, Tinyiko, Helen and data capturers; Laizer Phaladi and Florence Mtsweni, and the staff and patients of the Helen Joseph Hospital, Thembalethu Clinic and Tintswalo Hospital, Rixile Clinic for their invaluable assistance.

To my parents, Beatrice and Aaron Mphahlele, I wouldn't have come this far if it weren't for you. Thank you for your love, patience and constant support. Also, to the rest of my family for their continuous support and encouragement.

The Medical Research Endowment Fund of the University of the Witwatersrand, The Canon Collins Educational Trust and the National Research Foundation supported this work.

LIST OF FIGURES

Figure 1.1: Pain interference item scores for the total sample of 270 participants with pain and differences in pain interference item scores among the 3 pain severity groups, reported as means 22

Figure 1.2: Quality of life and pain by treatment setting.. 24

Figure 1.3: The World Health Organization analgesic ladder..... 29

Figure1.4: Analgesic medications prescribed for pain in ambulatory patients with AIDS..... 35

Figure 1.5: Proportion of patients receiving adequate and inadequate analgesic therapy based on the pain management index (PMI): A comparison between 3 studies. 38

Figure 2.1: Factor loadings plots of the South African versions of the Wisconsin Brief Pain Questionnaire..... 67

Figure 3.1: The four most prevalent pain sites identified by rural and metropolitan participants with pain who reported more than one (multiple) pain site..... 91

Figure 3.2: Pain-related functional interference in rural and metropolitan participants who had reported pain in the previous 30 days. 93

Figure: 3.3: Types of analgesic therapy reported by rural and metropolitan participants with pain in the last 30 days and who were receiving pharmacological treatment for their pain..... 95

Figure 3.4: Pain management indices (PMI) for the rural and metropolitan participants who had mild, moderate or severe pain in the last

30 days and who were receiving some form of analgesic therapy. 96

Figure 3.5: Median (interquartile range, range) percentage pain relief reported by rural and metropolitan participants who had mild, moderate or severe pain in the last 30 days and who were receiving some form of analgesic therapy. 98

LIST OF TABLES

Table 1.1: Studies documenting on the prevalence, intensity and distribution of pain in HIV/AIDS 8

Table 1.2: Proposed approach to ongoing assessment and treatment of HIV-related pain 31

Table 1.3: Types of analgesic medication prescribed according to the patient's worst pain rating 38

Table 1.4: Barriers to pain management 43

Table 1.5: Challenges and factors hampering opioid expansion and roll-out from 12 sub-Saharan African countries 46

Table 2.1: Medians and Interquartile range of pain intensity and pain interference items for the translated versions of the Wisconsin Bief Pain Questionnaire 64

Table 2.2: A summary of Item analysis and alpha values if an item is omitted for the English and translated versions of the Wisconsin Brief Pain Questionnaire 68

Table 2.3: Cronbach alphas of pain intensity and pain interference subscales of the Brief Pain Inventory and WBPQ in different countries and languages 72

Table 3.1: Demographic characteristics of rural and metropolitan cohorts 87

Table 3.2: Percentage of participants with mild, moderate or severe pain at the time of the interview (pain now), or within the last 30 days (worst pain) 90

Table 3.3: Univariate analysis of variable associated with having pain in the previous 30 days (rural cohort) 100
Table 3.4: Univariate analysis of variables associated with having pain in the previous 30 days (metropolitan cohort) 101
Table 4.1: Characteristics of the cohort who returned for a second interview (n = 92) with those who did not (n = 304)..... 120
Table 4.2: Change in pain intensity over six months..... 122
Table 4.3A: Number of pain sites at Visit 1 and Visit 2, for patients with different pain intensities at Visit 1..... 123
Table 4.3B: Most frequent pain sites at Visit 1 and Visit 2, for patients with different pain intensities at Visit 1..... 126
Table 4.4A: Pain characteristics for patients who were on HAART at Visit 1 and six months later (n = 55) 127
Table 4.4B: Pain characteristics for patients who were on HAART at both visits (n = 7) 128
Table 4.5: Mean pain interference at Visit 1 and Visit 2 129

LIST OF ABBREVIATIONS

HAART	highly active antiretroviral therapy
WHO	World Health Organization
HIV	human immunodeficiency virus
ARC	AIDS - related complex
AIDS	Acquired immunodeficiency syndrome
BPI	Brief Pain Imventory
VAS	visual analogue scale
QoL	quality of life
PTSD	post-traumatic stress disorder
NSAIDs	nonsteroidal anti-inflammatory drugs
HIV-SN	HIV-associated sensory neuropathy
PMI	pain management index
IDU	injecting drug user
WBPQ	Wisconsin Brief Pain Questionnaire
KPS	Karnofsky Performance Scale
CI	confidence interval
SD	standard deviation
IQR	interquartile range
TCA	tricyclic antidepressant
NRTI	nucleoside reverse transcriptase inhibitor
nNRTI	non- nucleoside reverse transcriptase inhibitor
PI	protease inhibitor

RESEARCH OUTPUTS

The following is a list of published peer-reviewed research articles, a submitted research article and conference presentations offered in support of this thesis.

Published papers

1. Noko R Mphahlele, Duncan Mitchell and Peter R Kamerman (2008). Validation of the Wisconsin Brief Pain Questionnaire in a multilingual South African Population. Journal of Pain and Symptom Management 36:4 335-450.

2. Noko R Mphahlele, Duncan Mitchell and Peter R Kamerman (2012). Pain in ambulatory HIV-positive South Africans. European Journal of Pain 16:3 447-458.

Submitted paper

Noko R Mphahlele, Duncan Mitchell and Peter R Kamerman. Pain in South African HIV-positive ambulatory patients: a longitudinal study. Submitted to Journal of Pain and Symptom Management.

International conference presentations

1. Mphahlele NR, Mitchell D and Kamerman P (2006) Pain in 392 urban HIV-positive outpatients in South Africa (poster presentation). At the XVI International AIDS Conference, Toronto, Canada 13-18 August.

2. Mphahlele NR, Mitchell D and Kamerman P (2008) Validation of the Wisconsin Brief Pain Questionnaire in a multilingual South African population (poster presentation). At the 35th Annual Congress of the Physiology Society of Southern Africa (PSSA), Glasgow, Scotland 16-21 August.

Local conference presentations

1. Mphahlele NR, Mitchell D, Fuller A and Kamerman P (2005) Under-treatment and under-estimation of HIV-related pain in an outpatient hospital setting in South Africa (oral presentation). At the 33rd Annual Congress of the Physiology Society of Southern Africa (PSSA), Sports Science Institute of South Africa, University of Cape Town 7-9 September.

2. Mphahlele NR, Mitchell D and Kamerman P (2006) Pain in HIV-positive patients (poster presentation). At the 34th Annual Congress of the Physiology Society of Southern Africa (PSSA), University of KwaZulu Natal, Durban 26-29 September.

3. Mphahlele NR, Mitchell D and Kamerman P (2007) Validation of the Wisconsin Brief Pain Questionnaire in a multilingual South African population (poster presentation). At the 35th Annual Congress of the Physiology Society of Southern Africa (PSSA), University of the Witwatersrand, Johannesburg 9-12 September.

AUTHORS' CONTRIBUTIONS

Contributions of each co-author to the published or submitted papers contained in this thesis are listed below:

Chapter 2 and Chapter 3

Noko R Mphahlele, Duncan Mitchell and Peter R Kamerman (2008). Validation of the Wisconsin Brief Pain Questionnaire in a multilingual South African Population. Journal of Pain and Symptom Management 36:4 335-450.

Noko R Mphahlele, Duncan Mitchell and Peter R Kamerman (2012). Pain in ambulatory HIV-positive South Africans. European Journal of Pain 16:3 447-458.

In consultation with my supervisors, I developed the objectives of the study, completed the ethics application and negotiated access to the study sites. I also researched which questionnaires should be used. I recruited interviewers, trained the interviewers on how to administer the questionnaire. I sourced companies that specialises with translations and back-translations. I was responsible for monitoring data collection (interview process) and data capturing. I also learned the necessary statistics for assessing the factor structure and internal consistency of the translated questionnaires. I interpreted the results and performed the

statistical analyses with guidance from my supervisors. I drafted the manuscripts and all authors edited the manuscript.

Chapter 4

Noko R Mphahlele, Duncan Mitchell and Peter R Kamerman. Pain in South African HIV-positive ambulatory patients: a longitudinal study. Submitted to Journal of Pain and Symptom Management.

I was responsible for monitoring data collection (interview process) and data capturing. With the help of the interviewers, I managed the patient follow-ups (telephone call to set-up appointments). I interpreted the results and performed statistical analyses with the help of my supervisors. I drafted the manuscript and all the authors edited the manuscript

CHAPTER 1

INTRODUCTION

In this chapter I firstly provide an overview of pain in human immunodeficiency virus (HIV), followed by a discussion about the prevalence and severity of pain before and after the introduction of highly active antiretroviral therapy (HAART). Thereafter I briefly discuss findings from longitudinal studies describing changes in pain over time in patients with HIV, and then discuss the interference that pain has on the quality of life on infected patients. My coverage of the topic of pain in HIV is followed by a discussion on the treatment of pain in HIV, focussing mainly on the use of the World Health Organization (WHO) ladder and measure of treatment adequacy and barriers to adequate pain management. I end this chapter by listing the aims of my thesis.

1.1. Pain in HIV, an overview

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, and is one of the most frequent and debilitating symptoms in HIV- infected individuals (Breitbart *et al.*, 1996a; Lebovits *et al.*, 1989; Norval, 2004; O'Neill and Sherrard, 1993; Rosenfeld *et al.*, 1996; Singer *et al.*, 1993). The pain experienced by HIV-infected individuals can be due to multiple sources, for example, HIV infection itself or infections and tumours secondary to immunosuppression, treatment of HIV/AIDS (HAART), or it can be from any other sources excluding HIV and its treatment (e.g., pains that are common in the community such as arthroides, low back pain) (Breitbart *et al.*, 1996a; Dalakas, 2001a; Hewitt *et al.*, 1997; Koeppe *et al.*, 2010; Penfold and Clark, 1992). The pain

experienced can interfere with every aspect of the patient's life (Larue *et al.*, 1997; Newshan, 1997). Most studies have shown that patients who had AIDS and who were receiving terminal care at home had pain prevalence and intensity ratings that were similar to and sometimes even exceeding those observed in terminal cancer patients (Larue *et al.*, 1994; Solano *et al.*, 2006; Wakeham *et al.*, 2010).

The intensity of the pain in HIV, like that of cancer-related pain, reportedly increases as the disease progresses with patients reporting more pain at more advanced stages of diseases (Breitbart et al., 1996a; Coughlan, 2004; Glare, 2001; Hewitt et al., 1997; Singer et al., 1993). In clinical practice, low CD4 T-cell counts have been used as the criterion for initiation of HAART, and the success of therapy has been measured on the rebound of CD4 T-cell count and the reduction of viral load. Therefore, one would expect an association between high pain prevalence or high pain intensity and the low CD4 T-cell count. Indeed, studies in the developing world have reported a significant association between increased pain and lower CD4 T-cell counts (Tsao and Soto, 2009), which supports the idea that increased pain is associated with advanced HIV disease (Dobalian *et al.*, 2004). However, other studies have also reported a high level of symptoms at all stages of HIV infection suggesting that, the WHO staging or the CD4 T-cell count may not be used to predict pain symptom prevalence in a patient (Vogl *et al.*, 1999; Wakeham *et al.*, 2010).

Similarly, in studies undertaken in sub-Saharan Africa, there has been no consistent correlation between CD4 T-cell count and measures of pain (Peltzer and Phaswana-Mafuya, 2008; Powers *et al.*, 2007; Rosen *et al.*, 2008; Van As *et al.*, 2009), showing that pain does not depend on the patient's disease status. Thus, pain does not depend strongly on disease status, at least while patients are ambulatory, and the success of HAART, in extending the life expectancy in HIV-positive patients, has not been complemented by the reduction in HIV-related pain (Harding *et al.*, 2006).

Sub-Saharan Africa is the region most affected by HIV, with almost 70% of the people infected with HIV (Joint United Nations Programme on HIV/AIDS (UNAIDS) and (WHO), 2009). Since pain is one of the most frequent and debilitating symptoms in HIV-infected individuals one can conclude that a significant number of the world's population of people infected with HIV have increased risk of experiencing some form of pain. Until recently studies providing direct assessment of the kind of HIV-related pain and the treatment strategies have taken place primarily in developed countries where the patient populations are mainly male and Caucasians (Koeppe *et al.*, 2012; O'Neill and Sherrard, 1993; Singer *et al.*, 1993). But recently that situation has started to change, and there now are an increasing number of studies that have been conducted in sub-Sharan Africa. These studies, which were undertaken in the developing world, reported similar pain prevalence levels to the prevalence reported in the developed world, and has been reported in the patient population that

were mainly female (Makoae *et al.*, 2005; Maritz *et al.*, 2010; Narasimooloo *et al.*, 2011; Norval, 2004; Peltzer and Phaswana-Mafuya, 2008; Powers *et al.*, 2007; Rosen *et al.*, 2008; Uwimana and Struthers, 2007; Voss *et al.*, 2007; Wadley *et al.*, 2011). Also, similar to the prevalence of the pain reported in both the developed and the developing countries, the type of the pain experienced and the sites of pain are similar. Patients usually reports multiple painful sites, with the most common pain sites reported in studies from sub-Saharan Africa being the lower limbs, headache, musculoskeletal and abdominal pain (Makoae *et al.*, 2005; Peltzer and Phaswana-Mafuya, 2008; Voss *et al.*, 2007; Wahab and Salami, 2011). These pain sites are similar to those previously reported in developed countries (Del Borgo *et al.*, 2001; Hewitt *et al.*, 1997).

Little is known as to what proportion of pain reported by HIV-positive patients, in any setting, is chronic pain, but in recent US cohort, Koeppe and colleagues (2010) identified the primary source of chronic pain in ambulatory HIV-cohort as peripheral neuropathic pain, which is thought to usually occur as a result of the HIV infection or its treatment (Kamerman et al., 2012). Similarly, in sub-Saharan Africa, HIV-associated sensory neuropathy has been found to also cause significant pain in HIV-infected individuals (Maritz *et al.*, 2010; Wadley *et al.*, 2011). Therefore, more information on chronic pain conditions in sub-Saharan African countries and in low socio-economic countries are required. The following sections

includes discussions of the data pertaining to the prevalence and intensity of pain in the pre-HAART and HAART era, highlighting changes in pain burden over time were appropriate.

1.1.1. Pre-highly active antiretroviral therapy (HAART) era

In this section I will report on the literature relating to HIV-related pain from before HAART, which is a combination of 3 antiretrovirals, became standard of care for people living with HIV. Although HAART became available differs between countries, only data where patients were not receiving HAART at that time is reported in this section. Table 1.1 highlights some of the studies that were conducted in the pre-HAART era. Most of the studies documenting pain before the introduction of HAART were conducted in first-world countries, and most of those studies were conducted in the hospital and/or hospice settings, in mainly AIDS patients. Also, these studies mainly employed retrospective review of patients' records for their data collection (Breitbart et al., 1996a; Hewitt et al., 1997; Lebovits et al., 1989; Lebovits et al., 1994) and only a few studies were based on HIV-infected patients without AIDS defining illnesses (Anand *et al.*, 1994; Singer *et al.*, 1993). Depending on the methodology, sample characteristics and the research setting (e.g., outpatient, inpatient, hospice), the prevalence of pain in patients ranged from 25 to 97% of infected patients (Lebovits *et al.*, 1989; Lebovits *et al.*, 1994; McCormack *et al.*, 1993; Moss, 1990; Newshan, 1997; Norval, 2004; Simmonds *et al.*, 2005; Singer *et al.*, 1993). To further elaborate on the point I raised above,

in the outpatients and inpatient studies, it was found that approximately 25% to 30% of patients with early HIV disease experience clinically significant pain (Breitbart *et al.*, 1996a; Larue *et al.*, 1997; Rosenfeld *et al.*, 1996) but their pain was not recognized or treated. In their study, Singer and colleagues (1993) studied 191 homosexual men and they found a significant association between disease stage and HIV-related pain prevalence, ranging from 28% in asymptomatic patients to 56% in patients with AIDS-related complex (ARC) and 80% in AIDS patients. These authors classified their participants as having ARC if they had constitutional symptoms (e.g., diarrhoea, weight loss, fever) or infections (e.g., oral candida, oral hairy leuko-plakia, herpes zoster). Thus, painful symptoms are present even in healthy HIV-positive patients, but symptoms increase with advanced disease. Similar to Singer and colleagues' study, Larue and colleagues (1997) studied a sample of 315 patients in a French multicenter study and found that pain prevalence was 30% in outpatients, 53% in day patients (patients admitted only for a day for monitoring) and 62% in hospitalized patients. In this study, hospitalized patients had more advanced HIV infection than day patients and outpatients. The more advanced HIV infection could have contributed to the higher prevalence of pain observed in HIV inpatients, suggesting that pain increases as the disease progresses, as it has reported previously by Singer and colleagues (1993).

Table 1.1: Studies documenting on the prevalence, intensity and distribution of pain in HIV/AIDS

Authors (Country of study)	Number of patients	HAART use	Pain prevalence (%)	Pain intensity	Pain distribution
Singer et al. 1993 (USA)	191 charts	Yes (19.9%)	80	None reported	Headaches (39%); back pain; throat pain (60%); peripheral neuropathy (18%).
Breitbart et al. 1996a (USA)	438	No	60	Brief Pain Inventory; 7.4	None reported
Breitbart et al. 1996b (USA)	366	No	81	Brief Pain Inventory; 110/296 worst pain (8-10)103/296; moderate pain (4-7); mean worst pain intensity (7.3); mean average pain intensity (5.2)	Joint pain (37%); peripheral neuropathy (28%); muscular pain (27%); headaches (25%); skin pain (15%); radiculopathy (12%)
Larue et al. 1997 (France)	116 day hospital; 118 inpatient; 56 ambulatory	No	61 in 116 day patients (53%); 73 in 118 patients (62%); 17 in 56 outpatients (30%)	Brief Pain Inventory (French language version); Worst pain (> 5/10) in 16% for outpatients and 51% (30/118) for inpatients	Mouth pain (33%); muscular pain (32%); joint or bone pain (20%); central nervous system pain (19%); painful peripheral neuropathis (13%)
Hewitt et al. 1997 (USA)	151	No	Not mentioned	Not mentioned	Headache (46%); joint pain (31%); polyneuropathy (28%); muscle pain (27%).

Del Borgo et al. 2001 (Italy)	152	Yes (52 patients or 34%)	61	Italian Pain Questionnaire; 6.05 ± 2.47 on VAS; 2.76 ± 1.1 on PPI. Mild pain (11.5%); moderate pain (32.8%); distressing pain (32.1%); exhausting pain (15.2%); unbearable pain (8.4%)	Head (34.3%); legs (27.6%); abdomen (19.8%); chest (14.5%)
Norval DA 2004 (South Africa)	103	85 had NO access; 4 had access and 14 unknown	98	Structured nurse-led questionnaire; Worst pain (34 – 38%)	Lower limbs (66%); mouth (51%); head (43%); throat (40%)
Aires and Bammann 2005 (Brazil)	197	Not mentioned	54	Wong Baker pain rating scale; 3.6 on VAS; mild pain (12.2%); moderate pain (27.1%); severe pain (60.7%)	Headache (27.1%); abdominal pain (26.2%); pain in the lower limbs (12.1%); chest pain (11.2%).
Nair et al. 2009 (India)	140	Yes (60%)	Inpatients (66.7%); outpatients (24.5%)	Brief Pain Inventory and Short-form McGill Pain Questionnaire; Least pain reported by: 73.08% of the patients as 0-3); 23.08% as 4-6; 3.84%. Average pain reported by: 50% of the patients as 1-3; 8.07% as 4-6; 1.92% as 7-10. Worst pain reported by: 13.47% as 1-3; 42.30% as 4-6; 44.23% as 7-10.	Headache (28.75%); soles/leg pain (25%); backache (19.23%)

Maree et al. 2010 (South Africa)	500	Not mentioned	87.2 (at night)	60-second pain test; Mild pain (< 5%); Moderate pain (57.2%); severe pain (37%).	Overall body pain (24%); headache (17.2%); mouth pain (13.4%); chest pain (8.6%); pain in the arms (2.8%); pain in the legs (2.4%); feet pain (0.6%).
Miaskowski et al. 2011 (USA)	296	Yes (74.4%)	91.2	Brief Pain Inventory; Mild pain (8.2%); moderate pain (38.1%); severe pain (53.7%).	Calf pain (62.5%); feet (56.8%); lower back (52.3%).
Wahab KW and Salami AK, 2011 (Nigeria)	79	Yes (100%)	27.8	4-point verbal rating scale; Mild pain (70%); moderate pain (10%); severe pain (15%).	Lower limbs (40.9%); head and neck (31.8%); abdomen (31.8%).
Wakeham et. al. 2010 (Uganda)	212	No	76	None reported	None reported
Namisango et al. 2012 (Uganda)	302	Yes (74.2%)	47	Brief Pain Inventory; Mild pain (53%), moderate pain (20%); severe pain (27%).	Chest (21.7%); back (20.3%); head (19.6%); abdomen (15.4%); legs (7.7%).

VAS = visual analogue scale PPI = present pain intensity

Breitbart and colleagues (1996a) reported that 60% of the 450 HIV-positive patients they recruited from a healthcare facility for ambulatory HIV-positive patients, reported experiencing some form of pain within the past two-week period.

Similar to what has been reported in the studies by Singer and colleagues (1993) and Larue and colleagues (1997), Breitbart and colleagues (1996a) found pain to be associated with the presence of AIDS-defining conditions. And, in a recent Ugandan study where 212 HIV infected individuals who were HAART naïve were enrolled, authors found a 76% prevalence of pain indicating that symptoms are a burden even before initiation of therapy (Wakeham *et al.*, 2010). In this study 99% (211 of the 212 patients) of the patients reported having multiple symptoms. The patients included in this study had a CD4 T-cell count of less than 200 cells/µl, indicative of advanced HIV infection. Thus the above studies highlight the fact that pain in HIV is present even before patients' initiate antiretroviral therapy, and may occur at any stage of disease. But, the pain experienced is likely to be greater in advanced stages of the disease.

1.1.2. HAART era

Highly active antiretroviral therapy (HAART) is the use of multiple antiretroviral drugs that act on different viral replication pathway targets. HAART is used for the management or treatment of HIV/AIDS in an attempt to control HIV infection, but does not eradicate infection. These drugs belong to several drug classes, namely nucleoside reverse

transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (nNRTIs), protease inhibitors (PIs), integrase inhibitors and fusion inhibitors. When HAART became available in South Africa, first line therapy typically involved patients receiving two NRTIs (for example, staduvine, didanosine, zidovudine, lamivudine) and one nNRTI (for example, nevirapine or efavirenz). The other drug classes are usually reserved for later when the HIV virus becomes resistant to any of the first line antiretroviral agents. With the introduction of newer antiretroviral agents within the NRTI drug class, mainly due to the side effects that some of the NRTIs had, the HIV treatment guidelines have changed where currently, tenofovir (TDF), emtricitabine (FTC), and abacavir (ABC) are recommended in place of stavudine and didanosine. The World Health Organization (WHO) has published guidelines for the use of antiretroviral agents in individuals who are HIV-positive (AIDSInfo, 2013), which South Africa recently adopted (NDOH, 2013).

I have mentioned in the past sections that the presence of pain does not depend strongly on the disease status. Thus there is lack of tight correlation between CD4 T-cell count and pain. With the introduction of HAART, HIV-related morbidity and mortality have dropped substantially (Brodt *et al.*, 1997; Ives *et al.*, 2001; Mocroft *et al.*, 2003; Palella *et al.*, 1998; Seyler *et al.*, 2007). Thus, as treatment with HAART prevents disease progression and reverses the decrease in the CD4 T-cell count, it may be expected that the burden of pain in HIV would be reduced.

Alternatively, because HAART prolongs life, it could be expected that the life-time burden of pain in this population would increase due to the side-effects of most of the early first line NRTIs (e.g., zalcitabine, stavudine, didanosine), which mainly include painful peripheral neuropathy (Ellis *et al.*, 2010; Koeppe *et al.*, 2011; Maritz *et al.*, 2010; Wadley *et al.*, 2011) The data supports a benefitial effect of treatment on pain. For example, Cervia and colleagues (2010) reported that in 41 HIV-infected individuals who were taking HAART, patients had less pain (pain prevalence of 39%) compared with previously reported pain prevalence in pre-HAART studies, and the pain intensity was also rated lower by patients (2.0). They also found that patients who reported severe pain were more likely to be receiving pain medication (87.5%) compared to patients who reported less severe pain (25%) (Cervia *et al.*, 2010). Similarly, Koepe and colleagues (2012) also reported a significant drop in median pain scores in 127 HIV-infected individuals whom they followed-up for 5.2 years. Over the 5.2 years they also reported increased usage of HAART, which related to increases in patients' CD4 T-cell counts and decreases in their viral loads. The above studies show the benefits of HAART where there is improvement in the patients' pain intensity scores. To further endorse the impact of HAART on the lives of HIV-positive patients, it has been shown that patients who remain on HAART have long-term gains in the ability to perform normal activities of daily living and reduced symptom prevalence (pain, fatigue, nausea and skin problems) (Rosen et al., 2010).

Yet, although the authors of the above-mentioned studies have highlighted the decrease in their patients' pain scores and also an improvement in patients' daily activities, other authors have reported contrasting results. In their study where they administered the Brief Pain Inventory (BPI) to 100 hospitalized HIV-positive patients, Narasimooloo and colleagues (2011) reported a pain prevalence of 83% in ninety-one per cent of their study participants. However, in a convenience sample of ambulatory South Africa HIV-positive patients, patients who commenced on HAART, pain symptoms were highly prevalent with 79% of patients reporting headaches and 65% of patients experiencing painful joints (Peltzer and Phaswana-Mafuya, 2008). In a US study, Miaskowski and colleagues (2011) conducted a study in 296 HIV-positive patients with 74.4% of the patients taking ARVs. Of the 296 recruited patients, 270 reported pain (91.2%) with 145 (53.7%) reporting the pain to be severe (Miaskowski et al., 2011). Similarly, in a study conducted in Pennsylvania on 156 participants of which 57% were male African Americans, the prevalence of pain was 96% (Merlin *et al.*, 2012), showing that even in the HAART era, pain and symptoms are still common.

In conclusion, the above data are inconclusive as to whether there is an improvement or worsening of pain symptoms in patients who have initiated HAART. Therefore, proper conclusions on the differences in the direction of change of pain with the introduction of HAART from the above studies could not be made as the authors have not mentioned the antiretroviral

agents given to patients in their respective studies. On the other hand, the cohorts where similar HAART pain prevalences were obtained as in pre-HAART era, were mainly those that were in socioeconomically disadvantaged areas, with more patients diagnosed HIV-positive when at advanced stages of HIV and also when admitted in hospital. It seems as if HAART reduces the burden of pain more in patients in well-resourced areas than in those living in areas with poor resources, and where the patients have more severe disease (inpatients and those who have AIDS).

1.1.3. Risk factors or predictors for developing pain in HIV

There are not many studies that have focussed on the risk factors for developing HIV-related pain.

In their Univariate analyses, Hewitt and colleagues (19977) found an association between lower CD4 T-cell count and the presence of headache, where low CD4 T- cell count and female gender each provided an independent statistically significant increase in the likelihood of being diagnosed with headache. The authors also reported that injection drug use was correlated with a higher incidence of joint pains. Other researches have reported an association between low CD4 T-cell count and increased prevalence of pain (Hitchcock *et al.*, 2008) and other authors reported CD4 T-cell counts to be independently associated with increased pain reports (Van As et al., 2009). These data provides evidence that a low CD4 T-cell count is a risk factor for developing some form of HIV-related pain,

possibly because patients are at increased risk of developing opportunistic infections, which may cause pain. In addition others have reported lower socioeconomic status as a predictor of pain in HIV-positive patients (Dobalian *et al.*, 2004) whereas female gender and less education were found to be associated with more severe pain (Miaskowski et al., 2011). In a recent report, where the APCA African Palliative Outcome Scale (APCA African POS) and the Medical Outcomes Study HIVHealth Survey (MOS HIV) were used to collect pain-related data in HIV outpatients attending HIV care and support facilities in two African countries, Kenya and Uganda, poorer, less educated people with impaired physical function and low CD4 count were more likely to have pain (Harding *et al.*, 2013).

Psychiatric illness and intravenous (IV) drug use have been shown to be common co-morbidities in patients with HIV (Tsao and Soto, 2009). Merlin and colleagues (2012) also published data to suggest a strong relationship between pain and psychiatric illness and IV drug use. In their study, which was undertaken in the HAART era, patients with psychiatric illness were 40% more likely to have pain. Other studies from before the current treatment era suggested that HIV-infected patients with a history of IV drug use have a higher prevalence of pain and increased symptom-related distress (Breitbart *et al.*, 1997; Vogl *et al.*, 1999). Therefore, there is a strong relationship between pain and psychiatric history and IV drug and the data are consistent in the pre HAART era and the current treatment era.

1.1.4. Longitudinal studies

Epidemiological research on HIV-related pain is dominated by cross-sectional studies, with a relative dearth of longitudinal studies. However, only through longitudinal studies can the temporal characteristics of the burden of pain be assessed.

Longitudinal studies on pain in HIV-positive patients started in the early 1990s. Singer and colleagues (1993) prospectively studied ambulatory HIV-infected homosexual/bisexual men and found that painful illnesses were reported at all stages of systemic disease with the illnesses being more common in the later stages of disease, and also in participants who progressed to a more advanced stage during the study period. Thus, pain is a common problem even at the earlier stage of the HIV illness. However, although the prevalence of pain of 80% was reported, the authors did not report on the intensity of the pain in their study group, which would have been a useful measure especially since patients had reported higher Karnofsky scores after two years compared to when they entered the study. To be able to determine the incidence, prevalence and characteristics of pain related to AIDS, Frich and Borgbjerg (2000) followed up 95 AIDS patients and interviewed them every 6 months for 2 years. The cumulative incidence of pain in their patients was 88%, and 69% of the patients reported moderate to severe pain intensity that was constant and interfered with their daily living. They reported that there was no change in the visual analogue scale (VAS) scores of 61 patients who reported worst pain and participated in at least two interviews. Therefore,

there is a significant risk for patients without pain to later experience some form of pain, and also a significant increase in the number of disturbing pain localizations in the last six months before death. Brechtl and colleagues (2001) studied 70 protease inhibitor naïve in-patients who were classified as having advanced AIDS. The patients were initiated on HAART and were followed-up for three months to see the effect HAART had on their clinical outcomes, pain, symptom distress and their psychological well-being. Of the 70 patients, only 50 patients who had no cognitive impairment were administered the questionnaire. Thirty-one patients of the 50 patients (62%) patients reported having pain in the past two weeks with the average intensity of pain of 5 on an 11-point numerical pain rating scale, corresponding to the “moderate” level of pain intensity. Pain intensity did not change over the three months of treatment. The study by Singer and colleagues (1993) included individuals who were HIV-positive, but not terminally ill, whereas the other two studies included individuals who were at the terminal stages of their disease. Also, all or some of the individuals who were included in the above studies were on some form of antiretroviral agent. It is well-known that some antiretroviral agents cause neuropathic pain, for example: didanosine, zalcitabine, and stavudine. However Breitbart and colleagues (1996a) reported that patients who were not receiving antiretroviral agents reported pain more frequently than patients receiving therapy. But, Brechtl and colleagues (2001) had patients who were on protease inhibitors, where the patients’ scores of pain intensity and pain interference neither improved nor

worsened over time. This therefore suggests that protease inhibitors may not contribute directly to pain production as does didanosine, zalcitabine and stavudine. Similarly, Singer and colleagues (1993) and Frich and Borgbjerg (2000) had some patients who were on zidovudine. Although it is not easy to compare these studies due to differences in the patients profile (e.g., HIV disease stage, treatment regimen), the two studies both showed an increase in pain at the later stage of the disease.

In their study, Smith and colleagues (2002) recruited 145 ambulatory patients with HIV/AIDS and through the use of the Brief Pain Inventory (BPI), obtained data on pain intensity (at baseline, a month later, and also 6 months later). They found a significant decrease in the intensity of worst pain over time, from a mean of approximately 8.3 to 6.5 on an 11-point numerical pain scale (Smith et al., 2002). Similarly, in a study where 127 HIV-positive patients were followed-up for a median of 5.3 years, median pain scores of patients decreased from 5.0 during the first year to 4.0, measured on an 11-point numerical pain scale rating, in the last year (Koeppe et al., 2012). The decrease in pain in this study was related to HAART use indicating long-term benefits of HAART. However, contrary to the above, in a recent longitudinal study where 391 patients who were either on HAART or starting HAART were followed-up for a median of 5.1 years, de Boer and colleagues (2011) found a significant increase in the prevalence and intensity of the following symptoms over time: pain in the legs, tingling hands and feet, and pain when urinating. It is recognized that

the incidence and prevalence of HIV-associated sensory neuropathy (HIV-SN) increased with the introduction of ART, because of the neurotoxicity of some nucleoside analogue reverse transcriptase inhibitor (NRTI) medications, notably stavudine (d4T), didanosine (ddI), and zalcitabine (ddC). The neuropathy is a length-dependent, predominantly small-fiber neuropathy affecting the lower (and occasionally the upper) limbs in a "stocking and glove" distribution, resulting in any or all of numbness, disordered sensation, and neuropathic pain (Kamerman *et al.*, 2012). Thus, the distal limb symptoms reported in de Boer and colleagues' (2011) study are probably related to the onset of peripheral neuropathy, of which increasing age is a significant risk factor (Kamerman *et al.*, 2012). In addition, the increase in symptom intensity was found to be related to lower levels of concurrent physical and mental quality of life (de Boer et al., 2011). The finding that increase in symptom intensity was related to physical and mental quality of life, could be due to the fact that impaired quality of life has been shown to be associated with worse survival (de Boer *et al.*, 2010). The quality of life in this study was measured using the Medical Outcomes Study HIV Health Survey (MOS-HIV) which contains 10 subscales from which a physical health summary (PHS) and a mental health summary (MHS) score can be calculated. The tool was developed specifically for assessing quality of life in HIV-positive individuals.

1.2. Pain interference on the quality of life in HIV-infected patients

As I mentioned earlier, the number and severity of painful symptoms has been shown to increase with HIV disease progression, thus producing greater interference in the performance of daily activities and a proportionate decline in enjoyment of life and mood (McCormack et al., 1993; Singer et al., 1993). The pain experienced has also been recognized as a source of considerable distress and disability amongst HIV-positive patients (Douaihy *et al.*, 2007a; Douaihy *et al.*, 2007b; Merlin *et al.*, 2012; Tsao *et al.*, 2005). In developed countries, and increasingly in developing countries too, HIV/AIDS has become a chronic manageable infectious disease due to the success of HAART (Liu et al., 2006a). Thus more attention is being given to managing acute recurring and chronic complications of the disease, thus improving patients long-term quality of life (QoL) (Liu et al., 2006b). In some surveys, the presence and intensity of pain was significantly associated with indicators of functional impairment, psychological distress, depression, hopelessness and impaired quality of life (Breitbart et al., 1996b; Larue et al., 1994). Similarly, in a cross-sectional survey of 438 ambulatory AIDS patients recruited in New York, there was a significant association between the presence and intensity of reported pain and level of psychological distress and poorer quality of life (Rosenfeld et al., 1996). An Indian study has revealed that two-thirds of HIV-infected individuals in their cohort reported pain as having an impact on their mood, sleep, general activity and ability

to carry on normal work (Nair et al., 2009). Miaskowski and colleagues (2011) also found a significant difference in all the pain interference items (i.e. general activity, mood, walking, what one does, relations, sleep, and enjoyment) measured using the Brief Pain Inventory and the total interference score and pain intensity in their study population (Figure 1.1).

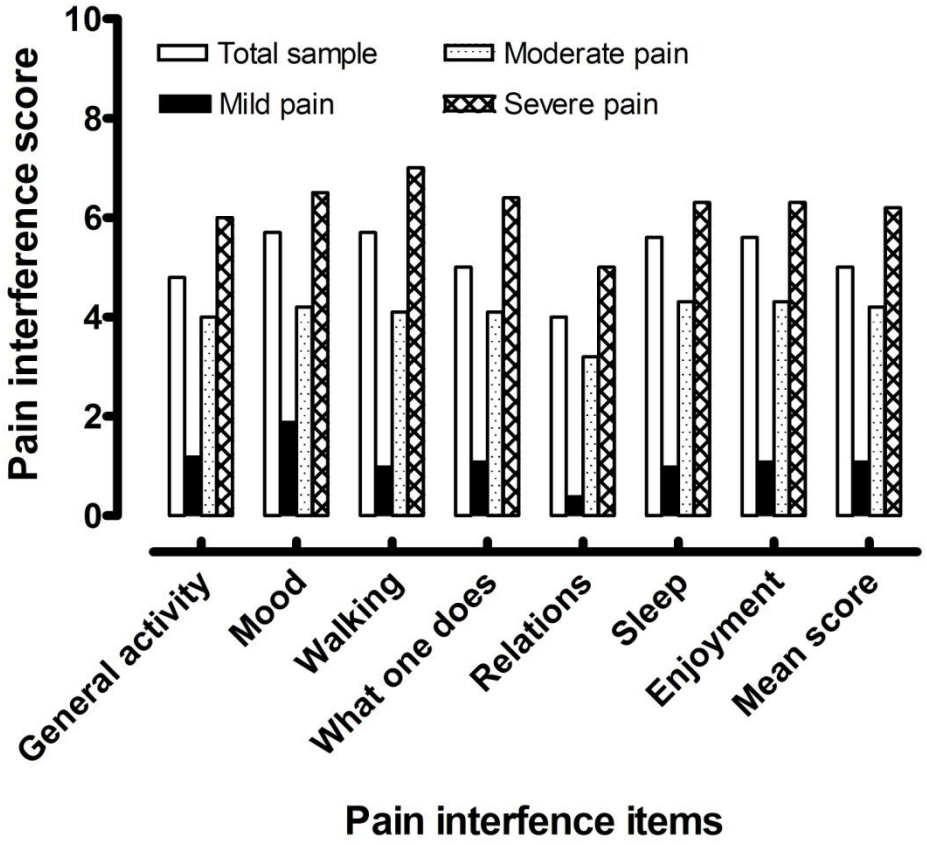


Figure 1.1: Pain interference item scores for the total sample of 270 participants with pain and differences in pain interference item scores among the 3 pain severity groups, reported as means. (All $p < 0.0001$; mild < moderate < severe) (Redrawn from Miaskowski *et al.* 2011).

In a recent South African study, Narasimooloo and colleagues (2011) also found a strong correlation between severity of pain and its interference

with daily life with general activity, mood, normal work, sleep and enjoyment all being affected by the presence of pain .

In their multicentre French study, Larue and colleagues (1997) found that patients with a worst pain score of greater than 5 on an 11-point numerical pain scale rating (moderate or greater pain), reported lower quality of life in the past week compared with patients who did not report pain (Figure 1.2). In addition, Lorenz and colleagues (2001) conducted a prospective cohort study including patients (n = 2267) from both rural and urban areas within the United States. Amongst other symptoms the authors found that oral pain and pain, numbness, or tingling of hands or feet were associated with worse perceived quality of life, whereas headache was associated with more disability days (Lorenz *et al.*, 2001). Surprisingly, in sub-Saharan Africa, where the HIV infection rates are high, examination of HIV-positive patients revealed that pain interferes minimally to their daily activities especially in resource-poor areas where patients prioritise coping with poverty, while pain is of low importance (Phaladze *et al.*, 2005; Uwimana and Struthers, 2007).

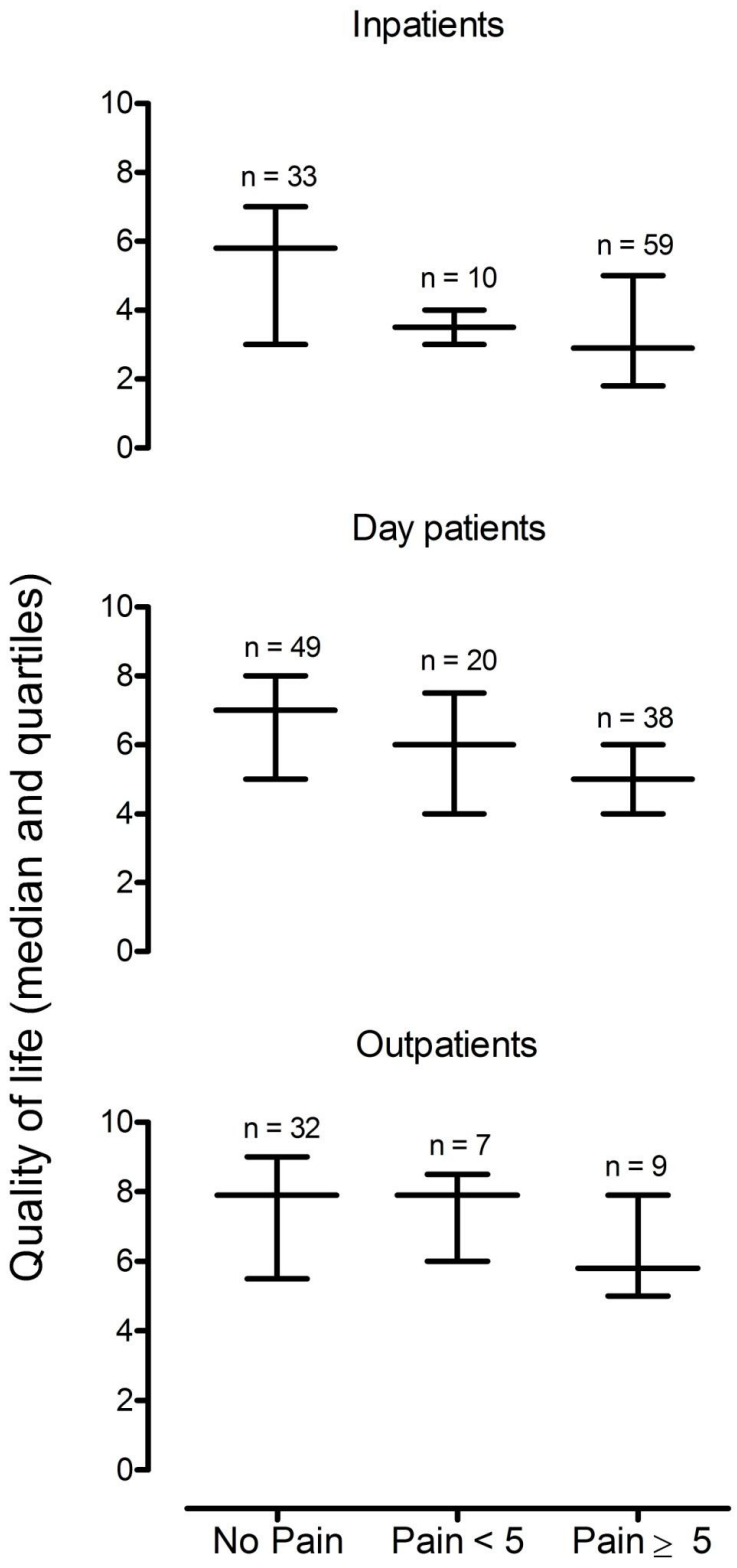


Figure 1.2: Quality of life and pain by treatment setting. Three-hundred-and-fifteen (315) patients were studies from 34 treatments centers in France. IIn this study, patients with significant pain reported lower quality of life compared with patients that had no pain. Redrawn from Larue *et al.* 1997.

Models have been developed and have conceptualised pain as a multidimensional construct incorporating both the biological, psychological and social aspects whereby investigators have started to focus on the impact of co-existing psychological and substance abuse use disorders on the experience of pain among HIV-positive patients (Douaihy et al., 2007a; Douaihy et al., 2007b). In a nationally representative sample of HIV-positive patients in the United States, approximately 48% of the 2864 patients recruited were positively screened for mood or anxiety disorders (Bing et al., 2001).

It also has been shown that the presence of pain in HIV-positive patients is strongly related to mood and anxiety, with Smith and colleagues (2002) having found that HIV-positive patients with post-traumatic stress disorder (PTSD) reported greater pain intensity and pain-related interference in performance of daily activities (e.g. working, sleeping, walking ability and general activity) and affect (e.g. mood, relations with other people, enjoyment of life) over time than those patients who were not diagnosed with PTSD. Similarly, in a nationally representative study of 1489 HIV-positive individuals in the United States, panic disorder showed a strong association with pain, which was significantly greater than PTSD but only marginally greater than major depression (Tsao *et al.*, 2004). In addition, after longitudinal analyses of the three psychological disorders (panic disorder, post-traumatic stress disorder and major depression), increasing pain from baseline to follow-up (an approximately 6-month period) was

associated with panic disorder after controlling for baseline pain scores, baseline HIV disease status and change in disease stage across time (Tsao *et al.*, 2004).

In a Chicago study, which included a subsample of 162 HIV-infected patients with current DSM-IV psychological and substance disorder, body pain scores were compared to the pain scores found in the United States general population and also compared to pain scores of HIV-positive patients who were screened negative for psychological disease (anxiety and depressive disorders) and substance abuse (Tsao and Soto, 2009). The authors reported the body pain scores were substancially greater that those of the general population. The bodily pain scores were measured using the short form (SF) bodily pain (BP) scale on a numerical scale where responses range from “none” = 1 to “severe” = 6. Similar to what other authors have reported previously, these authors also reported average pain scores that were nearly 12 points greater among patients with a current mood disorder compared to those without mood disorder (Rosenfeld et al., 1996; Singer et al., 1993).

In summary the number and severity of painful symptoms increases with HIV disease progression, thus producing greater interference in the performance of daily activities and a proportionate decline in enjoyment of life and mood. In addition, the type of pain measured and impact of pain has been shown to vary by race and ethnic group (Bates and Rankin-Hill,

1994). And, a number of studies have described racial and ethnic differences in coping with pain (Bates and Rankin-Hill, 1994; Jordan, 1999) and dysfunction associated with pain (Bates *et al.*, 1994). Thus, there may be ethnic group differences across measures of emotionality in response to pain and interference with daily functioning attributed to pain.

1.3. Pain management in HIV/AIDS

The available literature describing pain management in patients with HV/AIDS is mainly based on clinical experience and the use of the World Health Organization (WHO) analgesic ladder approach (Breitbart *et al.*, 1996b; Newshan and Wainapel, 1993; O'Neill and Sherrard, 1993). The WHO ladder shows no guideline difference in the pain management strategies between cancer pain and HIV-related pain (Frich and Borgbjerg, 2000), and it has not been validated for the treatment of HIV-related pain. However it provides general guidance from which to approach the treatment of pain in HIV-infected individuals. As such, without evidence-based treatment guidelines for HIV-related pain, the general recommendation for its treatment, which has been advanced for the last thirty years, has been to follow the WHO analgesic ladder (Edmunds-Oguokiri, 2007). There is lack of clinical trials to treat HIV-related pain, except in the cases of HIV-related sensory neuropathy (HIV-SN) (Clifford *et al.*, 2012). Also, in the case of HIV-SN, no trials of commercially available agents have proved better than placebo (Phillips *et al.*, 2010). However, in all studies the size of the placebo-effect was very large.

Numerous studies have shown that management of symptoms of chronic HIV disease, such as pain, fatigue, and insomnia, results in improved quality of life (Breitbart *et al.*, 1996a; Lorenz *et al.*, 2006; Selwyn, 2005). There is also evidence that symptom management improves virologic suppression and adherence (Clucas *et al.*, 2011).

1.3.1. Pharmacological treatment of HIV-related pain

The World Health Organisation published guidelines for treatment of cancer pain in a form of a “ladder” (Figure 1.3) (WHO, 1987). These guidelines have been validated for cancer pain (Grond et al., 1991) but not for HIV pain, and involve the selection of analgesics based on severities of pain reported by patients. From the guidelines, non-opioid analgesics which include nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended for pain of a mild nature and opioid analgesics are added if the pain is not controlled. For moderate pain, weak opioids are recommended and include drugs such as codeine, whereas strong opioids (for example, morphine), are recommended for severe pain. Adjuvant analgesics such as tricyclic antidepressants and anticonvulsants, can be added, especially if the pain is neuropathic in origin (Attal et al., 2010; Haanpaa et al., 2010; Simpson et al., 2010). However, it should be noted that in a recent systematic review and meta-analysis relating to the treatment of painful HIV-associated sensory neuropathy (HIV-SN), all commonly used adjuvants, assessed for treatment of painful HIV-SN, were no better than placebo (Phillips et al., 2010). Thus although the

above studies have followed reccomendations for the treatment of neuropathic pain based on the WHO analgesic ladder, it should however be noted that, when patients have neuropathic pain, managing that pain based on published neuropathic pain management guidelines may be a more rationale approach than employing the more opioid-focussed WHO analgesic ladder, which has known limitations in the treatment of chronic HIV-related pain (Koeppe *et al.*, 2010).

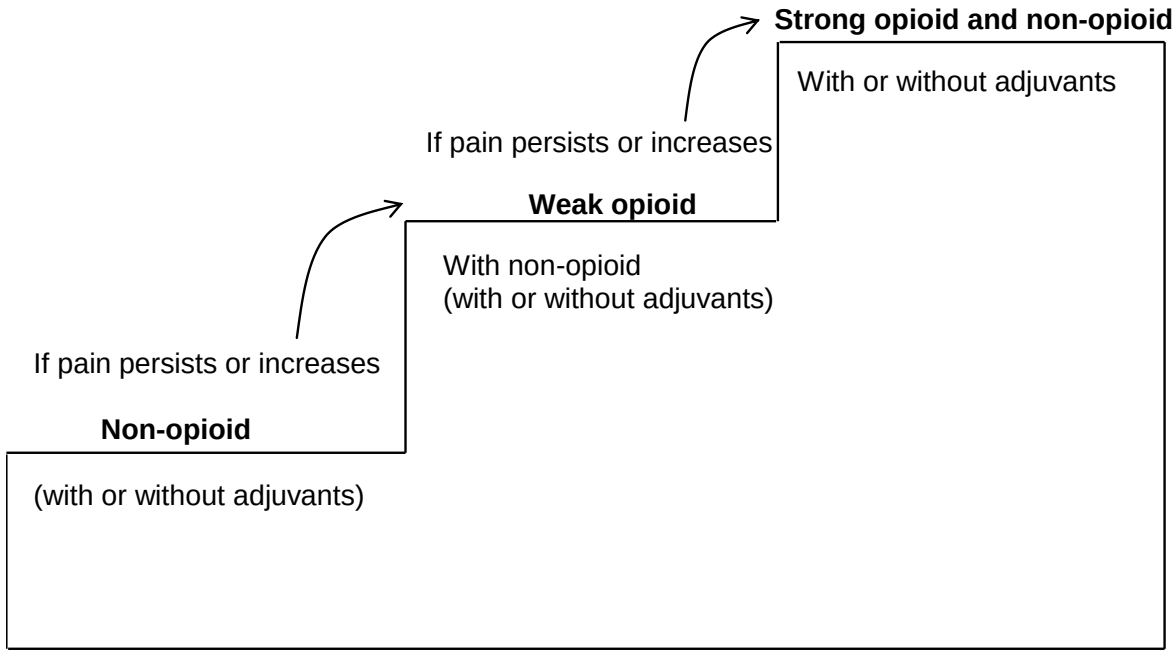


Figure 1.3: The World Health Organization analgesic ladder (adapted from the World Health Organization)

Kamerman and Mitchell (2011) provided a suggested treatment framework that incorporates parallel disease and pain management (Table 1.2). The framework emphasizes the need for thorough assessment and continual

reassessment of the patient's pain, and any dysfunction that the pain is causing. Only through proper pain assessment can a suitable pain management plan be developed and modified according to the changing needs of the patient. Care should be taken to minimize pain caused by diagnostic and treatment procedures; clinical procedures may be more painful in HIV-positive patients if they are already hyperalgesic, a possibility not yet investigated.

In a recent longitudinal study, where 127 HIV positive patients were observed for a median follow-up of 5.2 years, there was a negative association with opioid analgesia and pain intensity (Koeppe et al., 2012), thus none of the analgesics prescribed to patients improved pain. The authors related the negative association between opioids and decrease in pain to: 1) patients reporting pain scores out of proportion to the pain they are experiencing in an attempt to obtain opioid analgesics for their addiction, and 2) patients experiencing opioid hyperalgesia whereby there is remodeling of the nervous system that results in greater pain (Ballantyne and Shin, 2008; Koeppe *et al.*, 2010). Alternatively, patients with the most pain are also likely to be treated with opioids.

Table 1.2: Proposed approach to ongoing assessment and treatment of HIV-related pain (adapted from Kamerman and Mitchell (2011)

Disease management[†]

- Optimization of virological control
- Identification and treatment of underlying secondary complications[‡]

Pain management

- Continuing focused pain assessment.
- Continuing assessment of the patient's psychological and physical well being.
- Inclusion of the patient in management decisions, and provision of realistic expectations for pain relief.
- Use of the WHO pain ladder, or in the case of neuropathic pain, the latest guidelines for the management of neuropathic pain, for the pharmacological management of the patient's pain.
- Inclusion of other treatment modalities as required (e.g., psychotherapy and physiotherapy), and, where possible, ensuring that all relevant practitioners are aware of, and agree with, the goals of the treatment plan.
- Where possible, obtaining the help and support of the patient's social network to facilitate patient compliance with the treatment plan.

[†] HIV disease management must form the backbone of any strategy employed to prevent and manage HIV-related pain.

[‡] Appropriate steps should be taken to avoid or reduce procedural pain.

1.4. Under-treatment of pain in HIV

There are numerous studies that have investigated the level of pain under-treatment in HIV/AIDS (Breitbart *et al.*, 1996b; Cleeland *et al.*, 1994; Karus *et al.*, 2005; Larue *et al.*, 1997; McCormack *et al.*, 1993; Singer *et al.*, 1993). It is estimated that the level of HIV pain under-treatment is approximately 80% (Breitbart et al., 1996b); whereas pain under-treatment in cancer was found to be 40% (Cleeland et al., 1994). The above raises concern especially when it has been shown that pain intensity in HIV, like that of cancer-related pain, increases as the disease progresses (Breitbart *et al.*, 1996b).

The pain management index (PMI) is frequently used to assess the adequacy of pain treatment. A PMI, which assesses whether participants taking pain medication were taking appropriately potent analgesics based on WHO analgesic ladder guidelines, was calculated for each participant (Cleeland et al., 1994; WHO, 1990).

The PMI is calculated by comparing the analgesic potency of the pain medication individuals are taking with their pain intensity at its worst. The potency of medications is scored from 1 to 3 according to the WHO analgesic ladder (1990); a rank of 1 is given to non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen or adjuvants (e.g. antidepressants), a rank of 2 to weak opioids (including tramadol), and a rank of 3 to strong opioids (e.g. morphine). If a participant is taking medications from multiple levels of the WHO ladder, the score assigned is

that of the most potent analgesic medication they are consuming.Pain intensity, based on participants' rating of their worst pain in the last month, also is scored from 1 to 3, with 1 being assigned to mild pain (a rating of 1-3 on the WBPQ pain intensity scale), 2 to moderate pain (4-7 on the WBPQ pain intensity scale), and 3 to severe pain (8-10 on the WBPQ pain intensity scale). Participants who reports having no pain, and participants with pain, but who are not taking pain medication, are excluded from the analysis. The PMI is therefore calculated by subtracting the participants' pain intensity score from their analgesic medication score; where PMI values less than 0 indicate inadequate analgesic therapy (Cleeland et al., 1994). The PMI however has its own short-comings as it does not incorporate adjuvanct analgesics, which are medications of choice for neuropathic pain. The PMI also does not assess the patients' pain relief but only assess whether the doctors are following the analgesic ladder.

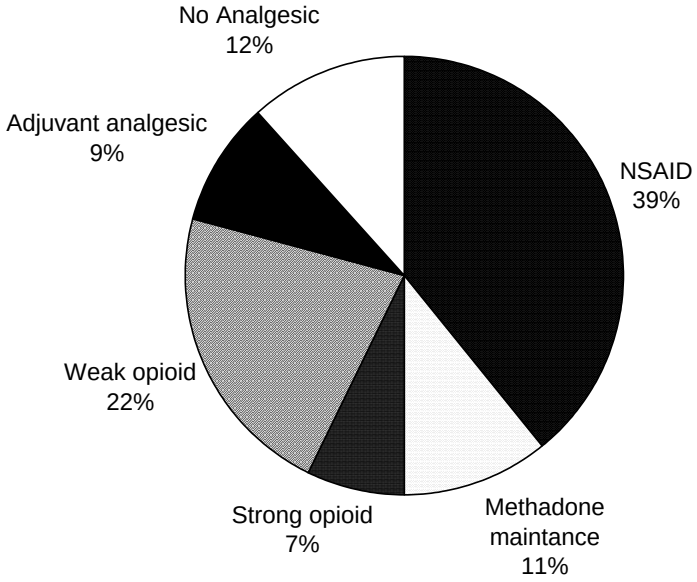
Breitbart and colleagues (1996b) conducted a study on 366 ambulatory AIDS patients to evaluate the adequacy of analgesic treatment and also to investigate the predictors of pain under-treatment in these patients. They found that of the 366 patients, 226 patients reported persistent pain over the two week survey period, with these patients reporting an average of 2.5 pain types. Fifty percent (50%) of the patients reported their worst pain as severe, 45.6% as moderate and 5.8% as mild. Also, 40 (15%) patients of the 266 patients who reported pain had no prescribed analgesics (Figure 1.4A). In addition, 91 (34%) patients were only prescribed non-

opioid analgesics, 41 (15.4%) patients prescribed weak opioids mainly used for moderate pain and only 13 (5%) patients were prescribed opioids mainly used for severe pain. One striking finding that they found was that 48% of patients reporting severe pain did not receive opioid analgesics (Figure 1.4B). Thus, although patients were in severe pain and would require the prescription of morphine, most of these patients were prescribed NSAIDs with only 6% of the patients prescribed adequate pain treatment.

Also, of the 266 patients who reported pain, 189 (84%) patients received inadequate analgesic therapy, with only 36 patients receiving adequate analgesic therapy (Figure 1.5A). These authors found the following to be predictors of pain under-treatment: being female, less educated, and an intravenous drug user as the mode of HIV transmission (Breitbart et al., 1996b). Therefore females could be receiving inadequate pain relief due to pregnancy where doctors are reluctant to prescribe opioids either to a pregnant or a breastfeeding woman.

Patients who are less educated have also been found to receive inadequate analgesic therapy. In my opinion, language barrier could be one of the reasons (at least in a South African population) or the inability to clearly explain the pain. Injecting drug-users' pain is also not being adequately treated as physicians are reluctant to prescribe opioids analgesics to this population group (Breitbart *et al.*, 1996b; Lum *et al.*, 2011).

A



B

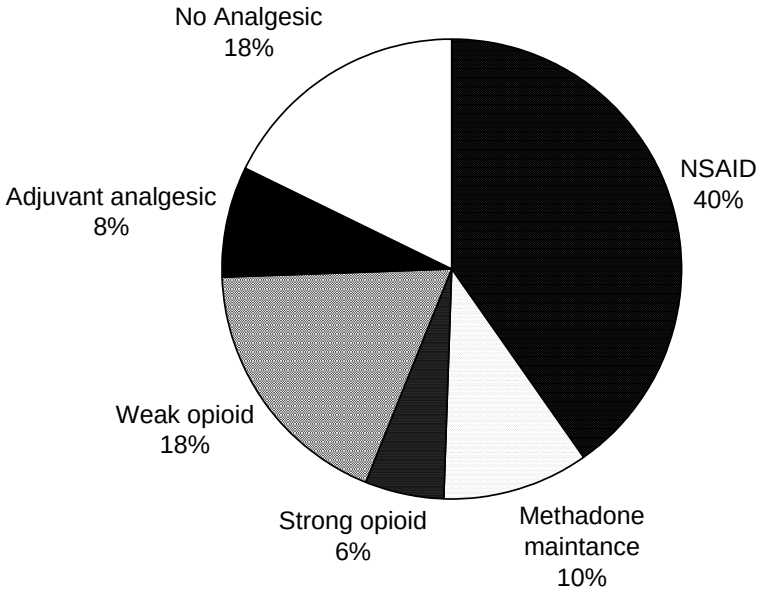


Figure 1.4: Analgesic medications prescribed for pain in ambulatory patients with AIDS. Chart A represents the total patients who had pain (n = 226) and Chart B represents the number of patients with pain, who reported severe pain (n = 110). Redrawn from Breitbart et al. 1996b.

Similar to Breitbart and colleagues' (1996b) results, Larue and Fontaine (1997) also reported under-treatment of pain in 123 of the 144 patients (85%) who rated their pain to be at its worst, a score of 10 on a numerical pain scale, in the past week (figure 1.5B). Of the 69 patients who reported severe pain in their study, only 10 (15%) patients received opioids, and only 5 of the 38 patients who reported moderate pain were given weak opioids (Table 1.3).

In a South African study, Narasimooloo and colleagues (2011) found that 91 of the 100 inpatients (91%) who participated in their study reported pain, with 30 patients of the 91 who reported pain (33%) not being prescribed any form of analgesic therapy. Of those patients who were prescribed analgesics (61 patients, 67%), 65% were prescribed only NSAIDs or paracetamol, irrespective of their pain intensity. One interesting finding was that of the 60 patients who reported severe pain, only seven patients were prescribed a strong opioid, 21% of the patients prescribed weak opioids, 51% paracetamol and one patient with no form of analgesic therapy (Narasimooloo *et al.*, 2011). The authors also reported the pain management index (PMI) of 66% and 34% for inadequate and adequate analgesic therapy, respectively (Figure 1.5C).

In another recent South African study, where 500 patients with chronic pain were recruited in a primary health care clinic (nurses led clinics in South Africa), 57.2% of patients reported moderate pain and 37%

experienced severe pain. Interestingly, only two patients had no analgesics prescribed; but this was a highly selected patient cohort (all had identified chronic pain). All prescriptions contained paracetamol. Ibuprofen was prescribed to 43.9% of the patients and aspirin to 18.1%. No codeine was prescribed, because it was not available in the clinic, and only one participant received morphine (prescribed by the doctor). Also the authors found that when analgesics were prescribed, almost 84.4% contained insufficient drug dosage and an insufficient number of tablets to last participants until the next appointment (Maree *et al.*, 2011).

In another African study undertaken in Nigeria, the authors reported that of the 22 patients who reported pain, 25% reported that pain was of moderate to severe intensity, with only 40% (2 of 5) of them reporting that they were on analgesics. Most of the patients reported little pain interference with their daily activity which could explain why there was only 40% on analgesics (Wahab and Salami, 2011).

Thus, from studies in Africa, it is clear that there is significant absence of treatment and under-treatment of HIV-related pain, and there is a lack of information on the efficacy of the available treatments, based on the gold standard of patient self-report of pain relief.

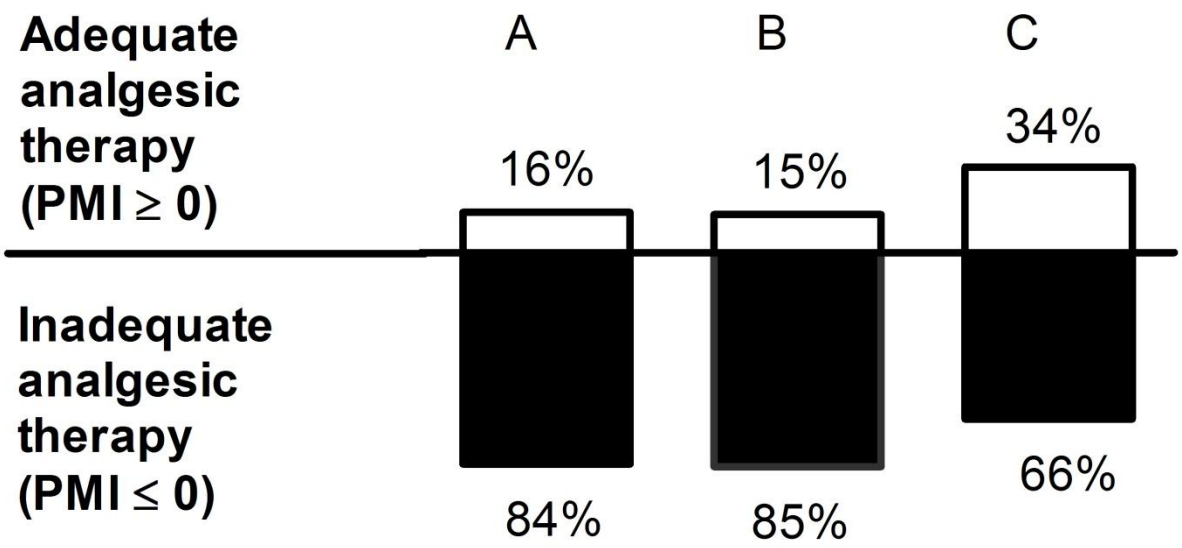


Figure 1.5: Proportion of patients receiving adequate and inadequate analgesic therapy based on the pain management index (PMI): A comparison between 3 studies - American, French and South African respectively (A: Breitbart *et al.* 1996b; B: Larue *at al.* 1997; C: Narasimooloo *et al.* 2011).

Table 1.3: Types of analgesic medication prescribed according to the patient's worst pain rating (adapted from Larue *et al.* (1997)

Treatment and PMI	Worst pain reported by patients		
	Mild (n = 37)	Moderate (n=38)	Severe (n = 69)
No analgesic treatment	31	29	32
Non-opioid analgesic	3	4	19
Weak opioid	3	4	8
Morphine	0	1	10
Negative PMI*	31 (84%)	33 (87%)	59 (85%)

PMI = Pain management index

* = inadequate treatment

In another US based study where 156 patients were enrolled, 56 (73.7%) of the 76 patients who reported pain were taking analgesic medications, with 32 patients (42.1%) prescribed opioids. Patients reported a median of 50% pain relief after taking medication. Of the 76 patients who reported pain, pain was documented in 51 (67.0%) of the clinical notes for that day. Healthcare providers were more likely to document pain of higher severity; mild pain was documented in 14 (50.0%) patients, moderate pain in 16 (76.2%) patients, and severe pain in 21 (80.8%) patients. There also was a trend towards more pain medication use as pain severity increased; 18 (64.3%) patients with mild pain took pain medication, as compared with 17 (77.3%) patients with moderate pain and 21 (80.8%) patients with severe pain (Merlin *et al.*, 2012). Therefore as it has previously been reported, pain in this group of ambulatory HIV patients was also not adequately managed, but there was much better than expected treatment of clinically relevant pain of moderate to severe intensity.

In this chronically ill patient population who are HIV-positive, there is evidence that pain symptoms are common. However, despite the substantial pain and symptom burden experienced by HIV-infected patients in the current treatment era, only three HIV-focused palliative care clinics have been described and focussed on AIDS patients at the end of life (Karus *et al.*, 2005; Perry *et al.*, 2013; Ruiz and Cefalu, 2011), with only two studies focussing on symptom relief (Karus *et al.*, 2005; Perry *et al.*, 2013). Karus and colleagues (2005) conducted a study where self-reported symptoms and their treatment were obtained from patients in

three different palliative care sites. In their study they found pain was a symptom reported by a majority of patients' at all three sites. In their study, half or more of the patients in all three sites experienced pain, nausea, difficulty swallowing, and mouth sores, also reported pain treatment, and only less than a third reported pain treatment. Thus, despite the availability of more efficacious treatments that relieves symptoms, many HIV/AIDS patients continued to experience significant physical and psychological symptomatology. Indeed, more patients experiencing symptoms did not perceive their symptoms as being treated.

Recently, a chart review of 124 HIV-positive patients attending a palliative care centre in Birmingham was conduted (Perry *et al.*, 2013). In this study, pain was the most common reason for referral (118, 95%), and most patients had chronic pain (113, 90%), which included back pain (26, 21%) and neuropathic pain (15, 12%). One-third of patients who were referred had depression, one-third had anxiety, and half had a history of substance abuse. These rates were reported as significantly higher than it had been seen in their entire clinic (all patients attending the clinic). Chronic pain and non-pain symptom management in patients with psychiatric and substance abuse comorbidities are important components of ambulatory palliative care for HIV-infected patients. This is an important issue to address especially since HIV primary care providers may feel uncomfortable addressing chronic pain, especially in the setting of substance abuse (Lum *et al.*, 2011).

I reported earlier on the relationship between psychiatric disorders, IV drug use and pain. Therefore understanding the risk factors for pain and cormobid infections or symptomps in HIV/AIDS is an important part of improving outcomes in patients with HIV. Thus, given the association between pain and symptoms and IV drug use and psychiatric illness, there is a need for these comorbidities to be addressed when treating HIV-infected patients with pain. Also there is a need for experienced palliative care practitioners to provide ambulatory services to HIV-infected patients with psychiatric illness and substance abuse.

All of the above studies have concluded that pain in HIV is poorly recognised and poorly managed. Having found this to be a global trend, the reasons for this poor management and recognition are discussed below.

Most studies have speculated that patient, clinician and healthcare barriers are possible factors that influences under-treatment (Breitbart *et al.*, 1999). Other studies have also mentioned attitude and demographic characteristics to be some of the barriers to adequate pain management (Breitbart et al., 1998; Ferrell, 1991).

Other studies found the concerns amongst AIDS patients with pain to be related to possible addiction towards opioids and the fear of discomfort associated with the administration these drugs (Breitbart et al., 1998; Ward et al., 1992). In their study, Breitbart and colleagues (1999) investigated what the barriers to pain management in AIDS patients by clinicians were,

by conducting a survey on 492 health care providers currently caring for AIDS patients. Their survey included several questions that evaluated the knowledge and attitudes regarding pain management, and questions regarding barriers to pain management (Table 1.4 for a list of questions). They found that the lack of knowledge about pain management or access to pain management expert are the most frequently accepted barriers to adequate pain management in patients with HIV/AIDS. Table 1.4 highlights results from their study where 51.8% of healthcare workers rated their lack of knowledge regarding pain management as “quite a bit” or “very much”. Overall, more than 50% of healthcare workers endorsed the following to be barriers to pain management in AIDS patients: 1) lack of access to professionals who practices specialised pain interventions 2) reluctance to prescribe opioids, and 3) concerns regarding drug addiction and/or abuse by patients (Table 1.4). Other studies have reported on the lack of specialists who would administer opioids and healthcare system barriers (Gee and Fins, 2003).

Also since it is said that “pain is what the patient says it is”, one author has concluded that the under-estimation of pain could possibly be due to the phenomenon that nurses and patients hold different beliefs about pain (Arber, 2004).

Table 1.4: Barriers to pain management (adapted and redrawn from Breitbart *et al.* 1999)

Barrier question	Mean(SD)	Overall rating % of respondents endorsing barriers as “quite a “bit” and “very much”
1. Lack of knowledge regarding pain management *	3.4 (1.2)	51.8
2. Reluctance to prescribe opioids	3.4 (1.2)	51.5
3. Lack of access to professionals who practice specialised pain interventions *	3.3 (1.2)	50.9
4. Inadequate ability to assess pain *	3.1 (1.1)	38.0
5. Focus of care on treatment of disease/infections rather than comfort/quality of life *	3.0 (1.3)	37.8
6. Excessive state regulation of prescribing analgesics	2.9 (1.3)	36.2
7. Concern regarding opioids side effects	3.1 (0.9)	32.0
8. Concern that opioids drugs prescribed for pain would be diverted or sold for profit *	2.7 (1.2)	26.1
9. Lack of access to a wide range of analgesics	2.6 (1.2)	26.0
10. Patient reluctance to report pain	2.8 (1.0)	24.9
11. Patient reluctance to take opioids	2.8 (1.0)	23.9
12. Concern that opioids will not adequately manage the AIDS patient’s pain	2.1 (1.1)	11.4
13. Concern that opioids would adversely affect the immune system of AIDS patients *	2.0 (1.1)	8.3

* Barriers to pain management that were significantly associated with pain management experience in AIDS patients.

To endorse the fear of administering opioids by healthcare providers, it has been shown that the total prevalence of substance abuse in patients with chronic nonmalignant pain may be as high as 48% (Fishbain, 1999; Manchikanti *et al.*, 2006; Morasco *et al.*, 2011). There is also evidence to suggest that patients with substance abuse disorders and chronic pain are more likely to be prescribed opioids at higher doses and have higher rates of unusual drug-related behavior or opioid misuse than patients without substance abuse disorders (Morasco *et al.*, 2011). In patients with chronic pain, the likelihood of developing iatrogenic opioid misuse or abuse has been found to be less than 1% in patients without a prior history of substance abuse (Noble *et al.*, 2010), but may be as high as 34% in populations with a history of substance abuse (Fishbain *et al.*, 2008). Therefore it will be a good idea for the diagnosis of substance abuse and other psychiatric comorbidities to become part of the palliative care providers' routine set of medical knowledge especially since the two frequently occurrence with chronic pain. The previous studies have been undertaken in developed countries where the patients' population are predominately males, Caucasians, with a history of substance abuse. Thus the data may be different in developing countries, where the study populations are mainly female, Black and none or less report of substance abuse. Thus, if substance abuse is not an issue in this setting, the chances of opioid misuse or abuse will be reduced.

Eleven out of forty seven African countries use morphine for chronic pain, with South Africa being the highest user of morphine (Logie and Harding,

2005). In a palliative care setting, the palliative care providers are familiar with many pharmacologic therapies available to treat pain. In particular, palliative care providers are likely to be familiar with the use of opioids, which are the cornerstone of cancer and end-of-life pain management (Portenoy and Lesage, 1999). However, there is a need for palliative care providers to understand the role of opioids in chronic pain especially where there is only limited evidence supporting their efficacy (Noble *et al.*, 2010). There is also increasing awareness, both in the medical community and in the lay public of the risks associated with opioids, including misuse, abuse, diversion, and overdose (Chou *et al.*, 2009; Compton and Volkow, 2006; Dunn *et al.*, 2010; Furlan *et al.*, 2006; Manchikanti *et al.*, 2008).

In a recent Malawian retrospective study, patients required oral morphine but did not receive it because healthcare workers do not have access to and knowledge of oral morphine to be able to provide to their patients (Tapsfield and Bates, 2011). Some of the challenges that has been reported includes; access to opioids, education of both the healthcare workers and influencing policy makers (Harding et al., 2010; Livingstone, 2003). Table 1.5 highlights some of the challenges and factors hampering opioid expansion and roll-out from 12 sub-Saharan African countries.

In an Asian study, Coughlan and colleagues (2003) discovered that lack of care and support services, lack of recognition and acknowledgement of pain in HIV/AIDS by healthcare professionals, widespread stigma and

Table 1.5: Challenges and factors hampering opioid expansion and roll-out from 12 sub-Saharan African countries (modified from Harding R *et al.* 2010).

1. Political

- Store supplies are unreliable
- Lack of political will
- Lack of national policy and motivation
- Bureaucracy

2. Clinical

- Professionals lack knowledge on HIV pain, assessment and management
- Professionals fear opioids
- Lack of professional training
- Lack of clinical interest in dying
- Public opioid fear

3. Site-specific

- Lack of storage facilities
- Rural distance from suppliers
- Specialist palliative care excludes other organisations

4. Resources

- Lack of prescribers and pharmacists
- Costs
- Lack of facilities to follow patients up at home

discrimination against injecting drug users (IDUs), restrictive government regulatory mechanisms which make access to opioids more difficult for the care services, a lack of understanding of pain relief and palliative care all contribute to lack of access to opioids and thus inadequate treatment of pain in HIV positive patients. Similarly, in their Taiwanese study, the authors concluded that healthcare providers have limited knowledge about self-care symptom management of HIV/AIDS, which contributes to inadequate treatment of pain in HIV-positive patients (Tsai *et al.*, 2002).

Heckman and colleagues (1998) conducted a study on 226 HIV positive men and women living in rural and urban Wisconsin. In their study they found that rural patients had more inadequate pain treatment compared to their urban counterparts. The inadequate treatment of these patients was a result of long distance travel to medical facilities, shortage of adequately trained medical professionals in rural areas, lack of public transportation, and stigma towards people living with HIV/AIDS by residents within the community.

In conclusion, there seem to be inadequate pain treatment and palliative care, and failure to improve access to pain treatment. The roll-out of more effective pain treatment to patients also seems to be a problem. Thus, with proper training in both pain management and the use of opioids, the challenges faced will be alleviated and thus provide better management of pain to patients who are HIV-positive. Also since palliative care providers are familiar with the use of opioids; palliative care should be incorporated

as one of the pain management strategies to effectively decrease some of the challenges for opioid use and thus better pain management of patients.

1.5. Aims of the thesis

Southern Africa has the highest rate of HIV infection in the world, with an estimated 11.3 million (10.6 million-11.9 million) people living with HIV/AIDS in 2009 (UNAIDS, 2011). For most of these patients, poor public health infrastructure (Heckman *et al.*, 1998; Tollefson and Usher, 2006) means that even as access to treatment for their HIV infection increases, identification and management of secondary complications of HIV infection and its treatment are likely to remain under serviced, especially if the extend of these secondary complications is poorly understood.

Validation of the Wisconsin Brief Pain Inventory (Chapter 2) and Pain in ambulatory HIV-positive South Africans (Chapter 3)

Almost all studies specifically designed to describe the nature of HIV-related pain have taken place in developed countries, and the patient populations that were studied consisted predominantly of males and Caucasians (Lebovits et al., 1989; Singer et al., 1993). The only one of these studies that included a significant number of HIV-positive non-Caucasians and female patients was conducted by Breitbart and colleagues (1996b), and the authors reported that both non-Caucasian

and female patients reported an average pain of greater intensity than that reported by Caucasians and males. The authors also reported that predictors of increased pain perception and pain under-treatment included being female, less educated, and non-Caucasian. Sub-Saharan Africa bears the main burden of HIV infections, with the majority of these people being Black, female and less educated (Joint United Nations Programme on HIV/AIDS (UNAIDS) and (WHO), 2009; UNESCO, 2008). As such, a considerable portion of the world population of people living with HIV/AIDS may have an increased risk of having some kind of HIV-related pain and also for their pain to be under-treated.

Data on pain from quality of life studies conducted in African HIV-positive patients, indicates that pain is a frequent symptoms in African HIV-positive individuals (Hughes *et al.*, 2004; Peltzer and Phaswana-Mafuya, 2008; Rosen *et al.*, 2008; Uwimana and Struthers, 2007; Voss *et al.*, 2007). However, at the time of undertaking the research for this thesis, there were no pain-focussed research in an African HIV-positive population, other than a description of the pain experienced by terminally ill AIDS patients in South Africa (Norval, 2004). Since undertaking my study, several pain-focussed studies in African HIV-positive cohorts have been published (Maree *et al.*, 2011; Namisango *et al.*, 2012; Narasimooloo *et al.*, 2011). These studies are discussed in the context of my findings in later sections of the thesis.

Objectives

The objectives of the studies were to:

1. Establish the prevalence, intensity and analgesic medications employed in a population consisting predominately of Black, female HIV-positive South Africans.
2. Assess whether the characteristics of HIV-related pain and its pharmacological treatment were similar in metropolitan and rural areas of South Africa, because location may influence factors such as access to healthcare, education and employment, which may in turn affect pain perception. In both cohorts, I investigated a population of ambulatory patients attending typical HIV outpatient clinics.
3. To validate translated versions of the Wisconsin Brief Pain Questionnaire (WBPQ), which assess pain intensity and the interference that pain has on daily life of patients, in indigenous South African languages, and in English when the questionnaire was completed by second-language English speakers. The above study was conducted as part of the process of conducting an epidemiological study on pain in a population who were not first-language English speakers.

Pain in South African HIV-positive ambulatory patients: a longitudinal study (Chapter 4)

Most studies on HIV-related pain are cross-sectional in nature thus there is a derth of information with regards to the changes in the pain characteristics over time. Only by knowing the prevalence of pain over time can we start to appreciate the true burden of pain within this group of patients. At the time of undertaking my research, there were only four studies, of which I am aware of, that have investigated the prevalence and treatment of HIV-related pain over time (Aires and Bammann, 2005; Brechtl *et al.*, 2001; Frich and Borgbjerg, 2000; Singer *et al.*, 1993) and none had been reported in Africa. Since undertaking my study, another two studies (Koeppe et al., 2012; Rosen et al., 2010) have been published. These studies are discussed in the context of my findings in later sections of the thesis.

Objective

The objective of this study was to investigate the change in pain intensity, pain sites, pain interference and pain treatment over a period of six months, in South African ambulatory HIV-positive patients, due to the lack of longitudinal studies of pain in HIV-positive patients in Africa, and in the world,

CHAPTER 2

VALIDATION OF THE WISCONSIN BRIEF PAIN QUESTIONNAIRE IN A MULTILINGUAL SOUTH AFRICAN POPULATION

Data presented in this chapter have been published:
Noko R Mphahlele, Duncan Mitchell and Peter R Kamerman (2008). Validation of the Wisconsin Brief Pain Questionnaire in a multilingual South African Population. Journal of Pain and Symptom Management 36:4 335-450.

2.1. Abstract

Assessment of pain intensity and its effect on quality of life is important for proper management of pain, but no validated pain assessment tools that assess pain intensity and the interference pain has on daily life are available in indigenous South African languages. Therefore, the aim of this study was to validate translated versions of the Wisconsin Brief Pain Questionnaire (WBPQ) in South African HIV-positive patients. The WBPQ was translated into three indigenous South African languages, Setswana, isiZulu, and Xitsonga. I interviewed 452 ambulatory HIV-positive patients (327 urban and 125 rural patients) between the ages of 20 and 76 years old. Factor analysis to assess construct validity identified a two-factor structure (pain intensity and pain interference) for the isiZulu ($n = 132$), Xitsonga ($n = 125$), and Setswana ($n = 66$) versions of the WBPQ, whereas a three-factor structure (pain intensity, mood interference, and activity interference) was identified for the English (completed by English second-language speakers, $n = 129$) version of the WBPQ. Cronbach alphas, calculated to assess the reliability of the pain intensity and pain interference scales, were greater than 0.70 for all scales in all four versions of the WBPQ, showing internal consistency within the dimensions. These results provide evidence of validity for an easily administered questionnaire, which assesses pain intensity and pain interference, in three indigenous South African languages, and for English second-language speakers, in a population of South African HIV-positive patients.

2.2. Introduction

Pain is one of the most frequent and debilitating symptoms in people infected with HIV (Lebovits *et al.*, 1989; O'Neill and Sherrard, 1993; Singer *et al.*, 1993). The prevalence of HIV-related pain ranges from 30% to 94%, (McCormack *et al.*, 1993; Norval, 2004; O'Neill and Sherrard, 1993) depending on disease severity and duration of infection. Despite physicians agreeing that HIV-related pain is a major complication of the disease, Laure et al. (1997) reported that 57% of HIV-positive patients who were in severe pain did not receive any analgesic treatment (Larue *et al.*, 1997). When analgesic therapy was prescribed, it frequently was inadequate (Breitbart et al., 1996b).

Almost all studies that have investigated HIV-related pain have been conducted in first-world countries and on patient cohorts that consisted predominantly of males, Caucasians, homosexuals, and intravenous drug users (Breitbart et al., 1996b; Hewitt et al., 1997; Singer et al., 1993). The only study on pain in HIV-positive patients in South Africa was of a limited nature, and focused on a highly selected group of patients who were under palliative care (Norval, 2004). Thus, there is a lack of knowledge on whether the prevalence of HIV-related pain is similar in a third-world environment, where the patient base is mainly women and blacks (Shisana et al., 2005). Because pain is a subjective experience that is dependent on ethnicity (Riley et al., 2002) and gender (Jackson et al., 2002), I believe that an authoritative study into HIV-related pain and its

treatment is required in the South African population. To adequately assess pain and the effect it has on the daily life of South African HIV-positive patients, a validated instrument to obtain pain-related information in the languages frequently spoken in South Africa is required.

The methods most commonly used by South African clinicians to assess pain are the visual analog scale, and verbal and numerical rating scales (Shipton, 1993). Although these tools are easy to administer, they only measure pain intensity and not the effect of pain on the quality of life of patients. Assessment of pain intensity and the effect of pain on quality of life can be achieved by co-administering quality-of-life questionnaires, such as the Patient Evaluated Problem Score, with a pain rating scale (Pratheepawanit *et al.*, 1999). However, simple, easily administered questionnaires like the Brief Pain Inventory (BPI) and the Wisconsin Brief Pain Questionnaire (WBPQ) assess pain intensity, pain interference and treatment efficacy.

The BPI, developed by Cleeland and colleagues (Cleeland et al., 1988), is widely used in the assessment of pain. The instrument measures the severity of pain and the impact of pain on quality of life of patients by asking patients to rate their pain intensity (pain at its worst, pain on average, and pain at its least during the last week, and pain right now) on a 0–10 numeric scale where 0 indicates “no pain” and 10 indicates “pain as bad as you can imagine.” The instrument also measures (on 0–10 numerical scales) how pain interferes with other aspects of patients' daily

lives, namely mood, relations with other people, walking ability, sleep, general activity, enjoyment of life, and normal work. The BPI comes in a short form and a long form, with the short form containing the same eleven core questions on pain intensity and pain interference as the long form, but less patient history and details of the quality of the pain are included. Although the instrument was developed in English, the simplicity of the semantic structure of the BPI questions means that it has been translated and validated for use in the assessment of cancer pain (Aisyaturridha *et al.*, 2006; Ger *et al.*, 1999; Klepstad *et al.*, 2002; Radbruch *et al.*, 1999; Saxena *et al.*, 1999) and non-cancer pain (Keller et al., 2004; Tan et al., 2004). Translated versions of the BPI have been used in South Africa in a study on cancer pain (Beck and Falkson, 2001) but apparently without validation.

The WBPQ is a self-report questionnaire, developed by Daut and colleagues before the development of the BPI, to assess pain intensity and pain interference in patients with cancer and other diseases (Daut *et al.*, 1983). Like the BPI, the WBPQ contains the same four core questions as the BPI that assess pain intensity, and the same seven core questions that assess pain interference. The rating of pain intensity in the WBPQ also uses a numerical rating scale anchored at 0 and 10, but the pain interference items are rated on a five-point scale, with 0 representing “no interference at all” and 4 representing “extreme interference.” In addition, the questions on pain intensity in the WBPQ ask patients to rate their pain intensity in the last month, not the last week. Although the underlying

structure of the WBPQ and BPI are similar, and the WBPQ was developed before the BPI, the BPI has been more widely adopted than the WBPQ.

For the present study, I chose to validate the WBPQ for non–English-speaking South African populations. The WBPQ was selected because the underlying psychometric properties of the core questions of the WBPQ and BPI are very similar, the main difference being the time period over which patients assess each item, and the time taken to complete the long form of the BPI would be too onerous on our patients. The short form of the BPI was sufficiently brief, but does not provide the supporting questions included in the WBPQ.

There are 11 official languages in South Africa, with nine being indigenous African languages. Most people in South Africa, especially in the indigenous African population, are at least bilingual and frequently use more than one language in their homes (Pan South *et al.*, 2002). Therefore, I set out to determine the validity of the pain intensity and pain interference items of translated versions of the WBPQ in South African patients, using rural and urban cohorts of HIV-positive patients. The questionnaire was translated into isiZulu, isiXhosa, Sepedi, Setswana, and Xitsonga. However, too few patients completed the isiXhosa and Sepedi versions to warrant evaluation of these two questionnaires. I also assessed the validity of the original English version of the WBPQ in second-language English speakers.

2.3. Methods

2.3.1. Participants

Three-hundred-and-twenty-seven (327) ambulatory HIV-positive outpatients between the ages of 20 and 76 from the outpatient clinic for HIV-positive people at the Helen Joseph Hospital, Johannesburg, Gauteng, South Africa, and 125 ambulatory HIV-positive outpatients from a rural hospital, Tintswalo Hospital, Bushbuckridge, Limpopo, South Africa were recruited between March 2005 and July 2006. Of the 327 urban patients, 244 were female. Patients' CD4 counts ranged from 1 to 861 cells/mm3 and viral loads ranged from 380 to 123,000 copies/mL. In the rural hospital, 98 patients were female and 27 were male; the patients' CD4 counts ranged between 4 and 963 cells/mm3 and the viral load ranged from 25 to 357,000 copies/mL. The research protocol was approved by The University of the Witwatersrand Human Research Ethics Committee (Clearance Number: M041112), and all patients were informed of the study procedures, and if they wished to take part in the study, they signed a written consent form.

2.3.2. Study Instrument and Procedure

I used the WBPQ, which consists of pain intensity and pain interference items similar to that of the BPI (Daut *et al.*, 1983). The WBPQ was forward

translated from English into isiZulu, isiXhosa, Sepedi, and Setswana, the four most frequently spoken and understood languages in urban Johannesburg, and also into Xitsonga, the predominant language spoken in rural areas of Limpopo Province, South Africa, by bilingual translators. The translated questionnaires were back-translated into English by bilingual translators who had not seen the English version of the WBPQ. I compared the back-translated versions of the WBPQ to the original English version to check that the meaning of the questions had been maintained. When the meaning of a question was not maintained, a third translator was asked to verify the accuracy of the forward and back-translations, and if no suitable wording could be found, the question was removed from the questionnaire. The meanings of the following questions were not maintained and the questions were removed: Average pain (Question 7) from all the translated versions, and mood (Question 14) from the isiZulu version. (Copies of the full English and isiZulu versions of the WBPQ are presented in Appendices B and C of this thesis; the Setswana and Xitsonga versions are available in Appendices F and G, and all are available in the Appendix section of this thesis). Only the data for the English-second language, isiZulu, Xitsonga, and Setswana versions of the BPQ are reported because the sample sizes were close to, or greater than 100, which is the minimum recommended sample size for factor analysis (Kline, 1994). The sample sizes for the Sepedi (Appendix E) and isiXhosa (Appendix D) versions of the WPBQ were 35 and 34, respectively. Therefore, data from these 69 patients were not analyzed. Because some

of the patients were illiterate, I trained interviewers to administer the questionnaire to all patients. Interviewers were trained so as to standardize the interview technique, and they were instructed to only clarify the questions asked in the questionnaires and not to add any additional information if they were asked by the patients. Thus, the interviewers were not allowed to explain, for example what worst pain means, and also not allowed to add any additional information when asked by the patients.

2.3.3. Statistical Procedure

I used the Kruskal–Wallis test with Dunn's multiple comparison test to assess for differences between scores for the 11 pain intensity and pain interference items between the different language versions of the WBPQ. To determine the construct validity of the questionnaires, factor analysis with Varimax rotation was performed to determine the number of factors underlying the relationships found among items in the English and translated questionnaires. That is, I wanted to determine whether the pain intensity items (worst pain, least pain, average pain, pain now) and the pain interference items (mood, relations with other people, walking ability, sleep, normal work, and enjoyment of life) for each version of the WBPQ were grouped logically under factors representing the different dimensions of the WBPQ, namely pain intensity and pain interference. Factors were retained if their eigenvalues exceeded one, and it was possible to interpret the factors. The extent to which each factor represented the data was

assessed by examining the amount of explained variance accounted for by the factors. The suitability of the grouping of items under each factor was assessed by examining the factor loadings for each item. If the loading for an item under a factor was greater than 0.4, the loading was considered meaningful (Mystakidou et al., 2001; Wang et al., 1996). Items that loaded on two factors, but highly on only one factor were considered as part of that factor. Items that loaded highly on more than one factor and the items that did not load on any factors were excluded as items within the questionnaire. All the removed items were not included in the reliability analysis. In addition, to confirm the criterion validity of the pain severity items on the WBPQ, I performed a Spearman's correlation between the scores patients gave for the “pain now” item on the WBPQ with their rating of their current pain intensity, assessed at the same time, using the Faces Scale (Appendix H). The Faces Scale consists of illustrated faces with expressions that range from a neutral face indicating “no pain” to a down-turned mouth indicating “worst pain ever.” The Faces pain scale has been used successfully to rate pain in a similar cohort of South African patients (Shipton, 1993).

To determine the reliability of the questionnaires, I computed coefficient alphas for the pain intensity and pain interference subscales in each questionnaire. Alpha values ≥ 0.7 were considered as evidence of acceptable internal consistency for the scale under consideration (Nunnally, 1978). To determine the contribution each item made to the underlying construct of a subscale, coefficient alpha values for the

subscales also were calculated when individual items in each subscale were deleted. Items that significantly compromised the underlying construct of a subscale (that is, the scale alpha value rose when the item was deleted) were removed (Caraceni et al., 1996). To determine whether patients had difficulty using the 11-point rating scale used in the pain intensity subscale of the questionnaires, I also determined how many patients, within each language group, rated the intensity of their average pain, least pain, or pain now greater than their worst pain (Saxena *et al.*, 1999).

2.4. Results

2.4.1. Descriptive Statistics for the WBPQ

Table 2.1 shows the descriptive statistics for all the translated versions of the WBPQ and the English version (completed by English second-language speakers). In general, I found that the group of patients from the rural community (Xitsonga questionnaire) rated their “pain now” and pain interference items significantly greater than patients in the urban cohort of patients (English, isiZulu, and Setswana questionnaires). However, there were no significant differences in the rating of “least pain” and “worst pain” between questionnaires.

2.4.2. Reliability and Validity of the English Version of the WBPQ When Completed by Second Language English Speakers

One hundred twenty-nine patients who were second-language English speakers completed the English version of the WBPQ.

The majority of these patients spoke Zulu (32%) or South Sotho (16%) as a first language. Factor analysis revealed that the questionnaire had a three-factor structure (Figure 2.1). Factor 1 included all the pain intensity items, Factor 2 included the pain interference items describing mood-related interference (mood, relations with other people, and enjoyment of life), and Factor 3 included interference items describing activity-related interference (walking, normal work, and sleep). The eigenvalues of the three factors were 2.56 for pain intensity, 1.86 for mood-related interference, and 1.63 for activity-related interference. The three factors explained 67% of the variance; factor loadings are shown in figure 2.1.

The Cronbach alpha for pain intensity items was 0.88, 0.73 for mood related interference, and 0.80 for activity interference (Table 2.2). Omission of any of the items in each of the subscales did not negatively affect the underlying construct of the subscales (Table 2.2). Eight percent of the patients who completed the English version of the WBPQ rated average pain, least pain, and pain now greater than their worst pain.

Table 2.1: Medians and Interquartile range of pain intensity and pain interference items for the translated versions of the Wisconsin Brief Pain Questionnaire

Variables	**Language**			
	English (n = 129)	**isiZulu** (n = 132)	**Setswana** (n = 66)	**Xitsonga** (n = 125)
Intensity items *				
Worst pain	5 (0, 7)	5 (3, 8)	4 (0.5, 8)	5 (0, 9)
Least pain	2 (0, 4)	3 (1, 5)	2 (0, 4)	3 (0, 5)
Average pain	3 (0, 5)	-	-	-
Pain now	0 (0, 1)	5 (0, 2)	0 (0, 5)	3 (0, 6) †‡
Interference items ≠				
Mood	0 (0, 1)	-	0 (0, 1)	1 (0, 3) †‡
Relations	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 2) †‡$
Enjoyment of life	0 (0, 1)	0 (0, 0)	0 (0, 1)	1 (0, 2) †‡ $
Walking	0 (0, 1)	0 (0, 2)	0 (0, 0)	0 (0, 2) †‡
Normal work	0 (0, 2)	0 (0, 0.3)	0 (0, 0)	1 (0, 3) †‡$
Sleep	0 (0, 1)	0 (0, 2)	0 (0, 1)	1 (0, 2) †‡

* Items rated on a 0 -10 point scale
\# Items rated on a 0-4 point scale
\- Average pain was removed from the isiZulu, Setswana and Xitsonga questionnaires because no appropriate translation was achieved; Mood was removed from the isiZulu questionnaire for the same reason.
† Significant difference between English second language and Xitsonga
‡ Significant difference between Setswana and Xitsonga
$ Significant difference between isiZulu and Xitsonga

2.4.3. Reliability and Validity of the WBPQ Translated into Three Indigenous African Languages

2.4.3.1. IsiZulu.

One hundred thirty-two patients completed the isiZulu version of the WBPQ. The first three eigenvalues for the factor analysis were 1.90, 1.82, and 0.27. All the pain intensity items loaded under Factor 1 and all the pain interference items loaded under Factor 2, except for “sleep,” which did not load on either of the factors (Figure 2.1). I, therefore, excluded “sleep” as an item from the pain interference dimension for the isiZulu version of the WBPQ. The two factors explained 69% of the variance; factor loadings are shown in figure 2.1. The Cronbach alpha was 0.80 for the pain intensity subscales and 0.73 for the pain interference subscale, after exclusion of “sleep” (Table 2.2). Nine percent of the patients who completed the isiZulu version of the WBPQ rated average pain, least pain, and pain now greater than their worst pain.

2.4.3.2. Setswana

The Setswana version of the WBPQ was completed by 66 patients. The first three eigenvalues from the factor analysis were 2.39, 2.22, and 0.22. The first two factors explained 73% of the variance and all the pain interference items loaded under Factor 1, except for “sleep” and all the pain intensity items loaded under Factor 2 (Figure 2.1). Thus, “sleep” was

excluded from analyses of the Setswana version of the WBPQ. After exclusion of “sleep,” the Cronbach alpha was 0.86 for pain intensity items and 0.80 for pain interference items (Table 2.2). Four percent of the patients who completed the Setswana version of the WBPQ rated average pain, least pain, and pain now greater than their worst pain.

2.4.3.3. Xitsonga

The Xitsonga questionnaire was completed by 125 patients. Factor analysis identified two factors, with the first three eigenvalues being 4.15, 2.35, and 0.12. All the pain interference items loaded under Factor 1 and all the pain intensity items loaded under Factor 2 (Figure. 2.1). These two factors explained 78% of the variance; factor loadings are shown in figure 2.1. The Cronbach alphas for the pain intensity and pain interference dimensions were 0.84 and 0.94, respectively (Table 2.2). No patients rated average pain, least pain, and pain now greater than their worst pain.

2.4.4. Construct Validity

A significant, positive relationship was detected when I correlated the scores from the “pain now” item on the WBPQ against the scores patients gave using the Faces Scale. The R^2 for the correlation was 0.31 and the *P*-value was <0.0001.

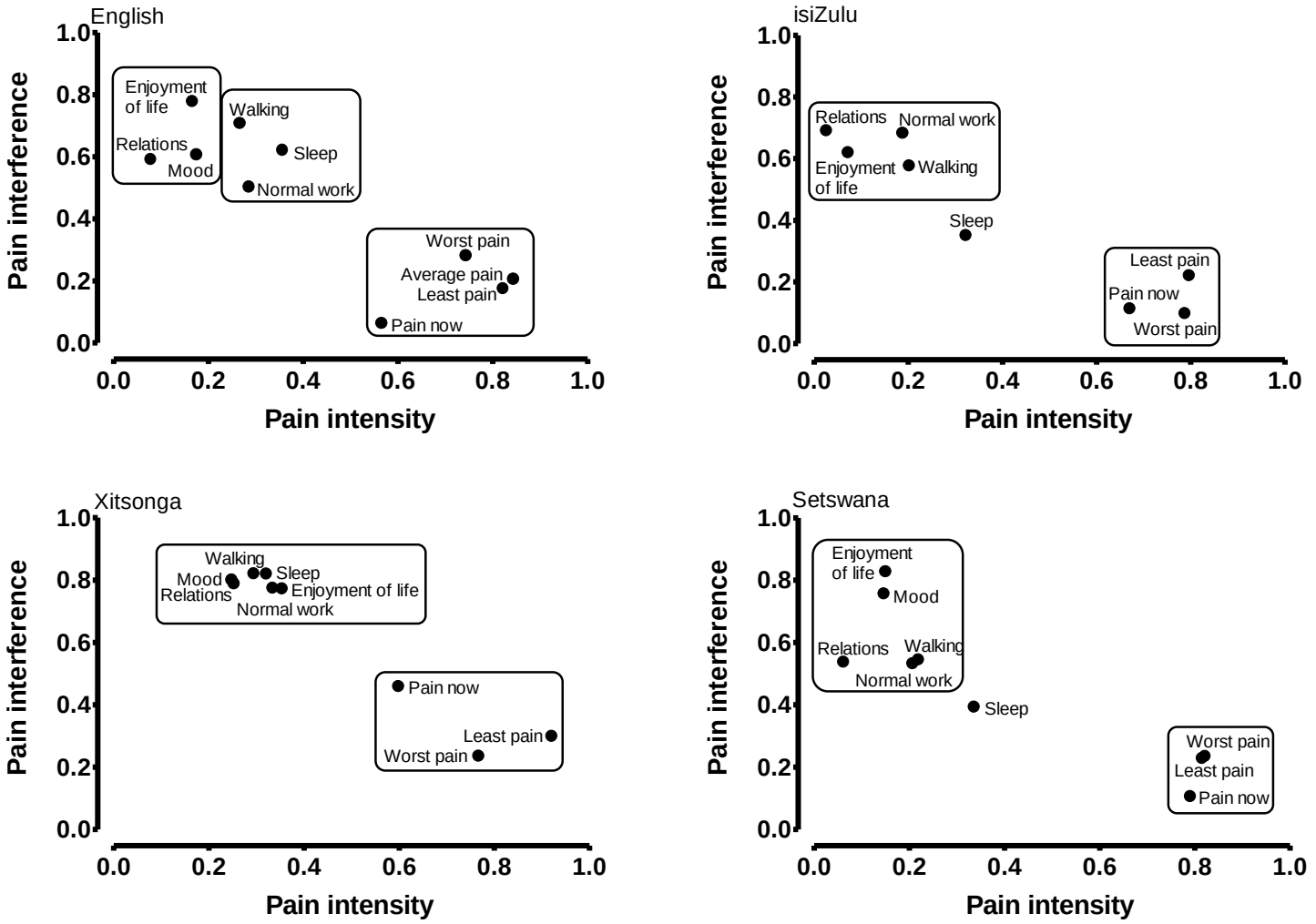


Figure 2.1: Factor loadings plots of the South African versions of the Wisconsin Brief Pain Questionnaire.

Table 2.2: A summary of Item analysis and alpha values if an item is omitted for the English and translated versions of the Wisconsin Brief Pain Questionnaire

Variables	**Language**			
	English	**isiZulu**	**Setswana**	**Xitsonga**
Pain intensity items	**α = 0.88**	**α = 0.80**	**α = 0.86**	**α = 0.84**
Worst pain	0.83	0.69	0.77	0.81
Least pain	0.82	0.70	0.81	0.71
Average pain	0.83	-	-	-
Pain now	0.88	0.78	0.82	0.84
Pain interference items	**α = 0.82**	**α = 0.73**	**α = 0.80**	**α = 0.94**
Mood	0.81	-	0.71	0.93
Relations with others	0.81	0.68	0.78	0.93
Enjoyment of life	0.78	0.68	0.70	0.93
Walking	0.78	0.71	0.77	0.93
Normal work	0.77	0.64	0.77	0.93
Sleep	0.80	*	*	0.92
Mood interference items	**α = 0.73**			
Mood	0.68			
Relations with others	0.68			
Enjoyment of life	0.56			
Activity interference items	**α = 0.80**			
Walking				
Normal work				
Sleep				

- Items removed from the questionnaires because an appropriate translation for the question was not achieved
***** Items that did not load on any of the factors and thus were removed

2.5. Discussion

To allow myself to assess pain severity and the effect pain has on the lives of patients who are HIV-positive in South Africa, I validated translated versions, and the original English version of the Wisconsin Brief Pain Questionnaire, in HIV-positive South Africans. I found that the questions in the English questionnaire, which was completed by English-second language speakers, could be grouped under a three-factor structure: pain intensity, mood interference, and pain interference. All the indigenous language questionnaires had a two-factor structure, with questions grouping under pain intensity and pain interference factors. However, in the isiZulu and Setswana versions of the WBPQ, “sleep” did not load on either of the two factors, shown by the loadings being less than 0.4 for both factors. Also, I was unable to provide a suitable translation of the meaning of average pain in any of the translated questionnaires and there was no suitable term to describe “mood” in isiZulu. Despite the omissions of these questions, there was good internal consistency within each factor for all questionnaires, and I believe that the translated versions of the WBPQ can be successfully used in a South African population. Correlations between the pain intensity items from the WBPQ and the pain rating scales from the Faces scale were performed to assess the criterion validity of the WBPQ. The correlation observed showed good agreement between the WBPQ and the Faces scale.

As I already have mentioned, I had to exclude some of the questions from the translated versions of the WBPQ because of a lack of suitable translations. For example, “mood” in isiZulu was excluded from the questionnaire because a single term in isiZulu is used to describe a person's mood, well being, and, sometimes, life. Similarly in all translated versions of the WBPQ, “average pain” was excluded because I could not identify a simple translation of the term “average pain” into the African languages I used. Typical translations of “average pain” included “medium pain,” “pain in between,” and “mild pain.” The exclusions of these items, especially “average pain,” from the questionnaires is unfortunate, and compromises the comprehensiveness of the questionnaires, but I do not believe that the exclusion of these items invalidates the use of the questionnaires even though I only assess the extremes of the intensity of pain experienced by patients, that is, their least pain and their worst pain. Also, like others who have validated the BPI, I also have had to exclude “sleep” as an item because of poor factor loadings (Caraceni *et al.*, 1996; Saxena *et al.*, 1999).

Coefficient alphas are used to identify if there are any errors during measurement. In this study, I have observed coefficient alphas that were in the range of those values calculated for BPI validations for other countries (Table 2.3). Although in this study I used the WBPQ, which has a narrower rating scale than the BPI for rating pain interference items, and the pain intensity items are rated over a month in the WBPQ and not a week as in the BPI, the core components of the BPI and the WBPQ

appear to be comparable. Yet despite the similarities in the psychometric properties of the WBPQ and the BPI, by validating the WBPQ and not the BPI, I may have limited the opportunity for comparisons to be made between data collected from South African populations using the WBPQ and patients from other countries, whose data were collected using the BPI. Also, validating the BPI may have facilitated inclusion of South African study sites in multinational pain studies. Nevertheless, by validating the WBPQ, I have provided scientists and health care professionals with the first validated multidimensional pain assessment instrument for indigenous South African populations.

Clinicians and researchers wanting to use the WBPQ should be aware that, like the BPI (Caraceni et al., 1996; Klepstad et al., 2002), there are no suitable methods for dealing with missing values in the WBPQ. However, I overcame this problem by using interviewers to administer the questionnaire to the patients, and I had no missing values. Also, like the BPI, I cannot be sure that the pain interference items on the WBPQ are assessing actual impairment caused by pain, or merely reflect changes in health-related quality of life. Lastly, there is a lack of normative data for the WBPQ.

Table 2.3: Cronbach alphas of pain intensity and pain interference subscales of the Brief Pain Inventory and WBPQ in different countries and languages

Country	Language	Pain intensity (α)	Pain interference (α)
BPI			
China	Chinese	0.86	0.91
France	French	0.86	0.90
Germany	German	0.88	0.92
Greece	Greek	0.88	0.85
India	Hindi	0.89	0.91
Italy	Italian	0.78	0.78
Japan	Japanese	0.81	0.81
Korea	Korean	0.85	0.93
Malaysia	Malay	0.81	0.88
Norway	Norwegian	0.87	0.92
Philippines	Filipino (Tagalog)	0.80	0.86
Spain	Spanish	0.87	0.89
Taiwan	Taiwanese	0.81	0.89
USA	English	0.87	0.91
Vietnam	Vietnamese	0.85	0.93
WBPQ			
South Africa	*isiZulu* [1]	0.80	0.73
South Africa	*Setswana* [2]	0.86	0.80
South Africa	*Xitsonga* [1]	0.84	0.94
South Africa	*English (*2nd language)	0.88	0.82

[1] Classified under the Nguni group of languages
[2] Classified under the Sesotho group of languages
All South African values were obtained using the Wisconsin Brief Pain Questionnaire, where pain interference items were measured on a scale of 0 to 4, whereas all other pain intensity items were obtained using a 0 to 10 point scale as in the BPI.

In contrast to the translated versions of the WBPQ, which all had a two-factor structure, I observed a three-factor structure in the English questionnaire completed by English second-language speakers. Patients had a choice of being interviewed in English or in their home language, and patients who chose to conduct the interview in English, and not their home language, did not give reasons for their preference. Three-factor structures have previously been reported in validations of the Norwegian and Hindi versions of the BPI, but not for English versions of the BPI being completed by second-language English speakers (Klepstad *et al.*, 2002; Saxena *et al.*, 1999). Unlike the three-factor structure of the Norwegian translation of the BPI where “sleep” loaded as an item within the mood interference dimension (Klepstad et al., 2002), I found that “sleep” loaded as an item within an activity interference dimension. It is possible that these patients considered “sleep” as a position of lying down, and hence an interference on activity.

All patients interviewed were at least bilingual, suggesting that the factor structure in my cohort was not determined by the language capabilities of patients, that is, monolingual or bilingual, as suggested by Saxena and colleagues (1999). It also has been suggested that differences in factor structure in translations of the BPI could be due to variations in the conceptual meaning of items during the translation process (Klepstad et al., 2002), or in my case, completing the questionnaire in a second language. Although loss of meaning caused by translation of the

questionnaire into another language could be a possible reason for differences in factor structure, in this study, back-translation of the translated questionnaires showed that the original meaning of questions had been maintained, so it is likely that the loss of meaning when completing the question in a second language may be responsible for the difference in factor structure I observed. Indeed, the factor structure of the BPI differed between the monolingual Hindi speakers completing a Hindi BPI, and bilingual Hindi and English speakers, who completed the English version of the BPI.

In conclusion, I believe that these translated and validated questionnaires can be best used to measure pain intensity and interference items in a population of South African patients who are HIV-positive.

2.6. Acknowledgments

I thank the interviewers, Ms. Edith Paledi, Ms. Thulile Makafola, and Ms. Zanele Msomi, and the staff and patients of Helen Joseph Hospital, Johannesburg and Tintswalo Hospital, Bushbuckridge for their invaluable assistance.

CHAPTER 3

PAIN IN AMBULATORY HIV-POSITIVE SOUTH AFRICANS

Data presented in this chapter has been published:
Noko R Mphahlele, Duncan Mitchell and Peter R Kamerman (2012).
Pain in ambulatory HIV-positive South Africans. European Journal of pain 16:3 447-458.

3.1. Abstract

I investigated the prevalence and intensity of pain, factors associated with having pain, and analgesic medications employed in a population consisting predominantly of Black African and female human immunodeficiency virus (HIV)-positive individuals attending outpatient clinics in a rural (n = 125; 79% female; 100% Black African) and a metropolitan (n = 396; 75% female; 94% Black African) area of South Africa.

Pain intensity, interference and treatment were assessed using the Wisconsin Brief Pain Questionnaire (WBPQ). Seventy-two percent of rural participants and 56% of metropolitan participants had pain at the time of the interview, and this pain was moderate to severe in intensity in 60% of rural participants and 59% of metropolitan participants. Forty-six percent of rural participants and 61% of metropolitan participants had multiple pain sites. The most common pain sites in rural participants were the abdomen (30%), chest (26%), head (19%) and genitals (15%), while in the metropolitan cohort the head (39%), feet (33%), chest (30%) and abdomen (20%) were the most common sites. In the rural cohort, antiretroviral therapy was independently associated with the reduced risk of pain [prevalence ratio (95% CI): 0.7 (0.5-0.9)], while in the metropolitan cohort increasing age was weakly, but independently associated with having pain [prevalence ratio (95% CI): 1.01 (1.005-1.012)].

Pharmacological management of pain was poor, with 29% of rural participants and 55% of metropolitan participants with pain not receiving any treatment. Of those receiving treatment, no participants were receiving strong opioids, and only 3% of metropolitan participants were receiving a weak opioid. Thus, HIV-related pain is common and is poorly treated in both the rural and metropolitan setting in South Africa.

3.2. Introduction

Pain is a common symptom in people infected with Human Immunodeficiency Virus (HIV), and this pain frequently is undertreated (for review: (Glare, 2001). However, almost all studies providing focussed assessment of the nature of HIV-related pain and its treatment have taken place in developed countries, and the patient populations that were studied consisted predominately of males and Caucasians (Lebovits *et al.*, 1989; O'Neill and Sherrard, 1993; Singer *et al.*, 1993). In the only study in the developed world that included appreciable numbers of non-Caucasian and female patients who were HIV-positive, Breitbart et al. (1996b) found that these two groups of patients experienced, on average, pain of greater intensity than their Caucasian and male counterparts (Breitbart et al., 1996b). Also, access to adequate pain management was lowest in females, and was positively correlated to level of education (Breitbart et al., 1996a). Therefore, sex, ancestry (ethnicity) and level of education affect pain perception and the treatment of pain in individuals infected with HIV.

Almost 70% of people infected with HIV live in sub-Saharan Africa. The majority of these people are Black, about 60% are women, and less than 60% have complete secondary-level schooling (Joint United Nations Programme on HIV/AIDS (UNAIDS) and (WHO), 2009; UNESCO, 2008; United Nations Educational and (UNESCO), 2008). Therefore, a significant portion of the world's population of people infected with HIV potentially have increased risk of experiencing moderate-to-severe pain, and for this pain to be undertreated. Indeed, studies on quality of life in African HIV-positive populations have shown that pain is a frequent complaint of infected individuals (Hughes *et al.*, 2004; Peltzer and Phaswana-Mafuya, 2008; Rosen *et al.*, 2008; Shawn *et al.*, 2005; Uwimana and Struthers, 2007; Voss *et al.*, 2007), with pain prevalence being over 90% in patients with advanced disease (Narasimooloo *et al.*, 2011; Norval, 2004).

Management of pain also was poor in hospitalized patients and those with chronic pain (Maree *et al.*, 2011). Yet, no studies have thoroughly investigated the characteristics of pain and its treatment in HIV-positive people living in sub-Saharan Africa and the risk factors for having pain (Kamerman and Mitchell, 2011). Indeed, the selective nature of the studies that have been performed precludes thorough assessment of the prevalence and impact of pain in the main group of HIV-positive people in sub-Saharan Africa, namely, ambulatory patients who either are on antiretroviral therapy or who still are in the early stages of the disease.

Because there are no comprehensive studies on HIV-related pain in ambulatory HIV-positive people in sub-Saharan Africa, and indeed there is a paucity of information on HIV-related pain from countries outside of North America and Europe, I investigated the prevalence, intensity and analgesic medications employed in a population consisting predominately of Black, female HIV-positive South Africans. Also, because of the differences in reported symptom intensity (Peltzer and Phaswana-Mafuya, 2008), and demographic variables that have been shown to influence pain intensity and treatment in HIV-positive individuals (StatisticsSouthAfrica, 2001), I also assessed whether the characteristics of HIV-related pain and its pharmacological treatment were similar in metropolitan and rural areas of South Africa.

3.3. Materials and Methods

3.3.1. Participants

I recruited 521 ambulatory HIV-positive between March 2005 and July 2006. Three-hundred and ninety-six (396) participants were recruited from a metropolitan outpatient clinic for HIV-positive people at the Helen Joseph Hospital, Johannesburg, Gauteng Province, South Africa. One-hundred and twenty-five (125) participants were recruited from a rural hospital, Tintswalo Hospital, Bushbuckridge, Limpopo Province, South Africa. Both cohorts were convenience samples recruited opportunistically from the clinics, without regard for whether the patients had pain or not; all patients

waiting to see a doctor were asked whether they would like to participate in the study. The response rate for both cohorts was 100%, which means that all potential participants approached to take part in this study consented to take part. To be eligible for the study, participants must have been ambulatory outpatients with a confirmed diagnosis of HIV infection, and have been 18 years or older at the time of the interview. Participants also had to be able to comprehend the contents of the interview in English, isiZulu, isiXhosa, Sepedi, Setswana or Xitsonga (Appendix B to G, respectively).

Sample size selection was based on a recommended sample size of 357-379 participants to obtain a true reflection of the overall patient population. The calculation was based on a confidence interval of 95%, a margin of error of 5%, a total possible clinic population size of between 5000 and 25, 000, and a response distribution of 50%. Because of resource limitations, I was only able to sample 125 participants at the rural clinic, which is estimated to serve an HIV-positive community of approximately 15, 000 individuals. At that sampling rate, the margin for error was calculated to be 8.7%, which I felt was acceptable.

3.3.2. Ethics

The research was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, South Africa (Clearance number: M041112). All participants gave written informed consent after

having read the subject information and consent forms. In cases where the participants were functionally illiterate (20 rural participants, and 12 metropolitan participants) the subject information and consent forms were read to the participant by an interviewer. All participants were able to sign their names.

3.4. Study Instruments and procedures

Participants' medical histories and current medications were obtained through participant personal recall, and confirmed and supplemented through hospital records. Ancestry classification was based on self-classification by participants.

3.4.1. Wisconsin Brief Pain Questionnaire (WBPQ)

The WBPQ was used to assess pain intensity, the extent to which pain interfered with function, and the efficacy of analgesic medications used. Both the pain intensity and pain interference dimensions of the questionnaire have been validated (Daut *et al.*, 1983; McCormack *et al.*, 1993). Because some of the participants were functionally illiterate, interviewers administered the questionnaire to all participants using a standardized interview. Participants had the choice of undertaking the interview in English, isiZulu, isiXhosa, Sepedi, Setswana, or Xitsonga. I have described elsewhere the validation of the Setswana, isiZulu, and Xitsonga versions of the WBPQ, and the validation of the original English

version of the questionnaire when used by English second-language speakers (Mphahlele *et al.*, 2008). The number of participants completing the isiXhosa and Sepedi versions of the WBPQ was too low (34 for isiXhosa and 35 for Sepedi) to allow statistical validation of the questionnaire in those two languages. Participants used an 11-point numerical pain-rating scale to rate pain intensity, if any, at the time of the interview, and their pain intensity on average and at its worst over the last 30 days, where 0 represented “no pain”, and 11 represented “pain as bad as you can imagine”. The magnitude of their pain relief achieved with analgesic treatments was rated on a percentage scale, where 0% represented “no pain relief” and 100% represented “complete pain relief”. The extent to which pain interfered with functionality, in terms of mood, sleep, enjoyment of life, relations with other people, walking ability and normal work, was rated on a 0 to 4 numerical scale, where 0 represented “no interference at all” and 4 represented “extreme interference”. Participants also answered questions regarding the timing of the onset of pain symptoms that had developed since the diagnosis of HIV, their reason for consulting a doctor that lead to their diagnosis with HIV, and they marked the site of pains experienced in the last month on an illustrated body chart.

3.4.2. Karnofsky Performance Scale (KPS)

Participants’ doctors rated their impression of the participants’ ability to perform activities of ordinary daily living on the Karnofsky Performance

Scale (Schag *et al.*, 1984) (Appendix I). The KPS rates individuals general well-being on a scale of 0 to 100%, where 0% indicates death, and 100% indicates normal, no complaints, and no evidence of disease. Doctors completed the KPS immediately after examining each participant.

3.5. Data analysis

Validation of the WBPQ revealed that there was no suitable translation of "pain on average" in any of the African-language questionnaires (Mphahlele *et al.*, 2008), so I have based my analyses of participants' pain intensity on their pain at the time of the interview and their pain at its worst in the last 30 days. For the pain interference items, my validation revealed that there was no suitable single term in isiZulu for 'mood'. Also, the term 'sleep' did not partition itself into either the pain intensity or the pain interference domains in the isiZulu and Setswana questionnaires. Thus, 'mood' data were excluded from the analysis of pain interference items for participants completing the questionnaire in isiZulu, and 'sleep' data excluded for participants completing the questionnaire in isiZulu and Setswana.

Consequently, I calculated an average pain interference score for each questionnaire, with the denominator being the number of valid pain interference items in that questionnaire.

A pain management index (PMI), which assesses whether participants taking pain medication, in theory, were taking appropriately potent analgesics, as indicated by the World Health Organization (WHO) guidelines, was calculated for each participant (Cleeland et al., 1994; WHO, 1990). The PMI is calculated by comparing the analgesic potency of the pain medication individuals are taking with their pain intensity at its worst. Potency of medications was scored from 1 to 3 according to the WHO analgesic ladder (1990); a rank of 1 was given to non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen or adjuvants (e.g. antidepressants), 2 to weak opioids (including tramadol), and 3 to strong opioids (e.g. morphine). If a participant was taking medications from multiple levels of the WHO ladder, the score assigned was that of the most potent analgesic medication they were consuming.

Pain intensity, based on participants' rating of their worst pain in the last month, also was scored from 1 to 3, with 1 being was assigned mild pain (a rating of 1-3 on the WBPQ pain intensity scale), 2 to moderate pain (4-7 on the WBPQ pain intensity scale), and 3 to severe pain (8-10 on the WBPQ pain intensity scale). Participants who reported having no pain, and participants with pain, but who were not taking pain medication, were excluded from this analysis. The PMI was calculated by subtracting the participants' pain intensity score from their analgesic medication score; PMI values less than 0 indicate inadequate analgesic therapy (Cleeland et al., 1994).

Prevalence data are presented as percent [95% confidence interval (95% CI)], continuous parametric data are presented as mean (standard deviation) and continuous non-parametric data are presented as median [interquartile range (IQR)]. Differences between the rural and metropolitan cohorts were quantified by calculating 95% CIs for the difference in mean/median/prevalence between the cohorts. Within each cohort, statistical comparisons for all demographic, pain intensity, pain interference and pain relief variables were made to determine which characteristics differentiated individuals with and without pain.

Continuous variables were analysed using unpaired t-tests, when data were normally distributed, and Mann-Whitney tests, when data were non-parametric. Categorical variables were analyzed using Fisher's Exact tests and Chi-square tests where appropriate, and Z-tests were used to compare between proportions. Spearman's correlation was used to detect for association between participants' ratings of pain interference and their doctors rating of their well-being on the KPS, and between pain intensity and the magnitude of pain relief achieved with analgesic medications.

Logbinomial regression analysis was performed, within each cohort, to determine if any of the variables measured were independently associated with having pain (RDevelopmentCoreTeam, 2011). All variables with a p-value < 0.1 in the Univariate analysis were included (rural cohort = age, educational level; metropolitan cohort = age, gender and educational

level). To maintain statistical power, I minimized the number of predictors included in the regression analysis by not examining interactions between predictors.

3.6. Results

3.6.1. Demographics

Table 3.1 summarizes the demographic characteristics of the rural and metropolitan cohorts. All participants from the rural cohort, and almost all participants from the metropolitan cohort, identified themselves as being Black Africans. The majority of individuals in the metropolitan cohort, who did not identify themselves as Black Africans, were of mixed race. Over three quarters of participants in both cohorts were female.

The CD4 T-cell counts of the two cohorts were similar, but a slightly lower proportion of participants in the rural cohort were on antiretroviral therapy than in the metropolitan cohort. Of those participants receiving antiretroviral therapy, over 90% of individuals in both cohorts had been exposed to dideoxyribonucleoside reverse transcriptace inhibitors, particularly stavudine. In both cohorts, the majority of participants had attained a secondary education, but unemployement was high; less than half of individuals in both cohorts had an income.

Table 3.1: Demographic characteristics of rural and metropolitan cohorts

Characteristic	Mean/Median/Percentage (95% CI)	
	Rural (n = 125)	Metropolitan (n = 396)
% female	79 (71 - 85)	75 (70 - 79)
% black race	100 (97 - 100)	93 (91 - 96)
Mean (SD) age *(years)*	36 (9)[a]	36 (8)
Education		
% no education	16 (11 - 23)	3 (2 - 5)
% primary[b]	16 (11 - 23)	14 (11 - 17)
% secondary[c]	65 (56 - 73)	77 (73 - 81)
% tertiary	3 (1 - 8)	6 (4 - 9)
% employed	38 (30 - 46)	48 (43 - 53)
Median (IQR) CD4 T-cell count *(cells.mm^{-3})*[d]	199 (120 - 346)	200 (99 - 309)
Antiretroviral (ARV) therapy		
% ARV use	53 (44 - 61)	68 (63 - 73)
% d4T or ddI use[e,f]	95 (87 - 98)	91 (88 - 94)

95% CI 95% confidence interval
SD Standard deviation
IQR Interquartile range
a Incomplete data: n = 116 for the rural cohort
b Estimated age: 6 - 13 years
c Completed secondary school
d CD4 T-cell count measured at the time of the interview. Incomplete data: n = 108 for the rural cohort, and n =266 for the metropolitan cohort.
e d4T: stavudine, ddI: didanosine
f Percentage calculated using the total number of participants in each cohort on ARV therapy as the denominator (n = 66 for the rural cohort, and n =270 for the metropolitan cohort)

3.6.2. Pain prevalence

The prevalence of pain was high in both the rural and metropolitan cohorts, with. 72% (64%-79%) of rural patients and 56% (51%-61%) of metropolitan patients, reporting having pain at the time of the interview (95% CI of the difference in prevalence: 6% to 25%). Similarly, a high proportion of participants in both cohorts reported experiencing pain within the 30-day period before the interview [67% (59-75%) of rural participants; 77% (73-81%) of metropolitan participants; 95% CI of the difference in the prevalence: -19% to 1%].

The majority of participants in both cohorts reported having pain at the time of their diagnosis with HIV [76% (68-83%) of rural participants; 60% (55-65%) of metropolitan participants; 95% CI of the difference in proportion: 6% to 24%], and this pain was the reason, particularly in the metropolitan cohort, that most of the affected participants sought the medical consultation that led to their diagnosis of HIV infection [73% (63-81%) of rural participants; 92% (88-95%) of metropolitan participants; 95% CI of the difference in proportion: -30% to -11%].

3.6.3. Pain intensity

In both cohorts, the median pain intensity experienced by participants with pain at the time of the interview was of moderate intensity [median (IQR): rural = 5 (3-7); metropolitan = 5 (2-7); 95% CI of the difference in median: -2 to 2], with 60% (50-70%) of the rural cohort and 59% (52-65%) of the

metropolitan cohort who had pain at the time of the interview reporting moderate-to-severe pain (95% CI of the difference in prevalence: -11% to 13%; Table 3.2). The median intensity of the worst pain participants had experienced within the last 30-day period before the interview was in the severe range in the rural cohort and in the moderate range in the metropolitan cohort, but the difference was marginal [median (IQR): rural = 8 (7.5-8); metropolitan = 6 (5.5-6); 95% CI of the difference in the median: -1 to 3], with a high proportion of individuals in both cohorts reporting that their worst pain in the last 30 days was moderate to severe in intensity [prevalence (95% CI) of moderate-to-severe pain: rural = 90% (82-95%); metropolitan = 84% (79-87%); 95% CI of the difference in prevalence: -2% to 13%; Table 3.2].

3.6.4. Pain sites

Figure 3.1 shows the four most common discrete pain sites reported by rural and metropolitan participants with pain in the previous 30 days. Both rural and metropolitan participants reported the head, chest and abdomen as being amongst their four most common pain sites. But, whereas genital pain was one of the four most common pain sites in participants from the rural cohort, pain in the feet was one of the most common pain sites in participants from the metropolitan cohort. On average participants in the rural cohort reported significantly fewer discrete pains per individual than did participants in the metropolitan cohort [median (IQR): rural = 1 (1-2) pains; metropolitan = 2 (1-3) pains; 95% CI of the difference in median: -

1.5 to -0.5], such that co-occurrence of two or more pains in an individual tended to be more common in participants from the metropolitan cohort compared with participants from the rural cohort [46% (36-57%) of rural participants; 61% (55-66%) of metropolitan participants; 95% CI of the difference in prevalence: -26% to -3%].

Table 3.2: Percentage of participants with mild, moderate or severe pain at the time of the interview (pain now), or within the last 30 days (worst pain)[a]

Pain intensity	Percentage of cohort (%)	
	Rural (95% CI)	Metropolitan (95% CI)
Pain now[b]		
Mild	40 (30 - 50)	41 (35 - 48)
Moderate	37 (27 - 47)	36 (30 - 43)
Severe	23 (16 - 33)	23 (18 - 29)
Worst pain[c]		
Mild	9 (5 - 18)	17 (13 - 21)
Moderate	37 (27 - 48)	45 (40 - 51)
Severe	54 (43 - 64)	38 (33 - 44)

a Only data from participants with pain at the time of the interview and participants with pain in the last 30 days were used in the analyses
b Rural n = 90, Metropolitan n = 222
c Rural n = 84, Metropolitan n = 305

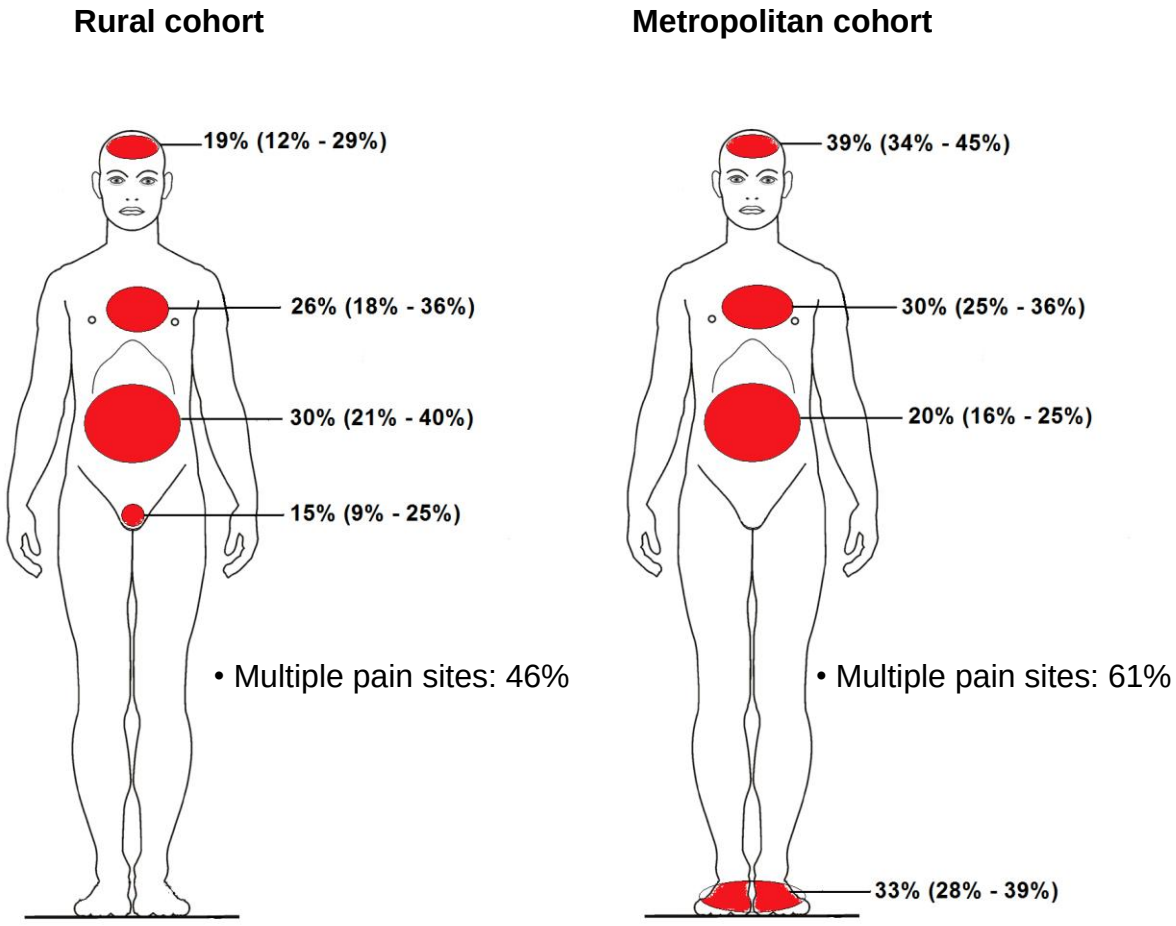


Figure 3.1: The four most prevalent pain sites identified by rural (left panel, n = 84) and metropolitan (right panel, n = 305) participants with pain who reported more than one (multiple) pain site. Data shown as prevalence [95% confidence interval (95% CI)]. 95% CI for the difference in prevalence between the rural and metropolitan cohorts at each of the four body sites: head = 9% to 29%, chest = -7% to 14%, abdomen = -21% to 0.2%, genitals = -21% to -5%, feet = 18% to 34%.

3.6.5. Functional interference

Pain-related functional interference data for the week preceding the interview are shown in Figure 3.2. In general, participants from both cohorts rated pain-related functional interference as low [median (IQR): rural average functional interference = 1.3 (0-2.3), metropolitan average functional interference = 0.5 (0-1.3); 95% CI of the difference in median: 0.4 to 1.2]. There was a significant, but weak, positive correlation between pain intensity ('pain now' and 'worst pain in the last 30 days') and participants' rating of their pain-related functional interference in the rural cohort ('Pain now': Spearman r = 0.509, $p < 0.001$; 'worst pain': Spearman r = 0.319, $p < 0.001$), and in the metropolitan cohort ('Pain now': Spearman r = 0.247, $p < 0.001$; 'Worst pain': Spearman r = 0.259, $p < 0.001$). On average, doctors rated participants in both cohorts as having a high level of ability to perform activities of ordinary daily living, but participants in the rural cohort were rated as having lower ability to perform those activities than that of participants in the metropolitan cohort [median (IQR): rural KPS = 80 (70-90), metropolitan KPS = 90 (80-100); 95% CI of the difference in median: -10 to -10; Figure 3.2]. There was a significant, but weak, negative correlation between metropolitan participants' rating of their functional interference and their doctors' rating of ability to perform activities of ordinary daily living (Spearman r = -0.231, $p < 0.001$), but there was no significant correlation in the rural cohort (Spearman r = -0.048, p = 0.59).

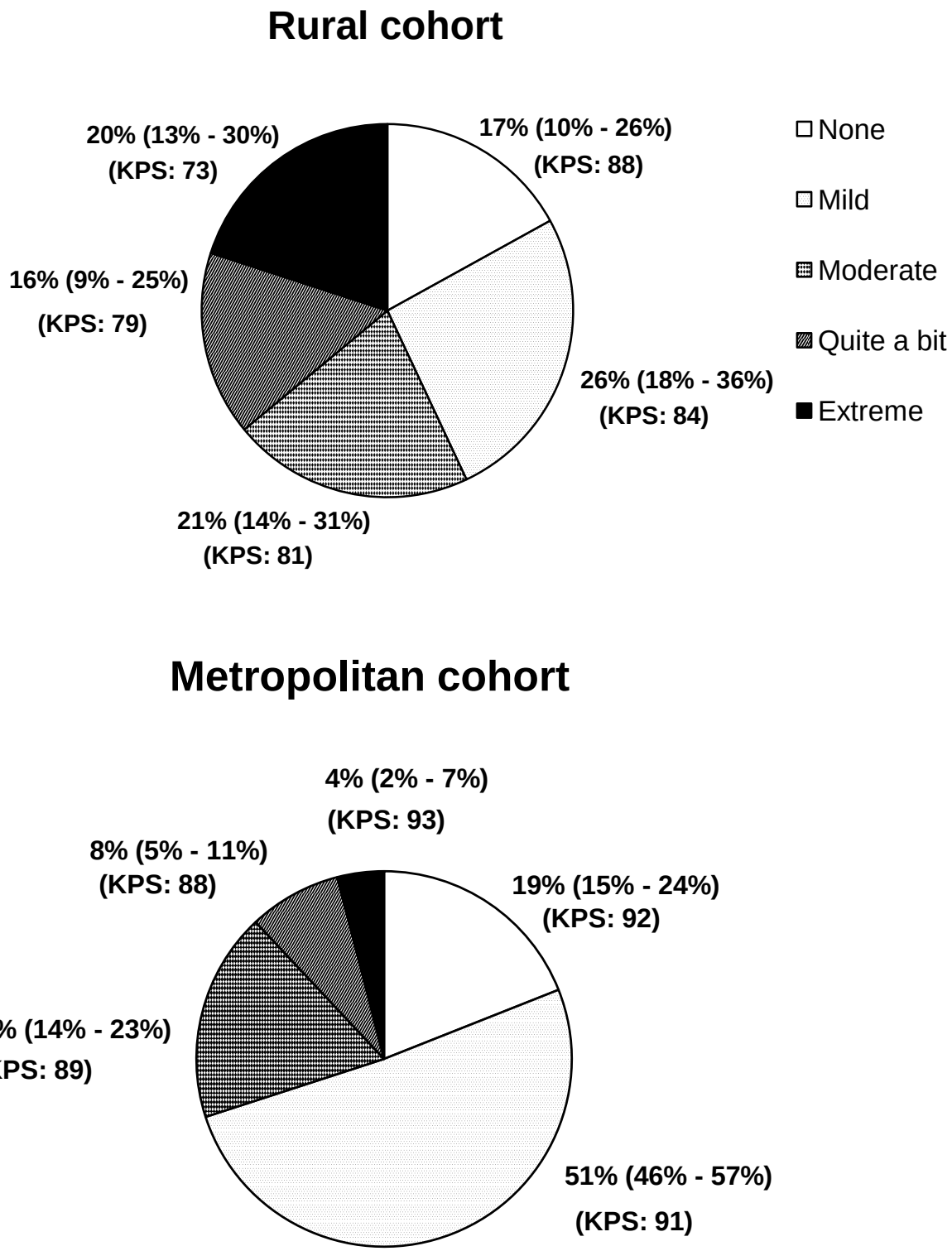


Figure 3.2: Pain-related functional interference in rural (upper panel, n = 84) and metropolitan (lower panel, n = 305) participants who had reported pain in the previous 30 days. Numbers in parentheses are average Karnofsky Performance Scale (KPS) scores for each category of self-reported pain-related functional interference. Data shown as prevalence (95% CI). 95% CI for the difference in prevalence of pain-related functional interference between rural and metropolitan cohorts: None = -7% to +10%, Mild = 13% to 35%, Moderate = -14% to +5%, Quite a bit = -17% to -0.5%, Extreme = -26% to -9%.

3.6.6. Pain relief

There was significant pharmacological under-treatment of pain in both cohorts, with 29% (20-39%) of the rural cohort and 43% (38-49%) of the metropolitan cohort who reported experiencing pain in the last 30 days not receiving any analgesic medications, with the proportion of untreated participants tending to be greater in the metropolitan cohort than in the rural cohort (95% CI for the difference in prevalence: 3% to 25%).

Figure 3.3 shows the agents being taken by participants who were receiving pharmacotherapy for their pain. In both cohorts, more than 90% of participants who were taking medication took NSAIDs or paracetamol. In the few cases in which an adjuvant was prescribed, the agent always was amitriptyline. Very few participants were receiving weak opioids (0% in the rural cohort, and 5% in the metropolitan cohort), and they always were prescribed in combination with paracetamol. No participants in either cohort were receiving strong opioids for their pain.

Figure 3.4 shows the pain management indices (PMIs) for participants who were in pain and who were using some form of analgesic therapy. As assessed by the PMI, all participants, in both cohorts, who were receiving analgesic therapy and who were in mild pain, were receiving analgesic therapy of appropriate strength. No participants in the rural cohort with moderate or severe pain were receiving analgesic therapy of appropriate strength. Only 8% of participants in the metropolitan cohort with moderate

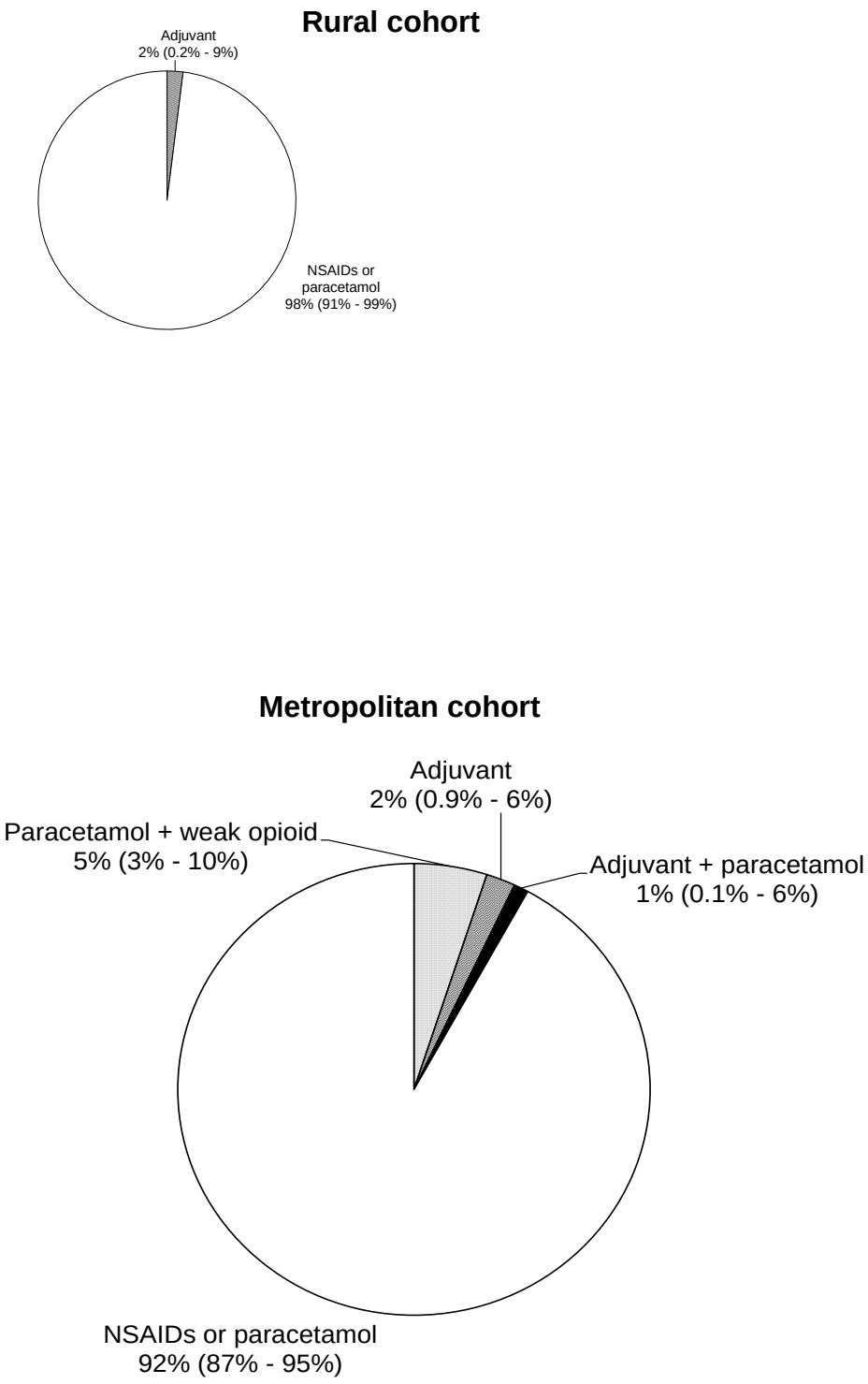


Figure: 3.3: Types of analgesic therapy reported by rural (upper panel, n = 60) and metropolitan (lower panel, n = 174) participants with pain in the last 30 days and who were receiving pharmacological treatment for their pain. NSAID = non-steroidal anti-inflammatory drug. Data shown as prevalence [95% confidence interval (95% CI)]. 95% CI for the difference in prevalence between the rural and metropolitan cohorts: NSAIDs or paracetamol = -12% to 1%, paracetamol + weak opioid = -1% to 10%, adjuvant = -7% to 4%, adjuvant + paracetamol = -5% to 3%.

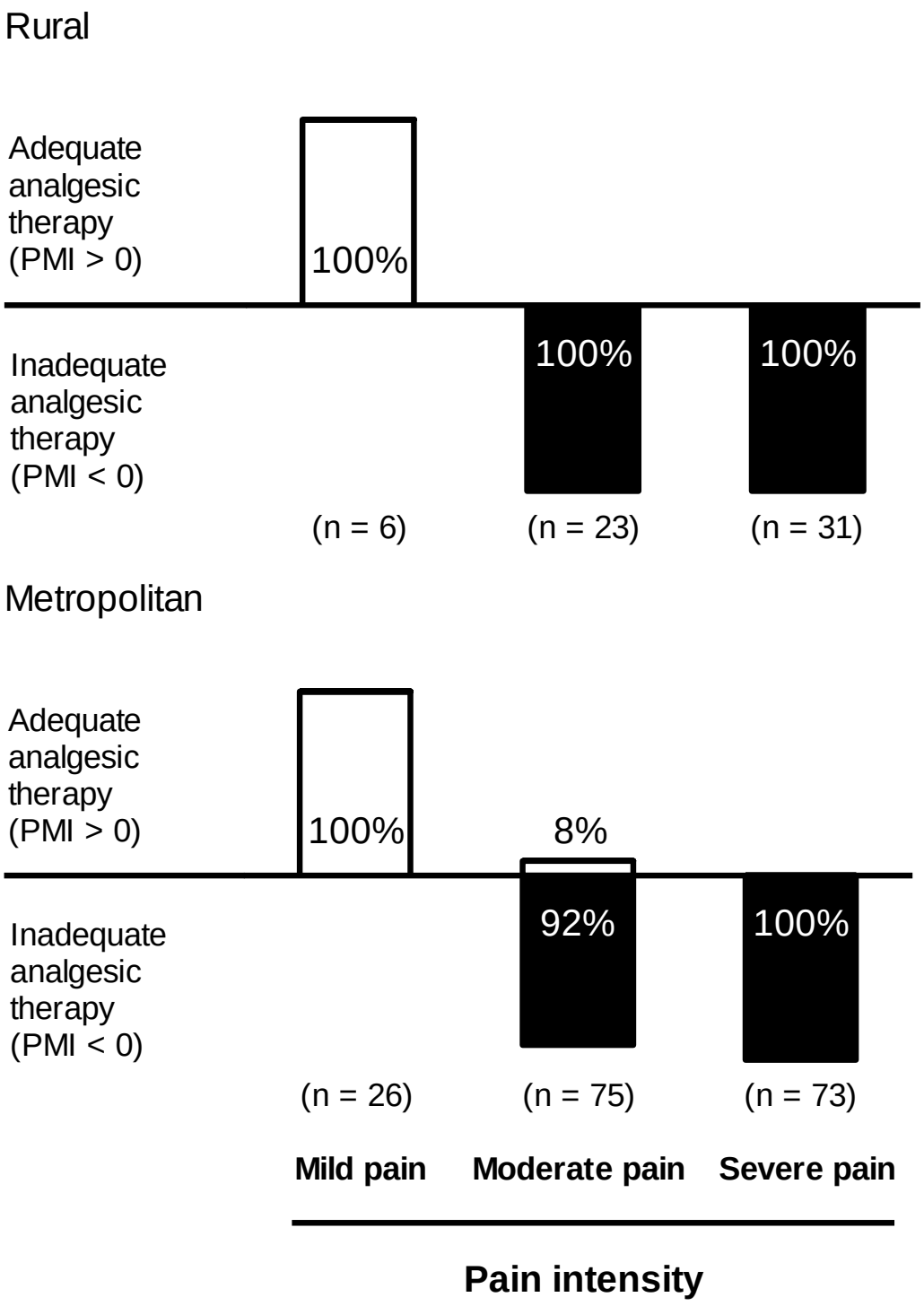


Figure 3.4: Pain management indices (PMI) for the rural (upper panel, n = 60) and metropolitan (lower panel, n = 174) participants who had mild, moderate or severe pain in the last 30 days and who were receiving some form of analgesic therapy.

pain were receiving analgesic therapy of appropriate strength, and no metropolitan participants suffering from severe pain received analgesic therapy of appropriate strength.

When assessing their own self-reported pain relief (Figure 3.5), participants in the rural and metropolitan cohorts reported significant, but similar, magnitudes of pain relief [median (IQR): rural = 55% (40-80%), metropolitan = 50% (30-90%); 95% CI of the difference in median: -6% to 16%].

And, most participants, in both cohorts, reported at least 30% pain relief (clinically relevant pain relief), [92% (82-96%) of rural participants; 77% (71-83%) of metropolitan participants; 95% CI of the difference in prevalence: -23% to -3%]. There was no significant relationship between percentage pain relief and pain intensity in the rural cohort (Spearman r = -0.023, p = 0.86), but in the metropolitan cohort, the magnitude of the pain relief decreased significantly as the intensity of pain increased (Spearman r = -0.196, p = 0.01). However, the relationship was weak.

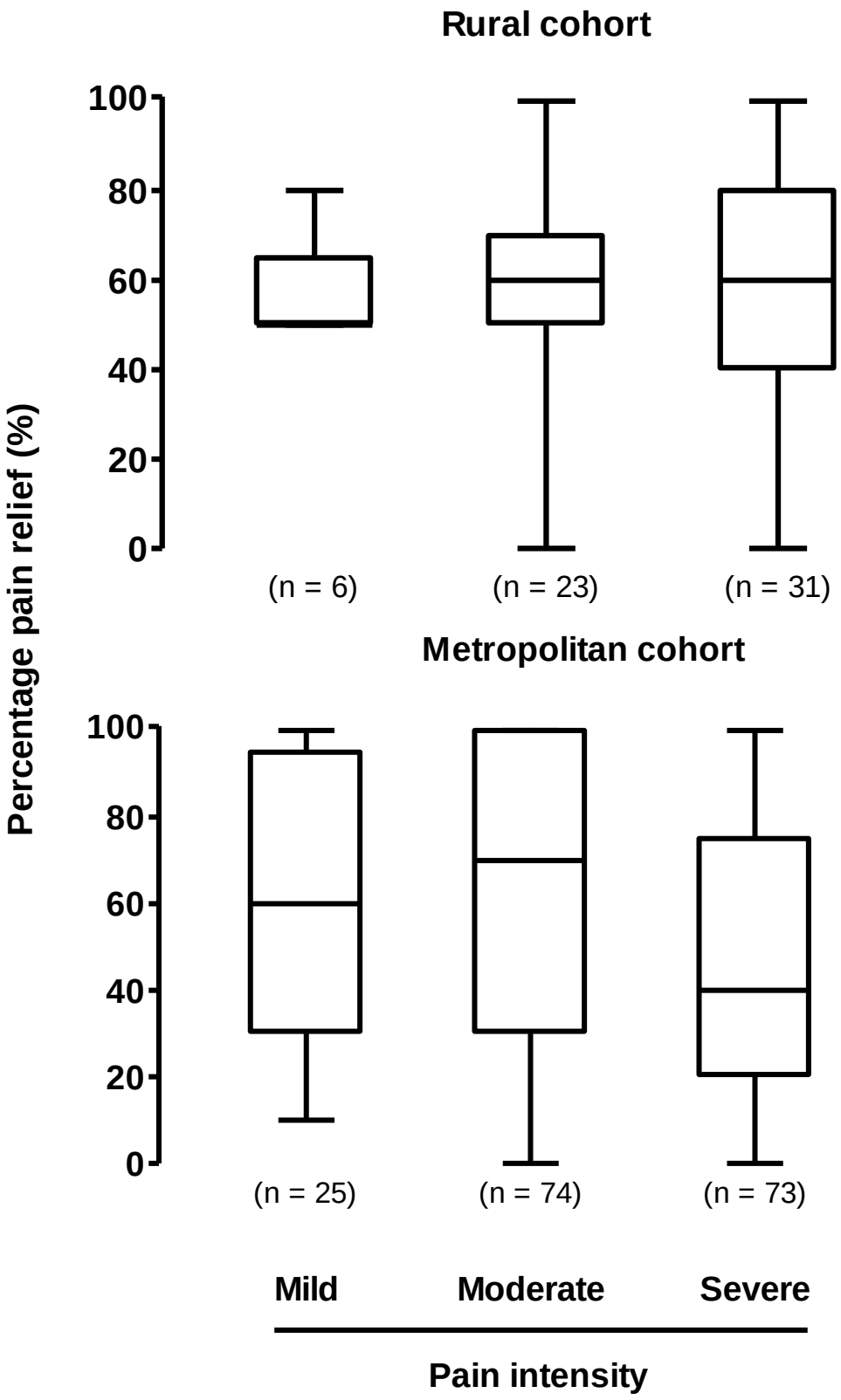


Figure 3.5: Median (interquartile range, range) percentage pain relief reported by rural (upper panel, n = 60) and metropolitan (lower panel, n = 172) participants who had mild, moderate or severe pain in the last 30 days and who were receiving some form of analgesic therapy.

3.6.7. Risk factors for pain

Statistical results of univariate analysis of variables associated with the presence of pain within the last month are shown in Table 3.3 (rural cohort) and Table 3.4 (metropolitan cohort). In the rural cohort, Univariate analysis showed that increasing age and higher current CD4 T-cell count were associated with having pain and antiretroviral therapy and increasing level of education with a reduced risk for having pain. However, multivariate log-binomial regression only detected antiretroviral therapy as an independent risk factor for reduced risk of pain [prevalence ration (95% CI): 0.7 (0.5-0.9)]. In the metropolitan cohort, Univariate analysis showed that increasing age, not having a tertiary education and female sex were associated with having pain.

However, multivariate log-binomial regression only detected age as an independent risk factor for having pain, and this effect was very small [prevalence ratio (95% CI): 1.01 (1.005-1.012)].

Table 3.3: Univariate analysis of variable associated with having pain in the previous 30 days (rural cohort)

Characteristic	Pain	No Pain	P value
Number of patients	84	41	
Age (years)			
Median (IQR)	36 (32 - 41)	33 (30 - 37)	Mann U = 1099; p = 0.024
Gender			
% female	77	78	Fisher's Exact; p = 0.818
Income			
Median (IQR)	0 (0 - 122)[a]	0 (0 - 122)[a]	Mann U = 1652; p = 0.71
Education (%)			
No education	21	5	$\chi^2_{(df = 3)} = 15.76$; p = 0.001
Primary	21	5	
Secondary	56	83	
Tertiary	1	7	
CD4 cell count (cells/mm^3)			
Median (IQR)	232 (136 - 379)	129 (69 - 241)	Mann U = 831.5; p = 0.003
Antiretroviral (ARV) therapy (%)			
ARV	42	76	Fisher's Exact; p < 0.001

a US Dollars (US$)

Table 3.4: Univariate analysis of variables associated with having pain in the previous 30 days (metropolitan cohort)

Characteristic	Pain	No Pain	
Number of patients	305	91	
Age (years)			
Median (IQR)	35 (32 - 41)	31 (29 - 37)	Mann U = 9537; p < 0.0001
Gender			
% female	77	66	Fisher's Exact; p = 0.039
Income			
Median (IQR)	55 (0 - 140)[a]	0 (0 - 156)[a]	Mann U = 12530; p = 0.158
Education (%)			
No education	3	4	$\chi^2_{(df = 3)} = 8.361$; p = 0.039
Primary	15	10	
Secondary	78	76	
Tertiary	4	10	
CD4 cell count (cells/mm^3)			
Median (IQR)	191 (92 - 308)	227 (107 - 315)	Mann U = 6428; p = 0.23
Antiretroviral (ARV) therapy (%)			
ARV use	61	61	Fisher's Exact; p = 1.000

a US Dollars (US$)

3.7. Discussion

3.7.1. Pain in HIV-positive individuals

I investigated the prevalence, intensity and analgesic medications employed in a population consisting predominantly of Black, female HIV-positive South Africans, and the variables associated with having pain. The cohort was obtained from adult individuals presenting for consultation at either a rural or a metropolitan HIV outpatient clinic. The cohorts were of low economic status and very few had any post-school education. About half the people in both cohorts had CD4 T-cell counts of less than 200 cells/mm^3 at the time of the interview, and about two-thirds of the metropolitan cohort and half the rural cohort were on antiretroviral therapy. Being on antiretroviral therapy was weakly, but independently associated with not having pain in the rural cohort, but not in the metropolitan cohort. In the metropolitan cohort, increasing age was the only independent factor I identified for having pain. However, in both cohorts the risk accorded by these factors was low.

More than half of the metropolitan cohort and nearly three quarters of the rural cohort were in pain when they were interviewed. For both cohorts, the majority of those who had experienced pain in the previous 30 days had experienced pain that was moderate to severe. Although the time lapse since diagnosis may have affected participant recall of whether they had pain at the time of the HIV diagnosis, about three quarters of rural

participants and nearly all metropolitan participants said pain was the reason for the initial consultation that led to their eventual diagnosis with HIV. Thus, in both cohorts, pain was widespread and profound.

Although there was a positive correlation between pain intensity and pain-related functional interference, the association was weak and participants in both cohorts reported pain-related functional impairment as being low, implying they were prepared to go about their daily lives in spite of the pain. The participants' stoicism was endorsed by their doctors, who rated most participants as having had the ability to carry on normal activity, with effort and minor signs and symptoms. In the metropolitan cohort, but not the rural cohort, doctors were able to estimate how impaired the patients felt themselves to be.

A third of the rural cohort and more than half the metropolitan cohort were not taking any pain medication, in spite of most being in pain at the time of their clinic visit. Thus, presumably, either they did not report their pain to the clinic staff, or they were not offered pain relief by the clinic staff who are the main source of medications for HIV symptom management (Sukati et al., 2005). Moreover, those participants in moderate or severe pain who were taking analgesic medication were taking medications that were not of appropriate strength, according to the crude estimate of the pain management index. Yet, on average, these participants reported more than 50% pain relief from their medications, irrespective of pain intensity.

3.7.2. Study limitations

Like all cross-sectional studies, this study describes one instance in what, for the participants, was a progression of disease, and these participants were at various stages of that progression. Unfortunately, although the hospital records to which I had access allowed me to check the medications that the patients reported taking, they did not record the stage of the disease, and did not contain sufficient information for me to deduce the stage retrospectively. The participants were ambulatory outpatients, though, and not in the advanced stage of disease of the participants in the study by Norval (2004) and Narasimooloo and colleagues (2011), who both reported pain prevalence of greater than 90%. I also did not have CD4 T-cell counts for all the participants. The level of missing data for the metropolitan and rural cohorts was 36% and 14%, respectively.

Female patients constituted about three quarters of both of the cohorts. That was a higher proportion than the 59% cited for HIV-infected individuals in sub-Saharan Africa (Gray and Berger, 2007), and much higher than the 13 to 30% female proportion in studies of HIV-related pain in North America or Europe (Aires and Bammann, 2005; Breitbart *et al.*, 1996b; Del Borgo *et al.*, 2001; Frich and Borgbjerg, 2000; Larue *et al.*, 1997). I recruited the participants from hospitals that provided prenatal and obstetric services, which may have contributed to the extra loading of female patients. In the event, female gender was independently associated with having pain in either cohort.

The measurement of patients' functional status using the Kanorfsky Perfomance Scale (KPS) could have been biased since the patients recruited in this study were ambulatory. That is, it is possible that the doctors could have automatically given the patients a functional score of 70, which according to the scale is given to patients who are able to carry on with their normal daily activity.

Unfortunately we did not use any specific quality of life measures (e.g., MOS-HIV, EQ-5D), but at the time of designing the experiment we wanted to focus on pain-related interference on daily activities, rather than general quality of life in HIV, which is affected by broader issues than just pain. Future studies will include additional measures of quality of life.

3.7.3. Pain prevalence

The prevalence of pain in this study participants (rural 72%, metropolitan 56%) was within the range reported for HIV-positive outpatients from the same hospital from which I recruited the metropolitan cohort (Rosen et al., 2008) and for other HIV-positive outpatients in sub-Saharan Africa (Hitchcock *et al.*, 2008; Hughes *et al.*, 2004; Peltzer and Phaswana-Mafuya, 2008; Shawn *et al.*, 2005; Uwimana and Struthers, 2007; Voss *et al.*, 2007). With the exception of the study of Hitchcock et al (2008), which was concerned specifically with neuropathic pain, none of the other studies reporting pain prevalence pursued the characteristics of the pain;

they mainly were quality-of-life studies, in which pain was reported as one of many symptoms accompanying HIV infection.

Pain in HIV-positive individuals may arise as a direct effect of the viral infection, from the antiretroviral therapy or adjunct therapies, from the malignancies or other pathological processes that result from the depressed immune system, or it may be incidental to the HIV infection (O'Neill and Sherrard, 1993; Singer *et al.*, 1993; Verma *et al.*, 2004). Estimating the true prevalence of pain related to the HIV infection requires measurement of pain prevalence in matched control populations without HIV infection. Logistical and ethical issues prevented me assembling control cohorts, but amongst 839 patients attending an urban clinic for sexually-transmitted diseases in Malawi, and known to be HIV-negative, pain prevalence ("body ache" in the previous months) was 17% (Powers et al., 2007). In a community sample from a resource-poor area of Cape Town, South Africa, where HIV status was not known, the prevalence of pain/discomfort was 33% (Jelsma et al., 2005). Thus, the pain prevalence that I observed was much higher than both those 'control' prevalences.

I am not the first to have compared the welfare of rural and metropolitan individuals infected with HIV in sub-Saharan Africa. In a study of symptomatology of HIV-infected individuals in the Eastern Cape, South Africa, urban residence was associated with higher HIV symptom (including pain) severity (Peltzer and Phaswana-Mafuya, 2008). That was

a counter-intuitive outcome, since studies in the developed world have identified unemployment, poverty and poor education, which is more typical of rural populations, as risk factors for HIV-related pain (Dobalian *et al.*, 2004; Gray and Berger, 2007; Mathews *et al.*, 2000). Although the participants in both of these cohorts came from resource-poor communities, the rural cohort was more severely underprivileged; overall it was more impoverished, and less well educated.

Yet, although the proportion of rural participants who had pain at the time of the interview was slightly more than that of metropolitan patients, both cohorts reported the same median pain intensity at interview. There were, though, proportionally more rural patients who had pain at first diagnosis of HIV infection, but proportionally fewer went to hospital because of the pain, perhaps implying delayed diagnosis, with clinics being placed far from the communities (Heckman *et al.*, 1998; Tollefson and Usher, 2006). Pain also appeared to cause greater self-rated and doctor-rated functional impairment in the rural patients than it did in the metropolitan patients.

Participants in both rural and metropolitan cohorts frequently experienced their pain in their heads, chests and abdomens, sites well documented in patients who are infected with HIV in the developed countries (Del Borgo *et al.*, 2001; Frich and Borgbjerg, 2000; Hewitt *et al.*, 1997; Lebovits *et al.*, 1989). The seriously-ill Johannesburg patients of Norval (2004) also frequently had head pain. Significantly more of the rural patients than metropolitan patients had genital pain; genital pain was not recorded in

another rural HIV-positive cohort in South Africa (Shawn et al., 2005). Significantly, more of the metropolitan cohort had foot pain, a symptom often associated with HIV-associated sensory neuropathy arising from the use of stavudine-based antiretroviral treatments (Maritz et al., 2010; Wadley et al., 2011); proportionally more of the metropolitan cohort were using antiretroviral medication.

Despite exposure to antiretroviral therapy increasing the risk of peripheral neuropathy, in our rural cohort having antiretroviral therapy was weakly, but independently associated with reduced chance of having pain; in agreement with Jelsma and colleagues (2005) and Rosen and colleagues (2008). However, the association between antiretroviral therapy and reduced risk of pain is not universal (Harding et al., 2006), and in our metropolitan cohort, being on antiretroviral therapy was not associated with reduced chance of having pain. In addition, the relationship between CD4 T-cell count and pain is ambiguous. In a resource-poor HIV positive population near Pretoria, South Africa, low CD4 T-cell count was associated with increased prevalence of neuropathic pain (Hitchcock *et al.*, 2008).

In our study, CD4 T-cell count was not independently associated with having pain, a finding similar to that reported for another group of HIV-positive individuals drawn from our metropolitan community (Van As et al., 2009), and in other South African HIV-positive populations (O'Keefe and Wood, 1996; Peltzer and Phaswana-Mafuya, 2008). Indeed, lower presenting CD4 T-cell count may be associated with fewer reports of pain

(Rosen et al., 2008), perhaps because patients who are HIV-positive without pain delay the consultation that leads to diagnosis.

3.7.4. Pain under-treatment

Even if an HIV-positive individual presents at hospital because of pain, that pain may be disregarded or downplayed by the doctor (Hewitt et al., 1997; Justice et al., 2001). In sub-Saharan Africa, doctors give low priority to pain and other symptoms exhibited by patients who are HIV positive, even though those symptoms may be worse than those exhibited by patients with terminal cancer (Maree *et al.*, 2011; Narasimooloo *et al.*, 2011; Norval, 2004; Peltzer and Phaswana-Mafuya, 2008). The doctors who examined participants in my study, at least a third of whom were in moderate-to-severe pain at the time of the examination, assigned the participants high Karnofsky Performance Scores, as did doctors who examined patients at a Ugandan clinic (Katwere et al., 2009). Those doctor attitudes certainly are not confined to sub-Saharan Africa (Singer et al., 1993).

The stoic attitude of my study participants to their HIV-related pain may have contributed to the attitude of the doctors. Even though many of them were in moderate-to-severe pain, the participants reported low levels of functional impairment, as did another sample of patients who were HIV-positive drawn from the metropolitan community (Kinsey *et al.*, 2008). Ambulatory HIV-positive patients in sub-Saharan Africa are very unlikely to

confine themselves to bed (Voss et al., 2007). Some (Dobalian *et al.*, 2004; Gray and Berger, 2007; Mathews *et al.*, 2000), but not all (Breitbart et al., 1996a), previous studies have reported that HIV-positive patients of African ancestry are less compromised by their pain than are patients of Caucasian ancestry.

The explanation for the stoic attitude to HIV-related pain in sub-Saharan Africa may well be social. Indeed, the problem of pain is considered relatively unimportant by impoverished patients who are HIV-positive in resource-poor communities overwhelmed by financial worries and the need for home care (Phaladze *et al.*, 2005; Uwimana and Struthers, 2007) and debilitated by fear and fatigue (Makoae et al., 2005). Indeed it has been reported that patients' belief that pain should be endured expected and endured, where patients tend to cope with the pain (Frich and Borgbjerg, 2000).

If patients appear to be coping with their HIV-related pain, and if doctors are not particularly concerned about the pain in any case, it is not surprising that patients are undertreated for HIV-related pain. In both of my cohorts, many participants in pain were receiving no analgesic medication, and those who were receiving medication were using medication of far too low an analgesic strength, according to the Pain Management Index. Similar findings have been reported before in South African cohorts of HIV-positive patients with chronic pain (Maree *et al.*, 2011) or who were hospitalized.

The under-treatment of pain in HIV-positive people is not unique to this setting, but the gravity of the problem was greater in my cohort than has been described previously (Breitbart *et al.*, 1996b; Larue *et al.*, 1997). The Pain Management Index has limitations (Breitbart et al., 1996b), but, irrespective of the Index, there were many participants with severe pain who were not receiving opioids. That African patients with severe pain are deprived of opioids has been reported previously (Harding *et al.*, 2010; Maree *et al.*, 2011). Yet, participants in my study reported remarkably good pain relief, however, from medications which ought not to have been strong enough, as did Rwandan HIV-positive patients typically taking ibuprofen (Uwimana and Struthers, 2007). Doctors treating HIV-related pain, however, do face the dilemma that, even if they treat the pain pharmacologically, it is far from clear what they should be employing for the virus-related pain itself.

3.7.5. Recapitulation

In summary, I have undertaken what I believe to be the first pain-focussed study of the pain experienced by ambulatory HIV-positive patients in sub-Saharan Africa. Not only do the majority of HIV-infected individuals live in sub-Saharan Africa, but, because they are predominantly female and heterosexual, the many studies of HIV-related pain in cohorts consisting of homosexual males may not be directly applicable to them. Also, people living with HIV in sub-Saharan Africa are more impoverished, less educated, and less able to access healthcare than are the populations in

which HIV-related pain has been studied conventionally, and those social factors may impact on patients' and clinicians' pain attitudes and management.

I have shown that pain is at least as prevalent and severe in the rural and metropolitan HIV-positive individuals whom I studied as it is in any other group studied, and, if anything, is managed less well than is HIV-related pain outside sub-Saharan Africa. The pain in my study participants had many features in common with HIV-related pain described in other studies, but my study participants were remarkably stoic about their pain, and the pain itself caused little impairment to their daily lives.

3.8. Acknowledgements

I thank the study participants, the interviewers, and the staff of Helen Joseph Hospital, Johannesburg and Tintswalo Hospital, Bushbuckridge for their invaluable assistance, and for granting permission to conduct my research in their hospitals. I also thank the Wits/MRC Rural Health and Health Transitions Research Unit for facilitating access to the patients at Tintswalo Hospital. I thank Catherine Cherry for assistance with the statistical modelling, and the University of the Witwatersrand, the Medical Research Council of South Africa, the South African National Research Foundation (Thuthuka Grant), the Carnegie Foundation and the Canon Collins Trust for financial support.

CHAPTER 4

PAIN IN SOUTH AFRICAN HIV-POSITIVE AMBULATORY PATIENTS: A LONGITUDINAL STUDY

Data presented in this chapter are submitted:
Noko R Mphahlele, Duncan Mitchell and Peter R Kamerman. Pain in South African HIV-positive ambulatory patients: a longitudinal study. *Journal of Pain and Symptom Management*.

4.1. Abstract

I investigated the change in the intensity of pain, prevalent pain sites, number of pain sites, pain interference and analgesic prescription in 92 HIV-positive South Africans attending an outpatient clinic, at Helen Joseph Hospital, Thembalethu clinic, located in Johannesburg. I assessed pain intensity, interference and analgesic prescription using the South African version of the Wisconsin Brief Pain Questionnaire (WBPQ), which was administered at visit 1 (first interview) and at visit 2 (six months later). I found a significant difference between the two visits in the direction of pain intensity change from moderate pain ($p = 0.0078$) and severe pain ($P < 0.0001$). I found the decrease in pain prevalence, pain intensity, number of pain sites in patients and the decrease in the number of reported chest pain in patients who were on HAART for six months, and no significant difference in these parameters in patients who were not on HAART.

The most prevalent pain sites reported by patients at both visits were: head, chest, and feet although ankle pain and pain in the thighs were reported more in visit 2 than visit 1. There was a significant decrease in the chest pain reported by patients who had mild pain at visit 1 (95% CI difference; 17 to 79); whereas patients who reported moderate pain during visit 1 had significantly decreased head pain (95% CI difference; 15 to 51) and chest pain (95% CI difference; 6 to 44) at visit 2. Patients who reported severe pain at visit 1 reported significantly decreased chest pain at visit 2 (95% CI difference; 3 to 44). Only 4 of the 78 patients were

prescribed non steroidal anti-inflammatory drugs (NSAIDs) and 74 patients (95%) were not prescribed any form of analgesics. Of the 78 patients who were in pain at visit 1, 48 were still in pain at visit 2 and 36 of those were not prescribed any form of analgesics. Thus I found that there was a decrease in pain intensity and the number of pain sites, less pain treatment and no changes in the pain interference over six months in the 92 South African ambulatory patients who were HIV-positive.

4.2. Introduction

Depending on the methodology and sample characteristics, the prevalence of HIV-related pain ranges from 30 to 94 % in infected patients (Frich and Borgbjerg, 2000; Norval, 2004; Wakeham *et al.*, 2010). In my recent South African study the prevalence of pain in the ambulatory patients interviewed was within the ranges that was previously reported (Mphahlele *et al.*, 2011). Common pain syndromes described by HIV/ AIDS patients include abdominal pain, oral cavity pain, throat pain, headaches, joint and back pain, and neuropathic pain (Hirschfeld, 1998).

Pain in HIV has also been found to have a negative impact on the health-related quality of life of patients infected with HIV (Lorenz *et al.*, 2001). This pain is also associated with greater impairment in functional ability, greater symptom and psychological distress (Vogl et al., 1999). However most studies investigating the prevalence, incidence, intensity and management of pain except for five were cross-sectional studies, thus

there is not much data available with regards to the changes in the prevalence and intensity of pain over time. Thus far, there are five studies that I am aware of, that had investigated the prevalence and treatment of pain over periods of 3 months to 8 years (Aires and Bammann, 2005; Brechtl *et al.*, 2001; Frich and Borgbjerg, 2000; Koeppe *et al.*, 2012; Singer *et al.*, 1993). The only longitudinal study that was conducted in South Africa focused mainly on the improvement in patients' functionality and symptom prevalence when exposed to antiretroviral therapy (Rosen et al., 2011). I therefore investigated the change in pain intensity, pain sites, pain interference and pain treatment over a period of six months, in South African ambulatory patients infected with HIV.

4.3. Materials and Methods

4.3.1. Participants

I recruited a total of 396 ambulatory HIV-positive outpatients from the Helen Joseph, Thembalethu Clinic, which is located in Johannesburg, South Africa, from March 2005 to July 2006. Participants were recruited during their routine clinic visits and without consideration for whether they were in pain or not. Eligibility criteria for inclusion in the study were that participants must have had a confirmed diagnosis of HIV infection, and they must have been ambulatory.

The research was approved by the Human Ethics Commitee (Medical) of the University of the Witwatersrand, South Africa (clearance number:

M041112). All participants were 18 years or older, and had a confirmed diagnosis with HIV. All patients provided written informed consent before participating in the study.

4.3.2. Study procedure

The patients were interviewed at the time of recruitment (visit 1) and again six months later (visit 2). Due to loss to follow-up, only 92 of the 396 patients interviewed at Visit 1 were interviewed again at Visit 2. The main reason for the loss to follow-up in this study was that patients did not return for their follow-up visit. At both visits I used the Wisconsin Brief Pain Questionnaire (WBPQ) which I translated into local languages and validated for use in South African HIV-positive patients (Mphahlele *et al.*, 2008), to characterise each patient's pain and the effect the pain had on functions of their daily lives.

The WBPQ was used to assess pain intensity, the extent to which pain interfered with function, and the efficacy of analgesic medications. Both the pain intensity and pain interference dimensions of the questionnaire have been validated (Daut *et al.*, 1983; McCormack *et al.*, 1993). Because some of the participants were functionally illiterate, interviewers administered the questionnaire to all participants using a standardized interview. Participants had the choice of undertaking the interview in English, isiZulu, isiXhosa, Sepedi, Setswana, or Xitsonga. I have described elsewhere the validation of the Setswana, isiZulu, and Xitsonga versions of the WBPQ, and the validation of the original English version of

the questionnaire when used by English second-language speakers (Mphahlele *et al.*, 2008). Participants used an 11-point numerical pain-rating scale to rate pain intensity, if any, at the time of the interview, and their pain intensity at its worst over the last 30 days, where 0 represented “no pain”, and 11 represented “pain as bad as you can imagine”. The extent to which pain interfered with function, in terms of mood, sleep, enjoyment of life, relations with other people, walking ability and normal work, was rated on a 0 to 4 numerical scale, where 0 represented “no interference at all” and 4 represented “extreme interference”. Participants also marked the site of pains experienced in the last month on an illustrated body chart.

Due to some of the patients being functionally illiterate, interviewers administered the questionnaire to all participants using a standardized interview technique. Patients’ medical histories (e.g., CD4 T-cell counts, co-infections, and medications) were obtained through personal recall, and these data were confirmed and supplemented using patients’ hospital records.

4.3.3. Statistical analysis

Data describing the characteristics and treatment of pain of the 396 patients recruited at visit 1 are described in Chapter 4 (Mphahlele *et al.*, 2011). This report only pertains to the 92 patients with data from visit 1 and visit 2. Because the 92 patients described in this report are a subset of a larger cohort of 396 patients I compared the demographic and pain

characteristics of this subset of patients at Visit 1 to the rest of the group to determine whether the subset was representative of the larger cohort at the time of recruitment. Thus the data presentation and analysis is based on the 95% confidence interval of the medians between the compared groups. Data are either presented as median (interquartile ranges) or as percentages of the 95% interval. I considered the 95% confidence intervals of the difference greater zero to be significant. Pain intensity, based on participants' rating of their worst pain in the last month, also was scored from 1 to 3, with mild pain being assigned 1 (a rating of 1-3 on the WBPQ pain intensity scale), moderate pain a 2 (4-7 on the WBPQ pain intensity scale), and severe pain a 3 (8-10 on the WBPQ pain intensity scale).

4.4. Results

4.4.1. Patients sampling

At recruitment (visit 1), the subset of 92 patients I have follow-up data for six months later was broadly representative of the rest of the cohort (Table 4.1). There was no significant difference in measured parameter between patients who returned for the second interview than those that did not return.

Table 4.1: Characteristics of the cohort who returned for a second interview (n = 92) with those who did not (n = 304)

Description	Returnees	Absentees	95% confidence (CI) of the difference between cohorts
	n = 92	n = 304	
Age (mean, 95% CI)	35 (21 to 65)	35 (20 to 67)	- 1.4 to 1.4
Female (%)	82	73	- 2 to 17 %
Education (%)			
No education	3	3	- 6 to 3%
Primary[a]	10	15	- 8 to 10%
Secondary[b]	84	75	- 17 to 1%
Tertiary	3	7	- 2 to 8
Patients with no income (%)	50	53	- 8 to 14%
Patients initially on antiretroviral therapy (%)	65	69	- 15 to 7
Patients with pain (%)	85	75	- 8 to 0%
Pain intensity (median, 95% CI)	6 (0 to 10)	5 (0 to 10)	0 to 2
Patients with pain on more than one site (%)	58	132	- 30 to - 8%
Patients CD4 T-cell ranges (%)[c]			
< 200 (cells/mm3)	53	48	- 19 to 10
200 – 499 (cells/mm3)	45	45	- 15 to 15
≥ 500 (cells/mm3)	2	7	- 4 to 9

a Estimated age: 6 – 13 years (the primary school age entry is 6 years whereas the primary school-leaving age is 13 years)

b Completed secondary school

c Incomplete data: n = 51 for the subsample (n = 92), and n =215 for the n = 304. CD4 T-cell count measured at the time of the interview.

4.4.2. Changes in pain intensity between visit 1 and visit 2

Table 4.2 summarizes the change in pain intensity over six months. Of the 92 patients who returned for their second interview, 78 (85%) of those reported some form of pain. There was a significant decrease in pain of moderate and severe intensity from visit 1 and six months later. Indeed of the 35 patients who reported moderate pain during visit 1, 20 (57%) of those reported mild pain by visit 2 with only 10 patients reporting no change in pain intensity. Also, 21 (66%) of the 31 patients who had severe pain at visit 1 reported to be experiencing moderate pain at visit 2, with 11 patients reporting pain that is still severe at visit 2.

4.4.3. Pain sites

Table 4.3A shows the number of pain sites at visit 1 and six months later, for patients who reported pain at visit 1 (n = 78). There was no significant change in the number of pain sites for patients who had reported no form of pain and mild pain.

There was however, a significant decrease in the number of patients who reported two or more pain sites for the pain intensity that was reported to be moderate and severe (moderate pain: 95% CI difference; 18 to 59; severe pain: 95% CI difference; 1 to 45).

Table 4.2: Change in pain intensity over six months

Pain category at Visit 1	n	Pain intensity (median, interquartile range)		95% CI of the difference between Visit 1 and Visit 2	Direction of change
		Visit 1	**Visit 2**		
All	92	6 (3 to 9)	3 (0 to 7)	2 to 8	Not significant
No pain	14	0	0 (0 to 0)	0	Not significant
Mild pain	11 (**4**)	3 (3 to 3)	2 (0 to 5)	- 1 to 7	Not significant
Moderate pain	35 (**10**)	6 (4.5 to 6.5)	3 (0 to 7)	2 to 6	Moderate to mild
Severe pain	32 (**11**)	10 (9 to 10)	5 (0 to 8)	4 to 10	Severe to moderate

Bold values – number of patients that were in the same category as in visit 1 at visit 2

Table 4.3A: Number of pain sites at Visit 1 and Visit 2, for patients with different pain intensities at Visit 1

Pain intensity at Visit 1	Number of pain sites	Number of patients (%)		95% CI of the difference in the percentage between Visit 1 and Visit 2	Direction of change
		Visit 1	Visit 2		
No pain	0	14 (100)	11 (79)	- 4 to 48	NS
(n = 14)	1	0 (0)	2 (14)	- 40 to 10	NS
	≥ 2	0 (0)	1 (7)	- 31 to 15	NS
All patients with pain	0	0 (0)	31 (40)	**- 51 to - 29**	↑
(n = 78)	1	21 (27)	16 (20)	- 7 to 20	NS
	≥ 2	57 (73)	31 (40)	**18 to 47**	↓
Mild pain	0	0 (0)	5 (45)	**- 72 to - 10**	↑
(n = 11)	1	4 (36)	3 (27)	- 27 to 42	NS
	≥ 2	7 (64)	3 (27)	- 4 to 64	NS
Moderate pain	0	0 (0)	15 (41)	**- 58 to - 23**	↑
(n = 35)	1	9 (24)	8 (24)	- 20 to 20	NS
	≥ 2	26 (76)	12 (35)	**18 to 59**	↓
Severe pain	0	0 (0)	11 (34)	**- 52 to -17**	↑
(n = 32)	1	8 (25)	5 (16)	- 11 to 29	NS
	≥ 2	24 (75)	16 (50)	**1 to 45**	↓

NS = not significant
↑ = increase
↓ = decrease

Table 4.3B shows the most prevalent pain sites at visit 1 and visit 2, reported by patients who were in pain at visit 1 (n = 78). The most frequently reported pain sites at visit 1 were head, chest, and feet, whereas at visit 2 patients reported pain in the following areas: head chest, ankle and feet and thighs. I only found a significant decrease in the percentage of reported chest pain in patients who had mild pain at visit 1 (95% CI difference; 17 to 79), whereas patients who reported experiencing moderate pain during visit 1 had significantly decreased head pain (95% CI difference; 15 to 51) and chest pain (95% CI difference; 6 to 44) at visit 2. Similarly, patients who reported severe pain at visit 1 reported a significant decrease in chest pain at visit 2 (95% CI difference; 3 to 44). On overall, there seem to be a general decrease in the prevalence of chest pain across all pain intensity items.

4.4.4. Highly active antiretroviral therapy (HAART) and pain

Pain characteristics for patients who were on HAART at visit 1 and six months later are shown in table 4.4A. Of the 78 patients who had reported pain at visit 1, 55 (71%) of those were on HAART. On overall, there was a significant decrease in the prevalence, intensity and pain on more than one side in patients who were on HAART at both visits. There also was a decrease in the number of reported chest pains over time, and no change in the number of pain on the head, feet and ankles. Although there was a decrease in some pain parameters, there was no change in the amount of prescribed analgesics.

Additionally, I found no significant change in the measured pain parameters in patients who were not on HAART at both visits (table 4.4B).

4.4.5. Pain interference

Table 4.5 shows the mean pain interference at visit 1 and at visit 2. On average pain interference was rated by patients as low, at both visits (median interference score of 0 meaning “no interference at all”; or 1 meaning “a little bit of interference”) and there was no change in the mean pain interference per pain intensity, from visit 1 to visit 2.

4.4.6. Pain treatment

Figure 4.1 shows the types of analgesic therapy prescribed to patients who reported pain at visit 1 (n = 78), who were still in pain six months later (n = 48), and who were no longer in pain six months later (n = 30). At visit 1, only 4 patients (5%) of the 78 patients who reported pain received analgesic treatment, and in all cases non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol were prescribed. Of, the 48 patients (62%) who were still in pain six months later; 36 (75%) of those patients still had no form of analgesics prescribed, with only 7 (15%) prescribed a non-steroidal anti-inflammatory drugs (NSAIDs), 4 (8%) prescribed tricyclic antidepressants (TCAs with amitriptyline as the main TCA prescribed), whereas 1 patient was prescribed a combination of an NSAID and a TCA.

Table 4.3B: Most frequent pain sites at Visit 1 and Visit 2, for patients with different pain intensities at Visit 1

Pain intensity at Visit 1	Three-most common pain sites (%)		95% CI of the difference in the percentage between Visit 1 and Visit 2	Direction of change
	Visit 1	Visit 2		
All	Head (41)	Head (19)	7 to 35	↓
(n = 78)	Chest (41)	Chest (12)	16 to 42	↓
	Feet (41)	Feet (27)	2 to 24	↓
Mild pain	Head (27)	Head (18)	-25 to 41	—
(n = 11)	Chest (55)	*Chest † (0)*	17 to 79	↓
	Ankles (0)	Ankle (27)	-57 to 4	—
	Feet (55)	Feet (36)	-21 to 50	—
Moderate pain	Head (40)	*Head* (6)	15 to 51	↓
(n = 35)	Chest (37)	Chest (11)	6 to 44	↓
	Feet (40)	Feet (23)	-5 to 37	—
	Thigh (3)	Thigh (11)	-23 to 5	—
Severe pain	Head (47)	Head (34)	-11 to 34	—
(n = 32)	Chest (41)	Chest (16)	3 to 44	↓
	Feet (38)	Feet (28)	-13 to 31	—

† = The pain sites in italics were not within the three-most common sites at a particular visit, but were at the other visit.
— = no change
↓ = decrease

Table 4.4A: Pain characteristics for patients who were on HAART at Visit 1 and six months later (n = 55)

Description	Visit 1	Visit 2	95% CI of the difference between Visit 1 and Visit 2	Direction of change
Patients with pain (%)	85	51	17 to 49 %	↓
Pain intensity (median, 95% CI)	6 (0, 10)	2 (0, 10)	2 to 6	↓
Patients with pain on more than one site (%)	56	35	32 to 38 %	↓
Pain interference (median)	1	1		
Patients not on analgesics (%)	95	96	- 12 to 8 %	NS
Most frequent pain sites of patients with pain (%)				
Chest	45	14	9 to 47	↓
Head	38	29	- 13 to 29	NS
Feet	32	43	- 32 to 11	NS
Ankles	11	18	- 26 to 8	NS

NS = not significant
↓ = decrease

Table 4.4B: Pain characteristics for patients who were not on HAART at both visits (n = 7)

Description	Visit 1	Visit 2	95% CI of the difference between Visit 1 and visit 2	Direction of change
Patients with pain (%)	100	86	- 23 % to 51 %	NS
Pain intensity (median, 95% CI)	6 (6, 10)	5 (4, 9)	- 4 to 6	NS
Patients with pain on more than one site (%)	71	43	- 19 to 62 %	NS
Pain interference (median)	1	2		
Patients not on analgesics (%)	71	57	- 30 to 52 %	NS
Most frequent pain sites of patients with pain (%)				
Head	29	29	- 41 to 41	NS
Chest	29	29	- 41 to 41	NS
Feet	29	29	- 41 to 41	NS
Ankles	14	0	- 23 to 51	NS

NS = not significant

Table 4.5: Mean pain interference at Visit 1 and Visit 2

Pain intensity	Median (interquartile range)		95% CI of the difference in the percentage between Visit 1and Visit 2	Direction of change
	Visit 1	**Visit 2**		
No pain (n = 14)	0 (0 to 0)	0 (0 to 1)	- 1 to 1	—
All patients with pain * (n = 78)	1 (0 to 2)	0 (0 to 1)	0 to 1	—
Mild pain (n = 11)	0 (0 to 1)	0 (0 to 0)	0 to 1	—
Moderate pain (n = 35)	1 (0 to 1)	0 (0 to 1)	0 to 1	—
Severe pain (n = 32)	1 (0 to 2)	0 (0 to 1)	0 to 1	—

***** Data analysed without sub-dividing patients according to pain intensity at Visit 1.
— No change

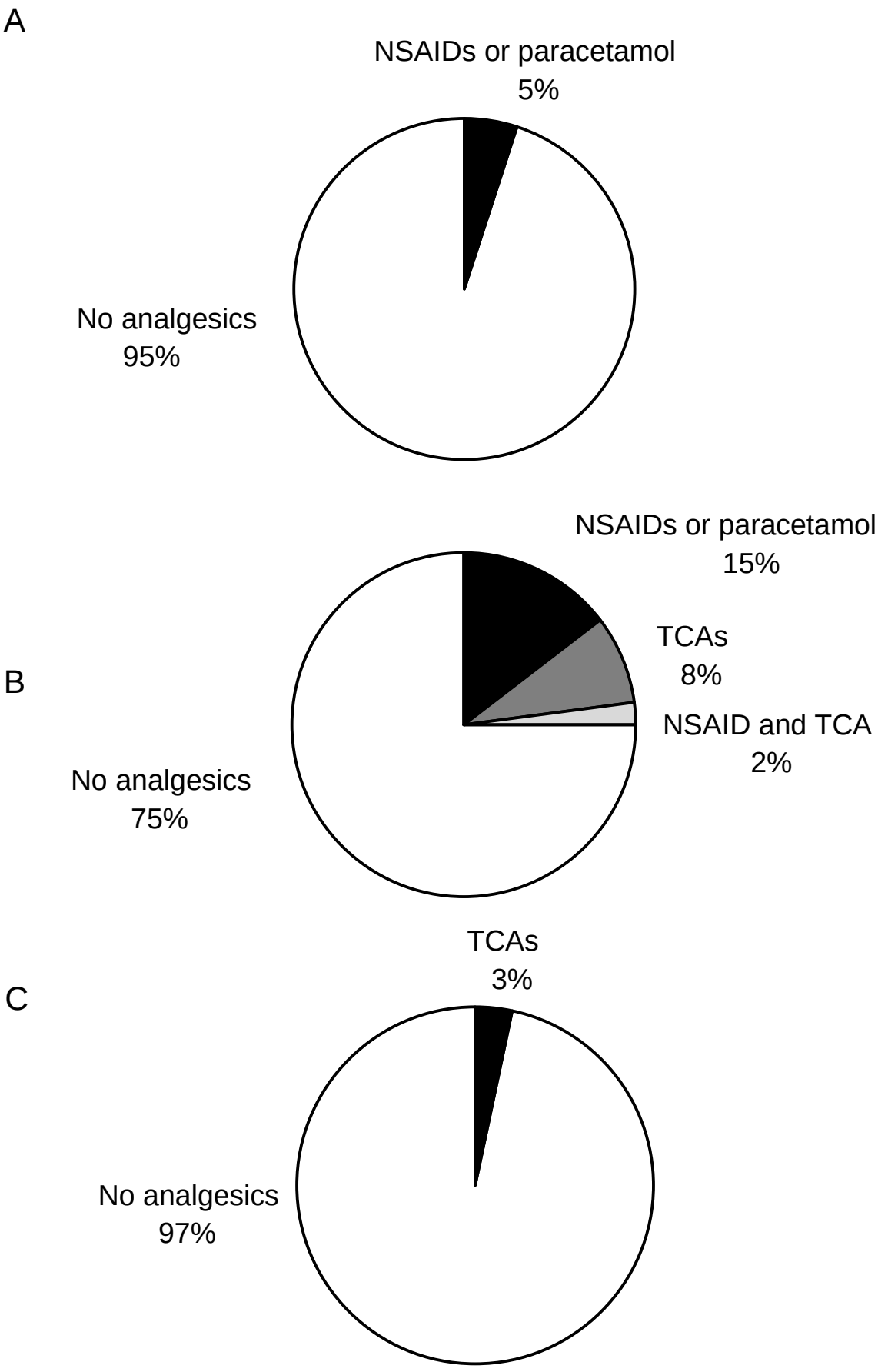


Figure 4.1: Types of analgesic therapy prescribed to patients in pain at visit 1 (n = 78; A), patients who were still in pain six months later (n = 48; B), and those patients who no longer were in pain six months later (n = 30; C). TCA = tricyclic antidepressant.

Thus, patients whose pain persisted for six months were more likely to receive analgesics. Similarly, 3% of the patients who were no longer in pain six months after their initial interview were prescribed only tricyclic antidepressants.

4.5. Discussion

I investigated the change in the intensity of pain, prevalent pain sites, and number of pain sites, pain interference, and the prescription of analgesics in a cohort of 92 HIV-positive South Africans attending a government HIV roll-out clinic. This cohort was a subsample of an original cohort of 396, where only 92 of the patients had data for two hospital visits. To my knowledge, this is the first comprehensive longitudinal study in Africa describing both the changes in pain intensity, symptom prevalence, number of pain sites and pain treatment over a six month period.

One limitation of this study was that, seventy-seven percent (77%) of patients were lost to follow up. During the first interview patients were informed that they will be interviewed again in sixth months. Participants gave the interviewers their contact details (e.g. residential address or contact number), so they could be reminded of their follow-up visits to the clinic and thus their second interview. Yet, despite efforts to contact the participants, only one third of participants participated in the six-month interview. Even with the 77% loss to follow up, the cohort of 92 was broadly representative of the original cohort of 396.

There was no significant change in the direction of pain from the first interview to six months later, in patients who reported mild pain, suggesting that patients who report mild pain are likely to not progress to high pain intensities, at least within a six months period. However, significantly more patients reported a decrease in pain from moderate and severe intensities to mild and moderate pain intensities, respectively from visit 1 (first visit) to visit 2 (six months after the initial visit). The reported reduction in the intensity of pain could be due to the efficacy of HAART (highly active antiretroviral therapy) which is related to decreases in viral loads and increases in CD4 T-cell counts. The association between decreases in the CD4 T-cell counts and the presence of some form of pain in HIV-positive individuals has been described (Hewitt *et al.*, 1997; Hitchcock *et al.*, 2008; Van As *et al.*, 2009). It also is know that one of the benefits of HAART is to prevent disease progression and to also reverse the decrease in the CD4 T-cell counts which would in turn minimise the risk of patients from developing opportunistic infection that sometimes lead to some form of pain. In this study, I have shown significant decreases in the pain prevalence, intensity, number of pain sites and also chest pain, in patients who have been on HAART for six months. Two previous studies have also concluded that the decrease in pain over time is associated with HAART usage (Koeppe et al., 2012; Rosen et al., 2011). I however, found no significant differences in the measured pain parameters in patients who were not on HAART for the six month period.

Except for the mild pain intensity results, that did not change over the six month period, my results are contradictory to the results presented by Brechtl and colleagues (2001) who reported no change in the level of pain intensity from baseline over three months. However, unlike my data that was collected in ambulatory HIV-positive patients, their data were collected from hospitalized patients with advanced HIV infection, and who were started on HAART only after their admission into hospital. Although it may seem as if exposure to HAART was beneficial with regards to viral load, CD4 count, depression, body weight, the authors could not conclude on the effect that HAART has on pain intensity.

In a combined cohort of 1130 Kenyan and Ugandan patients, Harding and colleagues (2013) reported an increase in the proportion of people reporting “no pain” over a three-month period, while the number reporting a score of 1 (a little bit of pain) increase only slightly and all other pain scores reduced in prevelance such that no participants reported overwhelming pain by the third visit..

Similarly to the study conducted by Brechtl and colleagues (2001), other authors have also reported that despite the presence of pain in some of their hospitalized patients, the pain was becoming progressively less persistent and less intense over time (Aires and Bammann, 2005). These authors concluded that the improvement of pain intensity and severity observed in their study cohort was not as a result of better pain management, as only four and three percent of the patients in pain received mild and strong opioids, respectively. These findings show a

similar trend to other literature, where prescription and availability of opioids was very low (Breitbart *et al.*, 1996; Larue *et al.*, 1997; Narasimooloo *et al.*, 2011; Newshan and Wainapel, 1993). In fact in my study, I found that despite the continuous reports of pain by patients, no forms of opioids were prescribed. It is noteworthy that I have seen an increase in the percentage of prescribed analgesics in patients who were still in pain six months after their initial interview. This increase in the percentage of prescribed analgesics may be due to continuous complaints that patients' make about their pain to their doctors. Similarly, Frich and Borgbjerg (2000) reported an increase in the pain management index (PMI) during their study period, relating it to the need for treatment and thus an increase in the prescription of analgesics for patients with pain. Although there is an increased demand for opioid use due to patient report of continuous pain and there are guidelines for opioid use in moderate to severe pain (although developed for cancer pain, not HIV-related pain), a study by Koeppe and colleagues (2011) revealed a negative association between opioid usage and decreasing pain, which means that the relief of pain was not related to opioid use. Thus, without evidence-based treatment guidelines for HIV-related pain, patients who experience other forms of HIV-related pains (for example; neuropathic pain) which respond poorly to opioids, will be better managed using published neuropathic pain management guidelines than employing the WHO analgesic ladder which promotes more the use of opioids and that has known limitations in the treatment of chronic HIV-related pain (Koeppe *et al.*, 2010).

In a recent Kenyan and Ugandan combined study, the authors reported that treatment with non-opioid analgesics was always slightly more common than pain assessment where non-opioid analgesics were received by over three-quarters of participants in each country although a similar proportion of participants had their pain assessed. Therefore, there was more usage of non-opioid analgesics than opioid analgesics (Harding *et al.*, 2013).

Amongst the 92 patients interviewed in this study, the frequently reported pain sites for mild, moderate and severe pain intensities during visit 1 were head pain, chest pain and feet pain. However, during visit 2 the frequently reported pains for mild pain were head pain, ankle pain and feet pain, whereas for moderate pain intensity the frequent pain sites were chest pain, feet pain and thigh pain. Frequent pain sites of patients who reported severe pain were similar at both visits. These pain sites are similar to those reported previously by other authors (Hewitt *et al.*, 1997; Maritz *et al.*, 2010; Norval, 2004; O'Neill and Sherrard, 1993). Thus over a six-month period, chest pain was no longer a frequent pain site in patients who reported mild pain, whereas in patients who reported moderate pain, head pain was no longer a frequent pain site.

I found a decrease in the direction of change of chest pain over six month, for all pain intensities which could be related to improvements or control of patients' respiratory infections like tubercolosis (TB) or pneumonia. However, data for patients who were receiving TB medication were

excluded in the analyses. Regardless, the fact that patients reported chest pain as one of the most common pain site, highlight one limitation of this study where there could have been misdiagnoses of respiratory infection (for example, TB) in some of the patients, by the healthcare practitioners. Although most studies have linked feet pain with exposure to d4T (stavudine) and/or ddI (didanosine) (Maritz et al., 2010; Wadley et al., 2011), I found no association between foot pain and antiretroviral exposure in this cohort at both visits.

I found a decrease in the number of prevalent pain sites from visit 1 to visit 2, which could be explained by a decrease in the pain intensity from visit 1 to visit 2. As with the trends in pain intensity and prevalent pain sites from visit 1 to visit 2 for mild pain, I found no change in the number of pains reported by patients. Also, I found a decrease in the number of pains from visit 1 to visit 2, reported by patients who reported moderate and severe pain. Singer and colleagues have reported that the mean number of pains that patients reports increases with systemic disease progression and also with the CD4 T-cell counts of below 200/mm^3 (Singer et al., 1993). The CD4 T-cell counts results reported by Singer and colleagues (1993) are similar to those reported by a South African-based study, where the authors reported that exposure to HAART and a low CD4 T-cell count are both associated with symptom number (Peltzer and Phaswana-Mafuya, 2008). Contrary to the above studies; Vogl and colleagues found the number of symptoms to be highly associated with poorer quality of life and

also that CD4 T-cell count was not associated with symptom number (Vogl et al., 1999).

I found no change in the mean pain interference per pain intensity, over the six months period. Rosen and colleagues (2011) have shown an improvement in patients' functional impairment after a year that they have been on HAART. However, the authors' data on patients' function were based only on "normal activity" whereas I interpreted my data as mean of functional interference, which is the mean score of all six pain interference items on the Brief Pain Inventory namely; mood, relations with other people, walking ability, sleep, normal work, and enjoyment of life (Cleeland and Ryan, 1994). Thus, it is possible that I may have still seen different results if I had followed the patients for longer than six months.
Harding and colleagues (2013) have also reported that pain caused less interference with patients' daily living over time showing which could be related to the improvement of pain scores over time.

I did not record constitutional and/or any infections in my study cohort, an item which could have made it easier to classify the patients' disease progression. I also did not have complete CD4 T-cell count data and Karnofsky Performance scores for all the patients which made it impractical to carry out some of the comparisons that would have benefited the depth of this study.

With this study being the first comprehensive longitudinal study in Africa to investigate the trends in pain intensity, pain prevalence, pain site and management of pain in paitients infected with HIV, I therefore believe that I have successfully shown that there are decreases in pain intensity, pain prevalence, and the number of pain sites over time, which could be due to improvements in the patients' CD4 T-cell count and decreases in the viral loads (Koeppe et al., 2012; Rosen et al., 2011). However, studies with bigger sample sizes, different patient disease classifications, longer duration of study and frequent visits are needed where the association between pain, pain sites, pain medication and HAART can be investigated in detail.

4.6. Acknowledgements

I thank the study participants, the interviewers, and the staff of Helen Joseph Hospital, Johannesburg for the invaluable assistance, and for granting permission to conduct our research in their hospital. I thank the University of the Witwatersrand, the Medical Research Council of South Africa, the South African National Research Foundation (Thuthuka Grant), the Carnegie Foundation and the Canon Collins Trust for financial support.

CHAPTER 5

CONCLUSION

The results presented in chapters 2 to 4 are comprehensively discussed in each respective chapter. Here I briefly summarize my findings, and suggests future work that needs to be done.

Chapter 2 and Chapter 3: Characteristics of pain and its treatment

I determined pain intensity and pain prevalence, risk factors for having pain, and analgesic medications employed in patient cohorts consisting predominantly of Black African and female human immunodeficiency virus (HIV)-positive individuals attending outpatient clinics in a rural (n = 125; 79% female; 100% Black African) and a metropolitan (n = 396; 75% female; 94% Black African) area. The data collected also were used to assess the factor structure and internal consistency of translated versions of the pain assessment instrument we used, the Wisconsin Brief Pain Questionnaire.

I report the prevalence of pain to be 72% in the rural participants and 56% in the metropolitan participants, yet despite this difference in pain prevalence, the median intensity of pain experienced in both cohorts was of moderate intensity (a score of 5 on the WBPQ). The prevalence data I collected at both study sites is within the range of what has been reported before in sub-Saharan Africa studies (Hitchcock *et al.*, 2008; Hughes *et al.*, 2004; Peltzer and Phaswana-Mafuya, 2008; Uwimana and Struthers, 2007; Voss *et al.*, 2007). All these studies, except for the study by

Hitchcock and colleagues (2008) which was concerned with neuropathic pain only, focused on quality of life and pain was only reported as one of the symptoms experienced by patients who are HIV-positive and no thorough assessment of the pain was attempted.

Although I found increased pain prevalence in the rural cohort compared to the metropolitan cohort I studied, it has been reported that urban living, athough there were comparable samples of patients from rural (48%) and urban areas (52%), is associated with increased severity of HIV-related symptoms (Peltzer and Phaswana-Mafuya, 2008). The results by Peltzer and Phaswana (2008) could be due to the likelihood that people who reside in the urban areas have more access to medical care compared with people that stay in rural areas, where access to healthcare facilities is difficult (Sibley and Weiner, 2011). With access being less of an issue for the people in urban areas, the possibility of receiving HAART in people infected with HIV in urban areas are much higher than those in rural areas (Wilson *et al.*, 2011). It is now know that the sources of pain experienced by patients living with HIV are HIV infection itself, secondary complications of the infection and immunosuppression, and iatrogenic causes (Hewitt *et al.*, 1997). Therefore one can postulate that the likelihood of developing HIV-related pain in patients who reside in urban area is greater than in their rural counterparts because urban-based patients have better access to HAART.

In contrast to the study by Peltzer and Phaswana (2008), my data are consistent with data from studies conducted in first world countries, which reported that poverty, factors associated with rural rather than metropolitan living, are associated with increased risk of having HIV-related pain. In rural areas, clinics are usually placed far from the communities (Heckman *et al.*, 1998; Tollefson and Usher, 2006), and patients may therefore only go to the healthcare facility when the pain is unbearable. Poverty, which is strongly related with poor nutritional status is known to be reflected in signs and symptoms related to infection, including HIV infection. The effects of malnutrition on the immune system are well known and include decreases of immune parameters such as CD4 T-cells (Gorbach *et al.*, 1993), which has been shown to be associated with increased pain (Dobalian *et al.*, 2004; Tsao and Soto, 2009).

While the prevalence of pain typically is high and comparable to those reported in early studies in resource-rich regions, the cause of pain in patients in sub-Saharan Africa has not been determined. But, there is no reason to believe that the causes of pain identified in studies in resource-rich regions should not apply to the African situation. Consequently, it can be broadly assumed that the pain experienced by patients who are HIV-positive in resource-poor regions like sub-Saharan Africa has the same aetiology as those previously described in resource-rich regions (Hewitt *et al.*, 1997). But, whether there are additional causes of pain, which are unique to developing contries, needs to be determined.

Patients who are HIV-positive can develop several different pains, with different aetiologies and locations (Martin *et al.*, 1999). Also, due to the multiple and coexisting illnesses, which most of the time are painful, these patients take multiple medications to treat these illnesses (Newshan, 1997; Vogl *et al.*, 1999). Some of the medications that patients take to treat their coexisting illnesses may cause or excacerbate the current pain, for example the use of isoniazid to treat TB, which has been shown to cause neuropathic pain (Subramanian and Morris, 2013). In my study, participants in both cohorts experienced frequent pain in the head, chest and abdomen, which are the pain sites that had been documented in patients who are HIV-positive in developed countries (Del Borgo *et al.*, 2001; Frich and Borgbjerg, 2000; Hewitt *et al.*, 1997). Headache occurs in 17% to 32% of HIV-infected individuals (Newshan and Wainapel, 1993) and since it is neurological, it may signal HIV-related involvement of the central nervous system (CNS). It has been reported that the causes of headache in HIV include primary CNS lymphoma and, metastatic Karposi's sarcoma, toxoplasmosis, papovavirus, and HIV (Gabuzda and Hirsch, 1987; Lewis and Warfield, 1990; McArthur, 1987). In a recent case study conducted in Cameroon, where 54 files out of 627 patient files were studied and confirmed for tuberculosis meningitis (TBM), the prevalence of headache was 74.1% (Berhe *et al.*, 2012; Luma *et al.*, 2013). TBM , is one of the first three causes of CNS opportunistic infections in HIV/AIDS patients in developing countries, including; sub-Saharan Africa, South America and Asia (Berhe *et al.*, 2012; Tan *et al.*, 2012). In South Africa

other causes of headache, which include muscle tension, stress-related headaches, sinus infections, vascular headaches, HIV drug side effects, were reported by 47% of rural HIV-positive patients in South African (Bhat *et al.*, 2010). Thus, headache is a prevalent symptom that is secondary to other infections prevalent in individuals who are HIV-positive. And, depending on the patient's disease status, any of the causes of head pain described in the preceding discussion may be experienced by patients.

The prevalence of abdominal pain is as high as 12% in individuals who are HIV-positive (Barone *et al.*, 1988). Abdominal pain is predominantly as a result of the high occurrence of opportunistic bowel infections (O'Keefe *et al.*, 1998) and malignancies such as Kaposi's sarcoma and lymphoma (O'Neill and Sherrard, 1993) There are however many other reasons why a person who is HIV-positive may experience abdominal pain. For example, in their study which involved review of HIV positive patients' records who visited the Emergency Department and complained of abdominal pain, Yoshida and colleagues (2002) found that the most common diagnosis was abdominal pain of unknown aetiology followed by gastroenteritis and ulcers (Yoshida and Caruso, 2002). However, other researchers have found that most individuals who are HIV-positive have high rates of gastrointestinal infections, with others having gastrointestinal side effects due to HAART (Hovanessian, 1999). Thus, results from the above studies, shows that the cause of abdominal is unclear. It is either

the pain is as a result of HAART or the pain is due to other opportunistic infections related to HIV (Yoshida and Caruso, 2002).

There are however cases where the cause of abdominal pain is of a known origin. For example, In a recent study, 180 patients who were HIV-positive were screened for abdominal TB and 30 (16.7%) showed sonographic signs of abdominal TB (Heller *et al.*, 2010). In their study approximately 77 patients presented with abdominal pain. Since side effects due to HAART have been associated with gastrointestinal infections and thus pain, it seems possible that as access to HAART increases, the prevalence of pain due to HAART-related side effects will increase.

Many metropolitan participants had foot pain, which is a symptom associated with HIV sensory neuropathy (Maritz et al., 2010; Wadley et al., 2011). HIV-related sensory neuropathy (HIV-SN) is often a painful condition, with the prevalence rate of up to 57% in ambulatory patients who are HIV-positive (Maritz *et al.*, 2010; Smyth *et al.*, 2007), and is the most frequent neurological complication associated with HIV infection and advanced AIDS (Harrison and Smith, 2011; Marcus *et al.*, 2000). It is estimated that nearly one-third of people with HIV/AIDS experience some peripheral nerve damage (Keswani *et al.*, 2002). In South Africa, 76% of patients who had HIV-SN had pain (Wadley *et al.*, 2011). In the late 1990's it was discovered that many patients who are HIV-positive typically experience a burning sensation, numbness, or tingling in the affected

extremities, which may be related to the toxic build up of antiretroviral drugs or direct viral effects, but the exact causes were unclear (Dalakas *et al.*, 2001b; Martin *et al.*, 2003; Verma *et al.*, 2004). HIV-SN is characterized by distal degeneration of long axons ("dying back") and it is believed that the density of small and large unmyelinated fibres, and in particular, of unmyelinated fibres is reduced (McArthur *et al.*, 2005). Neuropathy could also result from other associated causes, such as heavy alcohol consumption and vitamin deficiency. In a South African study, Martiz and colleagues (2010) found that of the 598 patients in their cohort, 30% were diagnosed with symptomatic sensory distal polyneuropathy. In their analyses the authors found HIV-SN to be independently associated with HAART use, especially stavudine, age and TB infection/treatment for TB. In another South African study where 395 patients who were HIV-positive and exposed to stavudine for six months were recruited, the prevalence of symptomatic HIV-SN was 57%. The authors found increasing age and height to be independently associated with the development of HIV-SN among patients who had been exposed to stavudine. In their study, three quarters of the participants always had pain present in the feet and only 23% patients experiencing symptoms proximal to the feet (Wadley *et al.*, 2011).

As I have shown above, foot pain is evidence of HIV-SN. Therefore if foot pain is evidence of HIV-SN, then the reason for a greater prevalence of HIV-SN in the metropolitan cohort as compared to the rural cohort is likely to be related to increased access to HAART in the metropolitan cohort.

Indeed stavudine was one of the main antiretroviral agents used in South Africa at the time of my data collection, where the probability of developing foot pain due to the side effects of stavudine were higher in the metropolitan cohort than in the rural cohort. Also, the improved access to healthcare increases the likelihood that participants in the metropolitan cohorts will access treatment before the onset of advanced HIV disease.

In my study, there were more rural patients who had pain at the time they were diagnosed with HIV but proportionally fewer went to hospital because of pain as compared with their metropolitan counterparts. This could be due to the fact that there could be delayed presentation in rural patients compared to metropolitan patients because patients stay far from the clinic (Heckman *et al.*, 1998; Tollefson and Usher, 2006). Also, though not quantified, another possible reason for the delayed diagnosis in these patients could be long working hours at the farms where patients only present at the healthcare facilities when the symptoms are unbearable.

Though I have reported pain of moderate to severe intensity in my study cohorts, the participants at both study sites reported little functional impairment due to pain. Similar results have been reported before in a South African study conducted by Kinsey and colleagues (2008). This could be because patients worry more about pressing poverty related issues (e.g., food, housing) relegating pain to a lower priority (Phaladze *et al.*, 2005; Uwimana and Struthers, 2007). Consistent with this low level of

patient-rated pain functional interference, doctors who examined the patients in my cohorts gave them a high Karnofsky Perfomance Scale (KPS) rating, even when they were experiencing moderate to severe pain. Similar results have been reported in Uganda (Katwere et al., 2009) and also in the developing world (Singer et al., 1993). While the KPS scores indicate that the effect of pain on performance status was not fully appreciated by the doctors treating my study participants, it probably is unrealistic to expect the KPS to be a sensitive enough tool for making an assessment of doctor-rated functional interference when the fact that the patient is ambulatory immediately means that the rater will give a minimum score of 70%. Therefore other performance status assessment tools should be looked into when conducting studies investigating performance status in ambulatory patients.

In terms of risk factors for having pain, I found antiretroviral therapy to be independently associated with the reduced risk of pain in the rural cohort. HAART increases patients CD4 T-cell counts and decreases viral loads thus decreasing the opportunistic infections, which can cause pain. Rural patients are known to present at the healthcare facilities when the pain is unbearable (Tollefson and Usher, 2006), thus one can conclude that the reduced risk of pain due to HAART could be related to the benefits of HAART in alleviating opportunistic infections which cause pain. In the metropolitan cohort, increasing age was weakly, but independently associated with having pain. In a population-based study conducted in

Zambia, the authors found the proportion of poor self-rated health status increased linearly with age (Siziya and Fylkesnes, 2005). They found that patients who were 24 years and older, infected with HIV and living in the urban area were twice as likely to rate their health status as poor compared to respondents who were not infected with HIV. Thus with a negative correlation that HIV infection had on self-rated health in persons of age greater than 24 years, and living in the urban area, I can speculate why age was independently associated with having pain in the metropolitan cohort. In my study, age was also associated with increased risk of HIV-SN, and there may have been more HIV-SN (more foot pain) in the metropolitan cohort as compared with the rural cohort, thus the association was detected in the metropolitan cohort but not in the rural cohort.

The reason for the discrepancy in risk factors between the rural and metropolitan cohorts is not obvious. Harding and colleagues (2006) have reported that the association between antiretroviral therapy and reduced risk of pain is not common, and in my study, in the metropolitan cohort, being on antiretroviral therapy was not associated with the reduced risk of having pain. One South African study, undertaken in a resource-poor HIV population reported a low CD4 T-cell count to be associated with increased prevalence of neuopathic pain (Hitchcock *et al.*, 2008). As it has been similarly reported in other South African studies, I found CD4 T-cell counts to be independently associated with having pain (O'Keefe and

Wood, 1996; Peltzer and Phaswana-Mafuya, 2008; Van As *et al.*, 2009), maybe because patients who are HIV-positive without pain delay the consultation that leads to their diagnosis.

Pain under-treatment

Pain in patients who are HIV-positive is often under-estimated by doctors even when the patient presents to the hospital due to pain (Hewitt et al., 1997). This under-estimation of pain and other symptoms accompanying HIV infection appears to be a universal problem (Breitbart *et al.*, 1996b; Karus *et al.*, 2005; Larue *et al.*, 1997; Maree *et al.*, 2011; Nair *et al.*, 2009; Narasimooloo *et al.*, 2011; Peltzer and Phaswana-Mafuya, 2008).

The pharmacological management of pain in my study participants was very poor, with 29% of rural participants and 55% of metropolitan participants with pain not receiving any pain treatment. Thus many participants in my study who were in pain received no analgesics, and even those who were given analgesic medication, were given medication that, in general, had low analgesic strength. This phenomenon of lack of treatment and under-treatment of HIV-related pain has been reported before in South African HIV-positive patients in the setting of chronic pain and hospitalisation (Maree *et al.*, 2011; Narasimooloo *et al.*, 2011). Also participants in my study that reported severe pain were not prescribed opioids, a finding that have previously been reported in African patients, where patients are denied opioids (Harding *et al.*, 2010; Maree *et al.*,

2011). The under-treatment of pain is not limited to sub-Saharan Africa. In an India study, Nair and colleagues (2009) have reported that less than one-third of out-patients with pain received analgesics, whereas none of these patients received an opioid. In addition, in Brazilian inpatients, approximately two-thirds of patients were receiving no analgesic therapy but less than 10% were receiving opioids of any kind despite about 90% of patients having moderate-to-severe pain (Aires and Bammann, 2005). Thus this poor treatment of HIV-related pain is not unexpected in low-resource countries because of high barriers to treatment, such as poor human resources, infrastructure and financial resources, needed for effective healthcare in these regions. It could be that there is a lack of access to pain medications, especially opioids, but these limitations in provision occur at all levels of the supply chain, even when there is government commitment to implement pain services (Harding *et al.*, 2010). As previously mentioned, Africa has the lowest consumption of opioid analgesics of all regions. There are several factors that contribute to this low opioid consumption, and general under-servicing of pain in sub-Saharan Africa, but adequate provision of palliative services is a likely contributor (Harding *et al.*, 2010). It also has been found that there is resource limitation and care-giver barriers to pain management in sub-Saharan Africa (Maree *et al.*, 2011). The researchers assessed pain management in patients who are HIV-positive with chronic pain attending an outpatient clinic in South Africa. Almost all patients were receiving analgesics, but these analgesics were limited to paracetamol

(acetaminophen) and/or ibuprofen in 99% of cases, because codeine was not available for dispensing, despite the South African guidelines indicating the use of codeine for the management of pain in patients infected with HIV. In their study, less than 10% of prescriptions at the clinic complied with the government guideline, and, in over 80% of cases, drugs were prescribed at insufficient doses or tablet numbers to last the patient until the next clinic appointment. In comparison to the abundant data, from multiple settings, for absence of treatment and under-treatment of HIV-related pain, there is a lack of information on the efficacy of the available treatments, based on the gold standard of patient self-report of pain relief.

Participants in my cohort reported good pain relief, from medication not strong enough to have alleviated the intensity of their pain, maybe due to a placebo effect. My comparison of self-reported pain relief and pain management index (PMI) data is unique to my study and reveals the short-comings of the PMI with regards to assessing treatment efficacy (a multi-factorial response that incorporates not only the effects of the drugs used, but the psychosocial issues related to the act of being listened to and being treated) compared to its real use in assessing whether the treatment recommendations of the WHO analgesic ladder have been systematically followed; itself an invalidated treatment approach for HIV-related pain.

In summary, my research has provided much needed data on the prevalence and characteristics of pain and its management in ambulatory

HIV-positive patients in two settings (metropolitan and rural) in South Africa, the country worst affected by the HIV epidemic. When comparing my data to that of other studies conducted in Africa and other regions of the world, there is a striking consistency in the findings that pain is common and is under-treated in this often indigent patient group irrespective of geographical location. However, the burden of pain and the extent of its under-treatment in the HIV-positive population relative to the same population, but who are HIV-negative remains unknown. This gap in the literature needs to be addressed before a true assessment of the additional burden contributed by HIV infection to pain prevalence, intensity and treatment can be made. Also, if patients appear to be coping with their pain, and if the doctors are themselves not particularly concerned about the pain, then patients will continue to be under-treated.

Chapter 4: Changes in pain prevalence and characteristics over time

At the time of my data collection, to my knowledge, there were few longitudinal studies that had investigated the prevalence and treatment of HIV-related pain (Aires and Bammann, 2005; Brechtl *et al.*, 2001; Frich and Borgbjerg, 2000; Singer *et al.*, 1993). A South African-based study published after I had collected my data also reported a time-dependent decrease in pain prevalence in their study cohort which they related to improvements in the patients' CD4 T-cell counts and decreases in the viral loads (Rosen et al., 2010). The study's primary focus, however, was on

the improvement in patients' functionality, employment and symptoms prevalence, including pain, when exposed to antiretroviral drugs whereas my study dealt with a mixed cohort of patients (on stable antiretroviral therapy, not on therapy, and starting therapy), typical of what would be expected in an outpatient clinic.

Another study that was published after I had completed my data collection was the study by Koeppe and colleagues (2012). These authors reported that in 127 patients who are HIV-positive with chronic pain, who were followed up (median of 5.2 years- range of patient follow-up of 2.0 to 7.6 years), that there was a positive association between decreasing pain and the use of HAART endorsing the fact that HAART increases the CD4 T-cell counts and decreases the viral loads thus decreasing the opportunistic infections that sometimes lead to pain. The authors also found a negative correlation between decreasing pain and the use of opioid analgesics. The authors speculated that the negative correlation was due to some patients reporting pain scores out of proportion to what they were really experiencing in an attempt to obtain opioid analgesics for their nonanalgesic properties. Thus, these results could be seen more in regions where the prevalence of addiction to opioids or morphine is great.

I have seen an increase in the percentage of prescribed analgesics, excluding opioid analgesics, in patients who were still in pain six months

after the initial interview. These increases in prescribed analgesics could rather be related to patients' continuous complaints to their doctors.

Thus, although I and other researchers have reported that in general there is a decrease in the prevalence and intensity of pain in HIV-infected individuals over time, none of us could determine whether the decreases observed was due to good pain management, good disease management, or simply regression to the mean. Longitudinal studies are therefore needed to further investigate the pain management, incorporating disease management.

With most patients who are HIV-positive now initiated and stable on HAART (Nakagawa *et al.*, 2012), these patients live longer and the focus of HIV care and research has shifted from finding the best antiretroviral regimen to managing highly prevalent comorbid conditions related to aging, such as cardiovascular disease, cirrhosis, and non-AIDS-defining malignancies, and optimizing quality of life (Perry *et al.*, 2013). It is therefore likely that chronic unremitting pain or multiple acute recurrent pains will have a large impact on long-term health-related quality of life of HIV-infected individuals, especially as increasing numbers of individuals gain access to antiretroviral therapy and therefore live longer. HIV infection has become a chronic, manageable disease athough the recognition and management of the pain that accompany HIV infection is still unclear.

Therefore it is important for us to ascertain the true long-term burden of pain, and the nature of that pain (chronic versus acute versus acute-on-chronic) in the modern era of HIV. We should however not forget that barriers such as inadequate human, infrastructural, or financial resources in resource poor countries may increase the problem of under-recognition and under-treatment of HIV-related pain. There have been numerous clinical trials of agents used to treat HIV-associated sensory neuropathiy (almost all negative), but none for other HIV-related pains. This lack of evidence for effective treatments means that new studies on treatment are essential. At the very least validation of the effectiveness of using the WHO analgesic ladder as an approach to pain management in the ambulatory HIV-positive population is needed. I therefore suggest that long-terms studies involving bigger sample sizes, patients with diverse disease staging and therapies are needed.

In conclusion, I have shown decreases in the pain intensity, pain prevalence, the number of pain sites and also decrease in chest pain over a period of six months, in ambulatory patients who were HIV-positive attending an outpatient clinic in a metropolitan area. These decreases were evident in patients who were on HAART for the duration of six months as compared to those who were not on HAART for six month.

CHAPTER 6

APPENDICES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Mphahlele

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M041112**
PROJECT	Pain Management in Patients Infected with Human Immunodeficiency Virus
INVESTIGATORS	Ms NR Mphahlele
DEPARTMENT	School of Physiology
DATE CONSIDERED	04.11.26
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 05.02.07 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : P Kamerman

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B

HIV PAIN

BRIEF PAIN QUESTIONNAIRE

Patient Reference Number: ……

Date: ……..

Dear Patient,

Please read and answer the questions below. We are interested in your answers even if you do not have pain. If you haven't had pain in the last month, you only need to answer the first four questions on pages 1 to 2. Please note that this is a voluntary procedure, and your treatment will not be affected if you choose not to fill in this questionnaire.

We are conducting a study of pain, its severity and its treatment. We want to compare the results of this questionnaire in different medical conditions. In order to do this, we might need to access your hospital records. All information will be kept confidential; known only to the study group. Also, we might contact you at a future date if we want more information. However, you are not obligated to answer any future questions just because you fill out this questionnaire. There is a university phone number on the last page, which you may call if you have any questions about the study.

If you agree to the study described here, please sign the last page.

---

1. When you first received your diagnosis, was pain one of your symptoms? Please tick an appropriate box.

□ Yes □ No

2. If you answered yes to the above question, cross one of the following boxes.

□ Pain was a reason I went to the doctor

□ Pain present but not reason for doctor visit

3. Have you **ever** had pain due to your present disease? Please tick an appropriate box.

□ Yes □ No □ uncertain

4. Have you **ever** had surgery in the past month? Please tick an appropriate box.

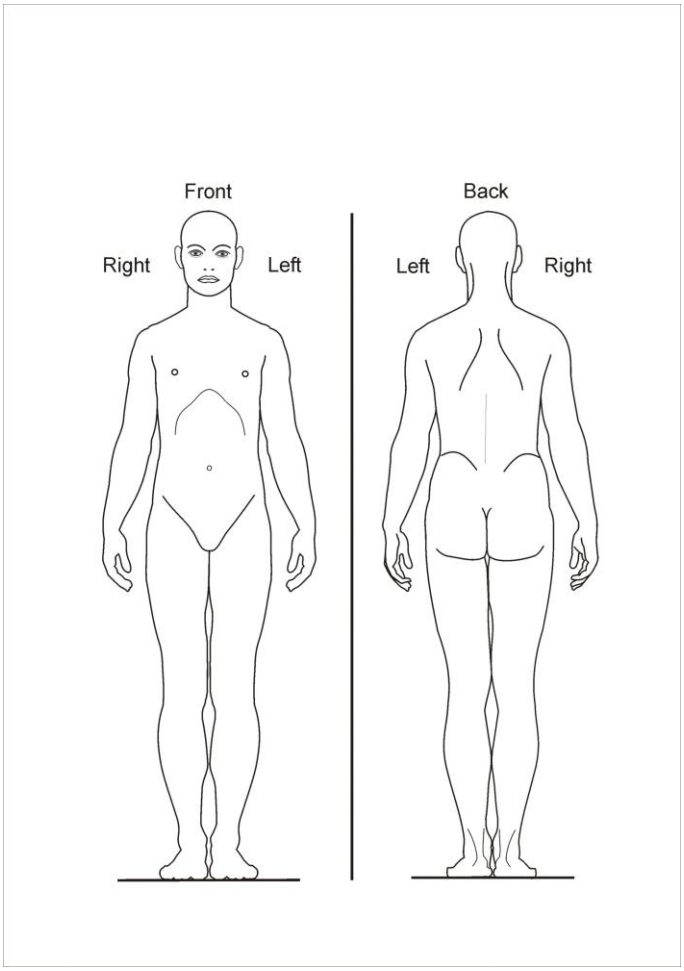
□ Yes □ No

5. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday kinds of pain during the last month? Please tick an appropriate box.

□ Yes □ No

If you answered yes to the last question, please answer all the following questions in this questionnaire.

6. Indicate on this diagram where your pain occurs by **shading** the painful area.
Label the drawings with “S” for pain near the surface of your body or with “D” for pain that is deeper. Also, indicate where your **PRIMARY** pain is located.



7. Please rate your pain by circling the **one** number that best describes your pain at its **worst** in the last month. (A rating of 10 would indicate pain so severe as to prohibit all activity; the worst pain you can imagine).

0	1	2	3	4	5	6	7	8	9	**10**
No Pain										Pain as bad as you can imagine

8. Please rate your pain by circling the **one** number that best describes your pain at its **least**. (A rating of 10 would indicate pain so severe as to prohibit all activity; the worst pain you can imagine).

0	1	2	3	4	5	6	7	8	9	**10**
No Pain										Pain as bad as you can imagine

9. Please rate your pain by circling the **one** number that best describes your pain on the **average**. (A rating of 10 would indicate pain so severe as to prohibit all activity; the worst pain you can imagine).

0	1	2	3	4	5	6	7	8	9	**10**
No Pain										Pain as bad as you can imagine

10. Please rate your pain by circling the **one** number that tells how much pain you have **right now**.

0	1	2	3	4	5	6	7	8	9	**10**
No pain										Pain as bad as you can imagine

11. What treatments or medications are you receiving for your pain?

(i) ……

(ii) ……...

(iii) ……...

12. How much relief do pain treatments or medications provide? (Please circle the one percentage that shows how much relief you receive).

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	**100%**
No Relief										Complete Relief

13. What do YOU think is the cause of your pain?

(i) ……

(ii) ……

(iii) ……

14. During the past week how much did the state of your health, including any pain, interfere with the following things: choose the one number, from 0 to 4 below, that best describes your state and write them in the appropriate box (i to vi).

0 Not al all
1 A little bit
2 Moderately
3 Quite a bit
4 Extremely

i. ☐ MOOD

ii. ☐ RELATIONS WITH OTHER PEOPLE

iii. ☐ WALKING ABILITY

iv. ☐ SLEEP

v. ☐ NORMAL WORK (includes both work outside the home and housework)

vi. ☐ ENJOYMENT OF LIFE

OTHER (specify) ……

1. Yes ……
2. No

15. Marital status: Please circle or choose one option.

1. Single
2. Married
3. Divorced
4. Widowed
5. Separated

16. Education …….. highest level

17. Occupation …….. (if you are not working tell us your previous occupation)

Spouse's occupation ……

18. How long has it been since you learned about your diagnosis?

…….. days
…….. weeks
…….. months
…….. years

AUTHORIZATION: I have read the description of the "Brief Pain Questionnaire" study and decide to participate in the research project described here. I understand there is a possibility I might be contacted in the future about this but that I am free to refuse any further participation if I wish.

…….. ……
Patient's Signature Date

…… ……
Interviewer or Investigator's Signature Date

Principal Investigator: Ms Noko Mphahlele

Address: School of Physiology, Brain Function Research Unit
University of the Witwatersrand, Medical School
7 York Road, Parktown, Johannesburg, 2193

Telephone: 011 717 2254/2363 **Fax:** 011 643 2765

IMINJUNJU KU HIV

IMIBUZO EMIFUSHA MALUNGANA NEMINJUNJU

Inombolo yeSiguli: ……

Usuku: ……

Siguli Esithandekayo,

Uyacelwa ukuba ufunde bese uphendula imibuzo engezansi. Sinentshisekelo yokuzwa izimpendulo zakho ngisho noma ungenazo izinhlungu. Uma ungazange waba neminjunju enyangeni edlule, kudinga uphendule kuphela imibuzo emine yokuqala esekhasini 1 kuya ku 2. Qaphela ke ukuthi lenkambiso ayinampoqo ingeyokuzikhethela, kanti ukwelashwa kwakho akuzuthinteka uma ukhetha ukungayiphenduli lemibuzo.

Siqhuba ucwaningo malungana nezinhlungu, ukuqaqamba kwazo kanye nokwelashwa kwazo. Sifuna ukuqhathanisa imiphumela yale mibuzo ngaphansi kwezimo ezehluka hlukene zokwelapha. Ukuze sikwenze lokhu, sidinga inombolo yakho yasesibhedlela, kumbe usuku lwakho lokuzalwa ukuze sithole imininingwane ephathelene namarekhodi akho. Lonke ulwazi luzokugcinwa luyimfihlo; luzokwaziwa kuphela yilabo abasethimbeni locwaningo. Futhi ke, singahle sikuthinte esikhathini esizayo uma sidinga eminye imininingwane. Kodwa ke, awunaso isibopho sokuphendula eminye imibuzo ngesikhathi esizayo ngoba nakhu uphendule lena. Kukhona inombolo yocingo yasenyuvesi esekhasini lokugcina, ongayishayela uma unemibuzo noma imiphi mayelana nalolu cwaningo.

Uma uvuma ukuzimbandakanya kulolu cwaningo oluchaziwe lapha, uyacelwa ukuba usayinde ekhasini lokugcina.

UYACELWA UKUBA UBHALE INOMBOLO YAKHO YASESIBHEDLELA KANYE NOSUKU LWAKHO LOKUZALWA LAPHA

Inombolo yesiguli : …… Usuku lokuzalwa: ……

---

1. Ngesikhathi kutholakala isifo kuwena **okokuqala** kungabe wawunenzinhlungu yini? Faka uphawu ebhokisini eliqondene nempendulo.

   □ Yebo □ Cha

2. Uma uphendule wathi “yebo” embuzweni ongenhla, faka isiphambano kwelinye lalawa mabhokisi alandelayo.

- □ Izinhlungu kwakuyisona sizathu sokuya kwami kwadokotela
- □ Zazikhona izinhlungu kodwa zazingeve ziyisizathu sokuya kwadokotela

3. **Wake** waba nazo izinhlungu ngenxa yesifo esikuphethe manje? Sicela ufake uphawu ebhokisini elifanele.

□ Yebo □ Cha □ ngiyangabaza

4. Uke wahlinwa kulenyanga eyedlule? Faka uphawu ebhokisini eliqondene nempendulo.

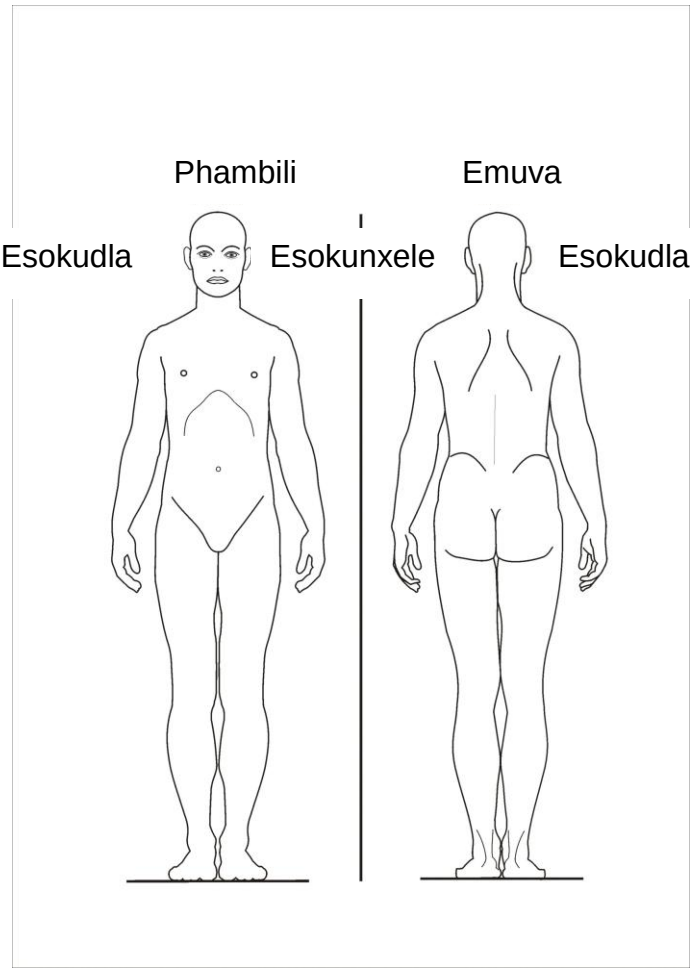
□ Yebo □ Cha

5. Ngokuqhubeka kwezimpilo zethu, abaningi bethu baye bahlangabezane nezinhlungu izikhathi ngezikhathi (njengokuphathwa yikhanda, ukwenyela, ukuphathwa amazinyo). Usuke waba nazo ezinye izinhlungu ngaphandle kwalezi ezejwayelekile enyangeni eyedlule? Uyacelwa ukuthi ufake uphawu ebhokisini elifanelekile.

□ Yebo □ Cha

Uma uphendule wathi Yebo kumbuzo wokugcina, uyacelwa ukuba uphendule umbuzo olandelayo kuloluhlu lwemibuzo.

6. Khombisa ukuthi uba nezinhlungu kuphi **ngokwakha ithunzi** kulomfanekiso kulezo ndawo ezibuhlungu.
Kumidwebo, faka u “S” uma ufuna ukukhombsa iznhlungu ezisothwethwesini eduze kwesikhumba, bese ufaka u “D” ukukhombisa izinhlungu ezidephile. Futhi khombisa ukuthi kukuphi lapho okunobuhlungu **OBEDLULELE** khona.



7. Uyacelwa ukuthi ukhombise izinga lobuhlungu obuzwayo ngokuzungeza inombolo **eyodwa** okuyiyona ilichaza njengoba izinga **eliphezulu** kunazo zonke lezinhlungu osuke wazizwa kulenyanga eyedlule. (Izinga likhomba izinhlungu eziqaqamba ngendlela yokuthi wehluleka ngisho ukwenzani; ubuhlungu obedlulele kubona bonke ongase ubucabange).

0	1	2	3	4	5	6	7	8	9	**10**
Abukho Ubuhlungu								Ubuhlungu obukhulu ngendlela engakaze ibonakale		

8. Uyacelwa ukuthi ukhombise izinga lobuhlungu obuzwayo ngokuzungeza inombolo **eyodwa** okuyiyona ilichaza njengoba izinga **eliphansi** kunawo onke ezinhlungu osuke wazizwa. (Izinga 10 likhomba izinhlungu eziqaqamba ngendlela yokuthi wehluleka ngisho ukwenzani; ubuhlungu obedlulele kubona bonke ongase ubucabange).

0	1	2	3	4	5	6	7	8	9	**10**
Abukho Ubuhlungu									Ubuhlungu ngendlela	obukhulu engakaze ibonakale

9. Uyacelwa ukuba ukhombise izinga lezinhlugu zakho ngokuba uzungeze inombolo **eyodwa** okuyiyona ichaza ubuhlungu obuzwayo **njengamanje.**

0	1	2	3	4	5	6	7	8	9	**10**
Abukho Ubuhlungu									Ubuhlungu ngendlela	obedlulele engecatshangwe

10. Kungabe kwelashwa kuni kumbe makhambi mani owatholela izinhlungu?

    (i) ……

    (ii) ……

    (iii) ……

11. Lokhu kwelashwa namakhambi kungabe kuzidambisa kangakanani izinhlungu? (Kekelezela iphesenti okuyilona likhombisa ubungako **bokudamba** oye ukuthole).

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	**100%**
Akubi Khona										Ziphela Nya

12. Kungabe WENA ke, ucabanga ukuthi yini imbangela yezinhlungu zakho?

    (i) ……

    (ii) ……

    (iii) ……

13. Esontweni eledlule, kungabe isimo sempilo yakho, kumbandakanya nezinhlungu, sibe nomthelela omngakanani kulokhu okulandelayo: khetha inombolo eyodwa, kusuka ku 0 kuya ku 4 ngezansi, okuyiyona isichaza kangcono isimo sakho bese uzifaka ebhokisini eliqondene (I kuya ku iv).

0 Awubanga bikho nhlobo
1 Kuthinteke kancane
2 Kuthintekile nje
3 Kuthintekile impela
4 Kuthinteke kakhulu

i. ☐ UBUDLELWANO NABANYE ABANTU

ii. ☐ UKUKWAZI UKUHAMBA

iii ☐ UMSEBENZI OWEJWAYELEKILE (kumbandakanya umsebenzi wangaphandle kwasekhaya nomsebenzi wasekhaya)

iv. ☐ UKWESASELA IMPILO

OKUNYE (chaza) ……

1. Yebo ……
2. Cha

15. Ukugana: Uyacelwa ukuba uzungeze okufanele okukodwa.

1. Angiganile/niwe
2. Ngishadile
3. Ngehlukanisile
4. Ngafelwa
5. Sihlukene

16. Imfundo …….. Izinga eliphezulu impela

17. Umsebenzi …….. (uma ungasebenzi sitshele umsebenzi owawuwenza phambilini)

Umsebenzi womlingani wakho ……

18. Wathola nini ngesigulo sakho?

…….. izinsuku
..... amasonto
..... izinyanga
..... iminyaka

IGUNYA: Sengiyifunde yonke incazelo yocwaningo “lohla olufushane lwemibuzo ngezinhlungu” futhi nginquma ukubamba iqhaza kulolu cwaningo oluchazwe lapha. Ngiyaqonda ukuthi ngingahle ngithintwe esikhathini esizayo mayelana nalokhu, nanokuthi ngikhululekile ukungavumi ukuzimbandakanya ngesikhathi esizayo uma ngifisa kanjalo.

…….. ……
iSayini yeSiguli Usuku

…… ……
iSayini yoMcwaningi Usuku

UMcwaningi oMkhulu: uNksz Noko Mphahlele

I**kheli:** Isikole se Physiology, isiZinda esiCwaninga ngokuSebenza kweNgqondo iNyuvesi yase Witwatersrand, Esikoleni sezokwelapha nemithi
7 York Road, Parktown, Johannesburg, 2193

Ucingo: 011 717 2254/2363 **IFeksi:** 011 643 2765

INTLUNGU YE-HIV

IPHEPHA LEMIBUZO ENGENTLUNGU YOMZUZWANA

Inombolo yesigulane: ……

Umhla: ……

Sigulane esithandekayo,

Nceda funda uze uphendule imibuzo engezantsi.Sinomdla kwiimpendulo zakho nokuba awuva ntlungu. Ukuba awukhange uve ntlungu kwinyanga ephelileyo, kufuneka uphendule kuphela imibuzo emine kumaphepha 1 & 2. Nceda yiqaphele ukuba le yinkqubo yokuzithandela kwaye ayisayi kuchaphazela unyango lwakho ukuba ukhetha ukungalizalisi eli phepha lemibuzo.

Senza uphando ngentlungu, ukuhlaba ngamandla kwayo nonyango lwayo. Sifuna ukuthelekisa iziphumo zeli phepha lemibuzo kwiimeko ezahlukeneyo zonyango. Ukuze sikwenze oku, sifuna inombolo yakho yasesibhedlele okanye umhla wokuzalwa ukuze sifumane ulwazi ngeerekhodi zakho. Lonke ulwazi luya kugcinwa luyimfihlo, luya kwaziwa kuphela liqela lofundo. Kwakhona , sisenokuqhagamshelana nawe kwixa elizayo ukuba sifuna olunye ulwazi oluthe vetshe. Phofu ke, awunyanzelekanga ukuba uphendule nayiphi na imibuzo yexesha elizayo ngenxa yokuba uzalise eli phepha lemibuzo. Kukho inombolo yeyunivesithi kwiphepha lokugqibela onokufowunela kuyo ukuba unemibuzo malunga nolu fundo.

Ukuba uyavuma ukuba kolu fundo luchazwe apha, nceda sayina iphepha lokugqibela.

NCEDA BHALA APHA INOMBOLO YAKHO YASESIBHEDLELE NOMHLA WOKUZALWA

Inombolo yesigulane : ……Umhla wokuzalwa

---

1. Xa kwafunyaniswa ngoxilongo **okokuqala** ukuba unesifo, ingaba intlungu yayiyenye yeempawu? Nceda yenza uphawu kwibhokisi efanelekileyo.

   □ Ewe □ Hayi

2. Ukuba uphendule ewe kumbuzo ongasentla, hlaba enye yezi bhokisi zilandelayo.

- Intlungu yiyo eyabangela ukuba ndiye kugqirha
- Intlungu yayikho kodwa ayiyiyo eyandenza ndaya kugqirha

3. Ingaba **wawukhe** wanentlungu ngenxa yesi sifo unaso ngoku? Nceda phawula ibhokisi efanelekileyo.

- Ewe
- Hayi
- andiqinisekanga

4. Ingaba ukhe wahlinzwa kwinyanga edlulileyo? Nceda phawula ibhokisi efanelekileyo..

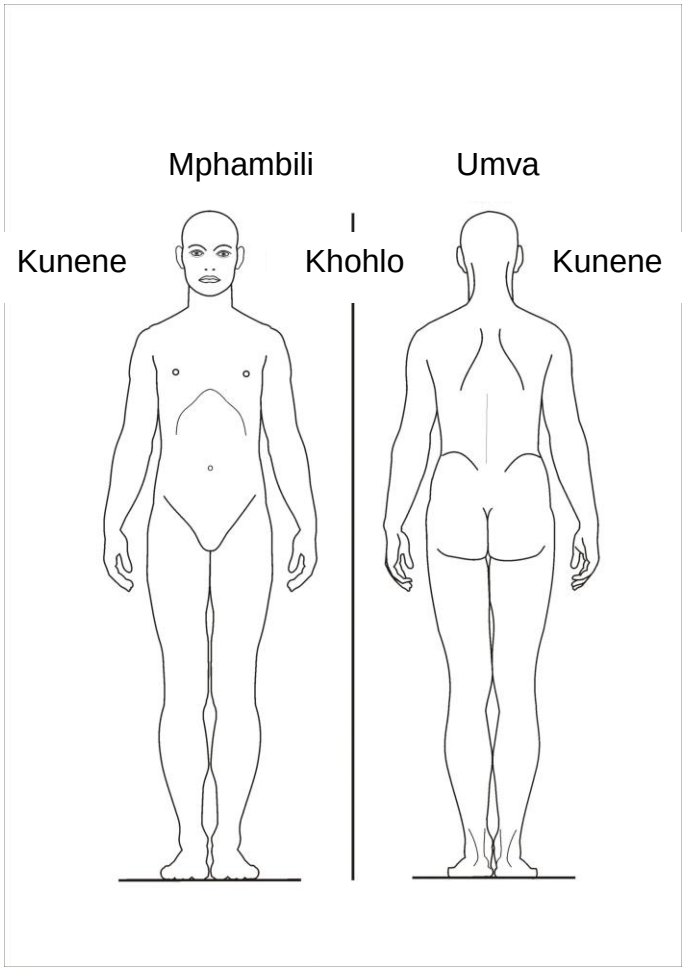
- Ewe
- Hayi

5. Kubomi bonke bethu uninzi lwethu lukhe lweva intlungu amaxesha ngamaxesha (njengentloko ebuhlungu , ukukruneka,nokuqaqanjelwa lizinyo). Ingaba ukhe wanentlungu ngaphandle kwezi zemihla ngemihla kule nyanga edlulileyo? Nceda yenza uphawu kwibhokisi efanelekileyo.

- Ewe
- Hayi

Ukuba uphendule ewe kumbuzo wokugqibela, nceda phendula yonke imibuzo elandelayo kweli phepha lemibuzo.

4. Bonisa kulo mzobo apho uyiva khona intlungu **ngokuhlikihla** le ndawo ibuhlungu. Lebhelisha imizobo ngo “S” xa intlungu isemazantsi kumzimba wakho okanye ngo”D” xa intlungu inzulu. Kwakhona bonisa indawo ekuyo intlungu yakho **EPHAMBILI.**



7. Nceda bonisa ubungakanani bentlungu yakho ngokuba wenze isangqa kwinani **elinye** eliyichaza kakuhle intlungu **egqithisileyo** obunayo kwinyanga edlulileyo.
(Inani 10 libonisa eyona ntlungu imandundu ekwenza ungakwazi ukwenza nantoni na, eyona ntlungu igqithisileyo).

0	1	2	3	4	5	6	7	8	9	**10**
Akukho Ntlungu										Eyona ntlungu igqithisileyo

8. Nceda bonisa ubungakanani bentlungu yakho ngokuba wenze isangqa kwinani **elinye** elichaza kakuhle intlungu yakho **engephi**. (Inani 10 libonisa eyona ntlungu imandundu ekwenza ungakwazi ukwenza nantoni na, eyona ntlungu igqithisileyo).

0	1	2	3	4	5	6	7	8	9	**10**
Akukho Ntlungu										Eyona ntlungu Igqithisileyo

9. Nceda bonisa ubungakanani bentlungu yakho ngokuba wenze isangqa kwinani **elinye** elichaza kakuhle intlungu yakho **ngalo mzuzu.**

0	1	2	3	4	5	6	7	8	9	**10**
Akukho Ntlungu										Eyona ntlungu igqithisileyo

10. Ufumana oluphi unyango okanye awaphi amayeza okunyanga intlungu yakho?

    (i) ……

    (ii) ……

    (iii) ……

11. Olu nyango okanye la mayeza ayiphungula kangakanani intlungu? (Nceda yenza isangqa kwipesenti enye ebonisa ukuba ufumana isiqabu esingakanani).

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	**100%**
Akukho Ithomalala										Siqabu gokupheleleyo intlungu

12. Ucinga ukuba yintoni engunobangela wentlungu yakho?

    (i) ……

    (ii) ……

    (iii) ……

13. Kwiveki edlulileyo ingaba imo yempilo yakho , kuqukwa nayiphi intlungu iziphazamise kanjani ezi zinto zilandelayo: khetha inani elinye ukusuka ku-1 uye ku-4 ngezantsi elibonisa imo yakho uze uwabhale kwibhokisi efanelekileyo (i –vi)

0 Khange konke
1 Kancinane
2 Phakathi nje
3 Ngokubonakalayo noko
4 Ngamandla

i. ☐ IMO

ii. ☐ UBUDLELWANE NABANYE ABANTU

iii. ☐ UKUKWAZI UKUHAMBA

iv. ☐ UKULALA

v ☐ UMSEBENZI WESIQHELO (kuqukwa umsebenzi ongengowasekhaya nowasekhaya)

vi. ☐ ULONWABO

EZINYE (xela) ……
1. Ewe ……
2. Hayi

14. Imo yomtshato: Nceda yenza isangqa okanye ukhethe ibenye.

1. Anditshatanga
2. Nditshatile
3. Uqhawulwe umtshato
4. Mhlolo/kazi
5. Sahlukene

15. Imfundo …….. inqanaba eliphezulu

16. Umsebenzi …….. (ukuba awusebenzi sixelele umsebenzi owawuwenza ngaphambili)

Umsebenzi womlingane ……

17. Lixesha elingakanani usazi ngesi sifo? …….. iintsuku
…… iiveki
…… iinyanga
…… iminyaka

UGUNYAZISO: Ndiyifundile inkcazelo yofundo engePhepha lemibuzo engeNtlungu yoMzuzwana" kwaye ndenza isigqibo sokuthatha inxaxheba kolu phando lofundo luchazwe apha. Ndiyaqonda ukuba kusenokuqhagamshelwana nam kwixa elizayo malunga nolu fundo kodwa ndikhululekile ukuba ndingala ukuthatha inxaxheba kwakhona ukuba ndiyafuna.

…….. ……
Utyikityo lwesigulane Umhla

…… ……
Utyikityo lalowo oqhuba udliwanondlebe Umhla

Umphandi oyiNtloko: Nkosz Noko Mphahlele

Idilesi: School of Physiology, Brain Function Research Unit
University of the Witwatersrand, Medical School
7 York Road, Parktown, Johannesburg, 2193

Ifowuni: 011 717 2254/2363 **Ifeksi:** 011 643 2765

BOHLOKO BJA HIV

LETLAKALANYAKIŠIŠO LE LE KOPANA KA GA BOHLOKO

Nomoro ya Molwetši:……

Tšatšikgwedi:……

Molwetši yo a rategago,

Ka kgopelo bala le go araba dipotšišo tše latelago. Re duma go kwa dikarabo tša gago le ge eba ga o na sehlabi. Ge e le gore ga se wa ka wa ba le sehlabi/bohloko mo kgweding ya go feta, o tla araba fela dipotšišo tše nne tša mathomo letlakaleng la 1 le 2. O lemošwa gore ga o gapeletšwe go dira se gomme le kalafo ya gago e ka se emišwe ge o ka kgetha go se tlatše letlakalanyakišišo le.

Re dira dinyakišišo ka bohloko/sehlabi, bogolo le kalafo ya bjona. Re rata go bapetša dipoelo tša letlakalanyakišišo le maemong a a fapanego a tša kalafo. Go phethagatša se, re tsoma nomoro ya gago ya sepetlele goba matswalo a gago gore re kgone go hwetša tshedimošo mabapi le direkoto tša gago. Ditaba ka moka mabapi le wena e tla dula e le sephiri; di tla tsebja fela ke sehlopha sa dinyakišišo. Gape, re ka ikopanya le wena mo lebakeng le le tlago ge re ka tsoma tshedimošo ye nngwe gape. Eupša ga o gapeletšege go araba dipotšišo tše dingwe ka moso ka lebaka la ge o ile wa tlatša letlakalanyakišišo le. Ge o ka ba le potšišo efe goba efe mabapi le dinyakišišo tše, o ka leletša nomoro ya Yunibesithi yeo e lego letlakaleng la mafelelo.

Ge o dumela go kgatha tema go dinyakišišo tše hlalositšwego fa, re kgopela gore o saene letlakala la mafelelo.

KA KGOPELO NGWALA NOMORO YA GAGO YA SEPETLELE LE MATSWALO A GAGO MO

Nomoro ya Molwetši:…… Matswalo: ……

---

1. Nako ya ge o hwetša dipoelo tša tlhahlobo ya bolwetši bja gago la **mathomo** naa go kwa bohloko e bile se sengwe sa dika tšeo o bilego le tšona?
   Ka kgopelo swaya lepokisi la maleba.

   □ Ee □ Aowa

2. Ge karabo ya potšišo ya ka godimo e le ee, thala sefapano ka gare ga le lengwe la mapokisi a a latelago.

 Bohloko e bile seo se nkišitšego ngakeng

 Bohloko bo bile gona eupša ga se lebaka le le nkišitšego ngakeng

3. A o kile wa ba le sehlabi ka baka la bolwetši bjo o nago le bjona gonabjale? Ka kgopelo swaya lepokisi la maleba.

 Ee Aowa Ga ke na nnete

4. A o kile wa ba le opareišene mo kgweding ya go feta? Ka kgopelo swaya lepokisi la maleba.

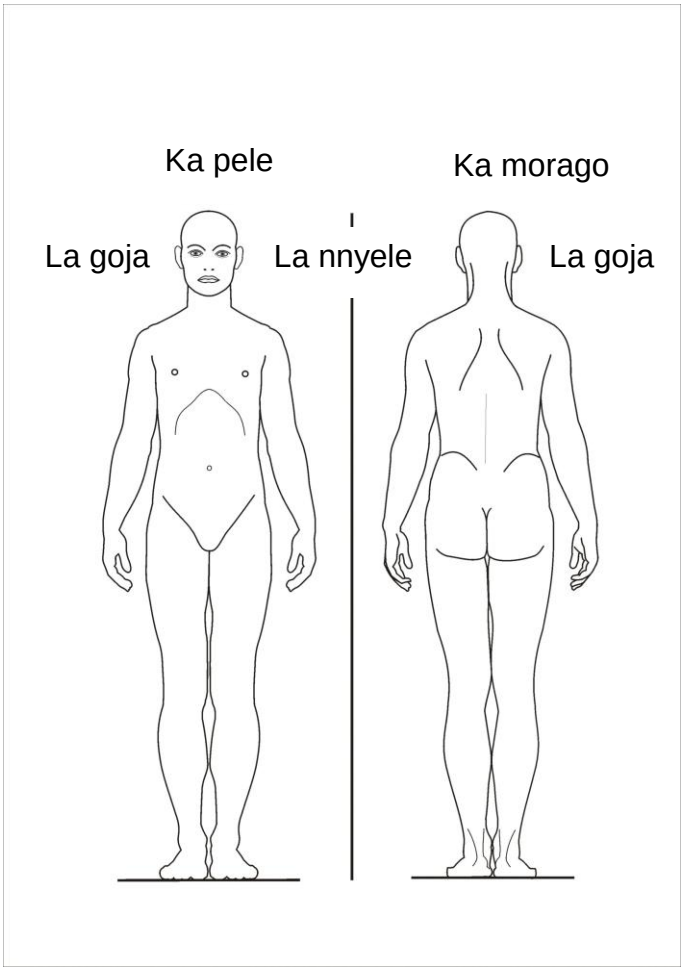
 Ee Aowa

5. Mo lebakeng la go phela ga rena, bontši bja rena re bile le dihlabi nako le nako (go swana le go rengwa ke hlogo e nnyane, go thinyega le go opša ke meno). Naa o kile wa ba le sehlabi se sengwe ntle le tše tša ka mehla mo lebakeng la kgwedi ya go feta? Ka kgopelo swaya lepokisi la maleba.

 Ee Aowa

Ge karabo ya gago go potšišo ya mafelelo e bile ee, o kgopelwa go araba dipotšišo tše di latelago ka moka tša letlakalanyakišišo.

6. Laetša godimo ga seswantšho ka go **tsikitla** lefelo leo o kwago bohloko gona. Laetša ka leswao la “S” godimo ga diswantšho lefelo leo o kwago bohloko bjo sa tsenelelago mmeleng goba leswao la “D” lefelong leo bohloko bo tsenelelago mmeleng. Gape, laetša fao bohloko bjo **BOGOLO** bo lego gona.



7. Ka kgopelo ela bohloko bjo o bo kwelego ka go thala sediko nomorong e **tee** yeo e laetšago gabotsebotse bohloko bjo **šorošoro** o bo kwelego mo kgweding ya go feta. (Kelo ya 10 e tla laetša bohlokohloko bjo bo go paledišago go šoma; bohlokohlokohloko).

0	1	2	3	4	5	6	7	8	9	**10**
Ga go bohloko										Bohloko-hlokohloko

8. Ela bohloko bjo o bo kwago ka go thala sediko nomorong e **tee** yeo e laetšago gabotsebotse bohloko bjo **bonyenyanenyenyane** o bo kwelego. (Kelo ya nomoro ya 10 e tla laetša bohlokohloko bja go go palediša go šoma; bohlokohlokohloko).

0	1	2	3	4	5	6	7	8	9	**10**
Ga go bohloko										Bohloko-hlokohloko

9. Ka kgopelo ela bohloko ka go thala sediko nomorong e **tee** yeo e laetšago gore o kwa bohloko bjo kaakang **gonabjale**.

0	1	2	3	4	5	6	7	8	9	**10**
Ga go bohloko										Bohloko-hlokohloko

10. O hwetša kalafo goba dihlare dife go alafa sehlabi/bohloko bja gago?

(i) ……

(ii) ……

(iii) ……

11. Kalafo goba dihlare tše o di dirišago di fokotša bohloko bja gago go go kaakang? Ka kgopelo thala sediko go phesente e tee yeo e laetšago gore o kaonafetše go go kaakang.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	**100%**
Ga go kaonafalo										Bohloko bo fedile

12. Wena o nagana gore bohloko/sehlabi sa gago se hlolwa ke eng?

(i) ……

(ii) ……

(iii) ……

13. Mo bekeng ya go feta, naa boemo bja bophelo bja gago go akaretša bohloko bofe goba bofe, bo amile go go kaakang dilo tše latelago: kgetha nomoro e tee go tloga go 0 go fihla go 4 mo tlase, yeo e laetšago boemo bja gago gabotse gomme o e ngwale ka gare ga lepokisi leo le swanetšego (i-iv).

0 Ga ka amega felo
1 Ganyenyane
2 Magareng
3 Kutšwana
4 Kudukudu

i. ☐ MAIKUTLO

ii. ☐ KAMANO LE BATHO BA BANGWE

iii. ☐ GO KGONA GO SEPELA

iv. ☐ BOROKO

v ☐ MOŠOMO WA KA MEHLA (go akaretša mošomo wa ka ntle le wa ka gae)

vi. ☐ GO IPSHINA KA BOPHELO

SE SENGWE (hlalosa)……

1. Ee ……
2. Aowa ……

14. Maemo a lenyalo: Ka kgopelo thala sediko goba o kgethe e tee.

1. Ga se ka nyala/ nyalwa
2. Ke nyetše/ nyetšwe
3. Hladile
4. Hlokofaletšwe
5. Kgaogane

15. Thuto …….. maemo a godimodimo

16. Mošomo …….. (ge o sa šome laetša mošomo wa mafelelo)

    Mošomo wa mogatšago……

17. Ke lebaka le le kaakang o tseba ka dipoelo tša tlhahlobo ya bolwetši bja gago?

…….. dibeke
…….. dikgwedi
…… mengwaga

TUMELELO: Ke badile tlhalošo ya nyakišišo ya “Letlakalanyakišišo le le kopana ka ga bohloko” gomme ke tšea sephetho sa go tšea karolo mo projekeng ya dinyakišišo bjalo ka ge e hlalositšwe fa. Ke kwešiša gore go na le kgonagalo ya gore nka latišišwa mo lebakeng le le tlago mabapi le se eupša ke na le tokelo ya go gana go tšwela pele ka go tšea karolo ge ke sa rate.

……..	……
Mosaeno wa Molwetši	Tšatšikgwedi
…….	……
Mosaeno wa Mmotšolliši	Tšatšikgwedi

Monyakišišimogolo: Mdi Noko Mphahlele

Aterese: School of Physiology, Brain Function Research Unit
University of the Witwatersrand, Medical School
7 York Road, Parktown, Johannesburg, 2193

Mogala: +27 11 717 2254/2363 **Fekese:** +27 11 643 2765

DITLHABI TSA HIV

DIPOTSOLOTSO TSE DIKHUTSHWANE KA GA DITLHABITSA NAKWANA

Nomoro ya Molwetse……

Letlha: ……

Molwetse yo o Rategang,

Tsweetswee, buisa o be o arabe dipotso tse di latelang ka fa tlase. Re na le kgatlhego maleba le dikarabo tsa gago le fa o se na ditlhabi. Fa e le gore ga o ise o nne le ditlhabi mo kgweding e e fetileng, o tshwanetse go araba dipotso tse nne tsa pele fela tse di leng mo tsebeng ya 1 go ya go ya 2. Tsweetswee, ela tlhoko gore e , ke tsamaiso ya maithaopo, gape kalafo ya gago ga e kitla e emisiwa fa o sa rate go tlatsa dipotsolotso tse.

Re dira dipatlisiso/dithuto ka ga ditlhabi re lebile boteng jwa tsona le kalafo ya tsona. Re rata go bapisa dipholo tsa dipotsolotso tse le maemo a mangwe a tsa pholo. Re tlhoka nomoro ya gago ya kwa bookelong kgotsa letlha la gago la matsalo gore re kgone go bona tshedimosetso ka ga rekoto ya gago. Tshedimosetso yotlhe e tla nna sephiri se se itseweng fela ke setlhopha se se dirang ditlhotlhomiso tse. Gape re ka nna ra ikgolaganya le wena mo nakong e e tlang fa e le gore re tla batla tshedimosetso e nngwe gape. Le fa go ntse jalo, ga o a patelesega go araba dipotso mo isagweng le fa e le gore o tladitse dipotsolotso tse gona jaanong. Mogala wa yunibesithi o mo tsebeng ya bofelo fa e le gore o na le dipotso tse o ratang go di botsa malebana le ditlhotlhomiso tse.

Fa e le gore o dumela go nna karolo ya ditlhotlhomiso tse, tsweetswee, saena mo tsebeng ya bofelo.

---

1. Fa o se na go senolelwa bolwetsi jwa gago lwa ntlha, a sesupo sa ntlha e ne e le ditlhabi? Tsweetswee, tshwaya lebokoso le le maleba.

□ Ee □ Nnyaya

2. Fa o arabile Ee mo potsong e e fa godimo, dira letshwao la sefapano ka mo gare ga nngwe ya mabokoso a a latelang.

□ Lebaka e ne e le setlhabi

□ Setlhabi se ne se le teng, fela e ne e se lebaka le le nkisitseng kwa ngakeng.

3. A o kile wa nna le setlhabi ka ntlha ya bolwetsi jwa gago jwa gona jaanong? Tsweetswee, tshwaya lebokoso le le maleba.

□ Ee □ Nnyaya □ ga ke na bonnete

4. A o kile wa karwa (opereitiwa) mo kgweding e, e e fetileng? Tsweetswee, tshwaya lebokoso le le maleba.

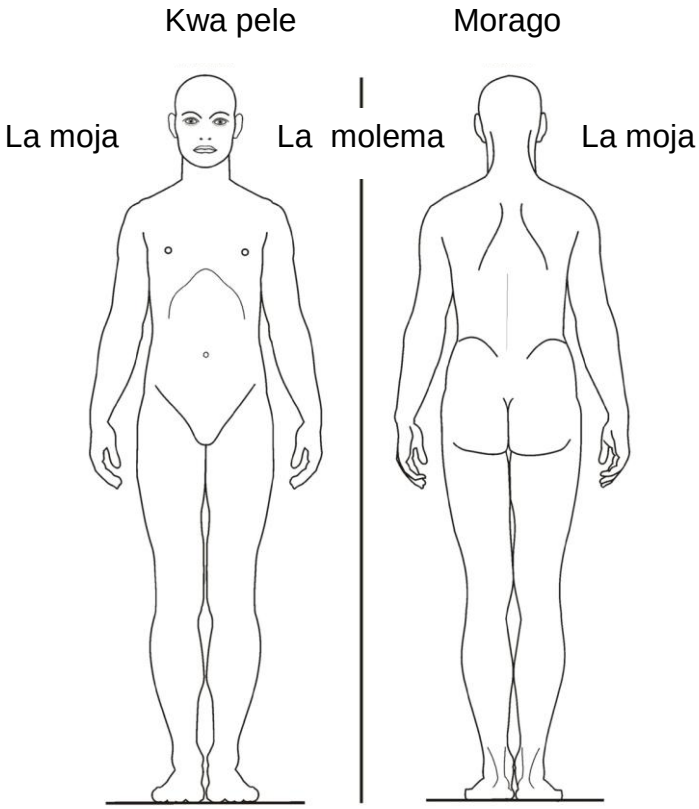
□ Ee □ Nnyaya

5. Mo botshelong, bontsi jwa rona bo kile jwa nna le ditlhabi kgafetsa kgafetsa (jaaka go opa ke tlhogo, go thinyega le setlhabi sa leino le le botlhoko). A o kile wa nna le setlhabi se sengwe kwa ntle ga ditlhabi tse tsa ka metlha mo kgweding e e fetileng? Tsweetswee, tshwaya lebokoso le le maleba.

□ Ee □ Nnyaya

Fa o arabile Ee, mo potsong ya bofelo, tsweetswee, araba dipotso tsotlhe tse di latelang mo dipotsolotsong tse.

5. Supa mo setshwantshong se ka go **ntshofatsa** karolo e e leng botlhoko.
   Tshwaya ditshwantsho ka go dirisa “S” fa e le gore setlhabi ga se se tseneletseng mme o tshwaye “D” fa e le gore setlhabi ke se se tseneletseng. Gape o tshwaye mo setlhabi se se **TONA** se leng mo teng..



7. Tsweetswee, sekeletsa nomoro e le **nngwe** e e tlhalosang ka botlalo setlhabi sa gago fa se le botlhoko mo go **fetisang** mo kgweding e e fetileng. (Fa o lekanyeditse ka 10, se se kaya fa setlhabi se le botlhoko jo e leng gore o ka se ke wa dira sepe, setlhabi se se ka se keng sa tlhalosiwa).

0 1 2 3 4 5 6 7 8 9 **10**

Nnyaya ga ke na setlhabi

Setlhabi se botlhoko jo o ka sekeng wa bo hlalosa

8. Tsweetswee, sekeletsa nomoro e le **nngwe** e e tlhalosang ka botlalo setlhabi sa gago fa se se botlhoko **thata** mo kgweding e e fetileng. (Fa o lekanyeditse ka 10, se se kaya fa setlhabi se le botlhoko jo e leng gore o ka se ke wa dira sepe, setlhabi se se ka se keng sa tlhalosiwa).

0 1 2 3 4 5 6 7 8 9 **10**
Nnyaya ga ke na setlhabi — Setlhabi se botlhoko jo o ka sekeng wa bo tlhalosa

9. Tsweetswee, lekanyetsa setlhabi sa gago ka go sekeletsa nomoro e le **nngwe** e e supang gore o na le setlhabi se se kanakang gona **jaanong**.

0 1 2 3 4 5 6 7 8 9 **10**
Nnyaya ga ke na setlhabi — Setlhabi se botlhoko jo o ka sekeng wa bo tlhalosa

10. O amogela kalafi kgotsa ditlhare tse di ntseng jaang go alafa setlhabi sa gago?

(i) ……

(ii) ……

(iii) ……

11. O ikutlwa go okobetse ga kanakang morago ga kalafi kgotsa ditlhare tse o di dirisang? (Tsweetswee, sekeletsa porosente e e supang gore o ikutlwa go okobetse ga kanakang).

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% **100%**
Nnyaya ga go na kokobalo — Kokobalo e e feletseng

12. O bona e kete setlhabi sa gago se tlholwa ke eng?

(i) ……

(ii) ……

(iii) ……

13. Mo bekeng e e fetileng, a maemo a pholo ya gago, go akaretsa setlhabi sengwe le sengwe, a ne a ama dilo tse di latelang: tlhopha nomoro e le nngwe, go tswa go 0 go ya go 4 fa tlase, e e tlhalosang sentle maemo a gago mme morago o a tshwaye ka mo lebokosong le le maleba. (i go ya go vi).

0 Ga ke ise ke tshwenyege ka gope
1 Go le gonnye
2 Ga nyenyane
3 Ga ntsinyana
4 Thata

i. ☐ MAIKUTLO

ii. ☐ BOTSALANO LE BATHO BA BANGWE

iii. ☐ GO KGONA GO TSAMAYA

iv ☐ TIRO E E TLWAELEGILENG (e akaretsa tiro ya ka kwa ntle ga lelapa le tiro ya lelapa)

v. ☐ GO ITUMELELA BOTSHELO

TSE DINGWE (tlhalosa ka botlalo) ……

1. Ee ……..
2. Nnyaya……

14. Maemo a lenyalo: Tsweetswee, sekeletsa kgotsa o tlhophe karabo e le nngwe.

1. Nnosi
2. Nyetswe
3. Tlhadilwe
4. Botlhologadi
5. Kgaogane

15. Thuto …….. maemo a a kwa godimo

16. Tiro …….. (fa e le gore ga o dire, re bolelele gore o ne o dira tiro efe pele)

Tiro ya molekane ……

17. Ke nako e e kanakang o itse ka ga boletsi jwa gago? ……malatsi
……dibeke
……dikgwedi.
……dinyaga

TUMELELO: Ke buisitse thadiso ya dipotsolotso ka ga ditlhotlhomiso ya "Ditlhabi tsa Nakwana" mme ke tsere tshwetso ya go nna le seabe mo porojekeng e ya ditlhotlhomiso jaaka e tlhalositswe mo. Ke tlhaloganya gore go na le kgonagalo ya gore go ka ikgolaganngwa gape le nna mo isagweng maleba le ditlhotlhomiso tse, fela ke lokologile gore nka nna ka gana go tswelela go nna le seabe fa ke rata.

…….. ……
Tshaeno ya Molwetsi Letlha

…… ……
Tshaeno ya Mmotsolotsa-dipotso Letlha

Motlhotlhomisi-mogolo: Ms Noko Mphahlele

Aterese: School of Physiology, Brain Function Research Unit
University of the Witwatersrand, Medical School
7 York Road, Parktown, Johannesburg, 2193

Mogala: 011 717 2254/2363 **Fekese:** 011 643 2765

SWITLHAVI SWA HIV

SWIVUTISO SWO KOMISIWA HI SWITLHAVI

Nomboro ya muvabyi: ……

Siku: ……

Eka Muvabyi,

Hi kombela leswaku u hlaya swivutiso leswi swi landzelaka kutani u swi hlamula. Hi navela ku twa nhlamulo ya wena hambi u ri hava xivavi kumbe xitlhavi. Loko kuri leswaku a wu si tlhaveka hi mpfhuka ka nhweti leyi yi nga hundza, hlamula swivutiso swa mune swo sungula eka matluka ya 1 na 2. Tiva leswaku u hlamula swivutiso leswi hi ku rhandza ku nga ri hi nsindziso kutani ni loko u hlawula ku kala u nga hlamuli swivutiso leswi u ta tiya u kuma mhirhi ya wena ya vutshunguri.

Hi endla ndzavisiso hi switlhavi/swivavi, ntikelo wa swona ni matshungulelo ya kona. Hi lava ku pimanisa mbuyelo lowu hi wu kumaka ni mavabyi ya mukhuva un'wana. Kutani ku va hi endla leswi, hi ta fanela ku va hi fikelela matsalwa ya wena lawa ya nga hlayisiwa hi xibedlhele. Marungula hinkwawo ya ta va ya xihundla; ya ta tiviwa ntsena hi ntlawa wa dyondzo leyi. Naswona, hi ta tlhelela eka wena hi siku rin'wana loko ku ri ni leswi hi navelaka ku tiva swona. Kambe ke, a swi ku bohi ku va u hlamula swivutiso leswi swi nga ta landzela hikuva u hlamurile swivutiso leswi swo sungula. Nomboro ya rinqingho ya yunivhesithi yi tsariwile hala ndzhaku ka tluka ro hetisela, u nga bela rinqingho eka nomboro leyi loko u ri ni swivutiso.

Loko u pfumela ku pfuneta hi ku nghenela dyondzo leyi hi ku hlamula swivutiso, sayina tluka ro hetelela.

---

1. Loko u hlahluviwa ro sungula, xin'wana xa swikombeto swa vuvabyi bya wena ku ve xitlhavi xana? Fungha xibokisana lexi faneleke.

□ INA □ AWA

2. Loko ku ri leswaku u hlamule xivutiso u ku ina, bana xihambano eka xibokisana
lexi xi landzelaka.

 Xitlhavi hi xona xi nga endla leswaku ndzi ya eka dokodela

 Xitlhavi ndzi ve na xona kambe a hi xona xi nga endla leswaku ndzi ya eka dokodela

3. Xana u tshama u va ni xitlhavi lexi xi vangiwaka hi vuvabyi lebyi u nga na byona sweswi? Fungha xibokisana lexi xi fanelaka.

 INA AWA A NDZI SWI TIVI

4. Xana u tshama u xekiwa hi madokodela eka nhweti leyi yi nga hela? Fungha xibokisana lexi xi faneleke.

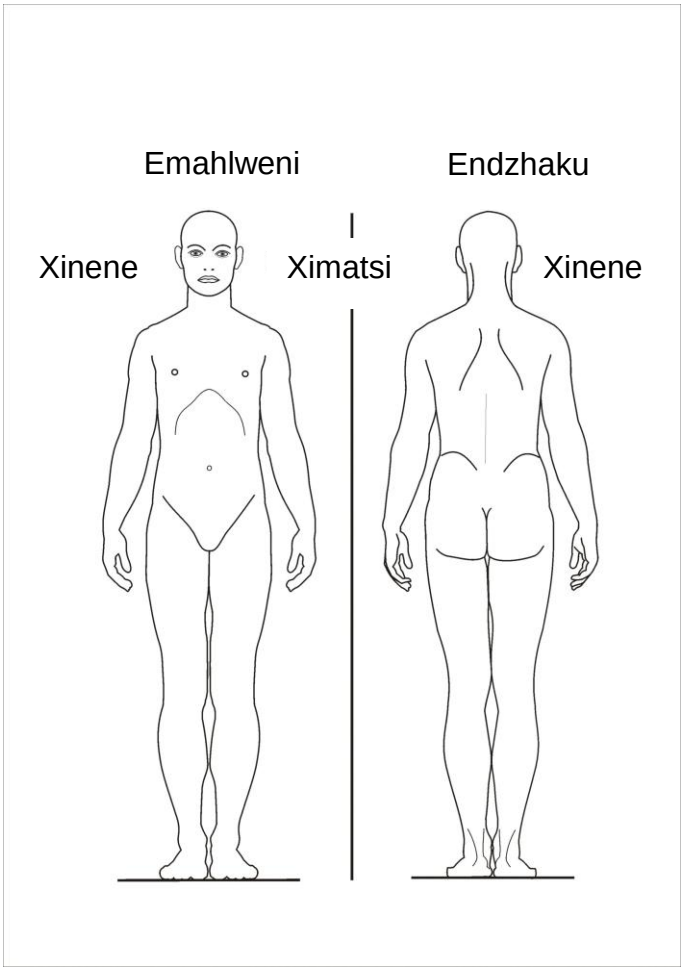
 INA AWA

5. Vutomi bya hina hinkwabyo, vunyingi bya hina ha tlhaveka eka minkarhi yin'wana (hi pandziwa hi nhloko, hi suleka kumbe hi pandziwa hi tino). Handle ka switlhavi leswi swi boxiweke swa siku ni siku xana u ve ni switlhavi swa muxaka un'wana eka nhweti leyi yi hundzeke xana? Fungha xibokisana lexi xi faneleke.

 INA AWA

Loko ku ri leswaku u hlamule u ku ina eka xivutiso lexi wa ha ku xihlamulaka, hi kombela ku va u hlamula swivutiso hinkwaswo leswi swi landzelaka.

6. Eka xifaniso lexi xi u xi nyikiweke kombeta lomu xivavi xa wena xi nga kona hi ku penda (tota) hi penisele lomu u vaveriwaka kumbe ku tlhaviwa kona.
   Fungha xifaniso hi “S” ku komba leswaku xitlhavi xi laha handle a xi le ndzeni kutani u fungha hi “D” ku komba leswaku xitlhavi xi entele endzeni. Naswona komba lomu **xitlhavinkulu** xi nga talela kona.



7. Pima xitlhavi xa wena hi ku endla xirhendzewutana eka nomboro **yin’we** leyi yi kombetaka mpimo wa xitlhavi xa wena **xo vava ku tlula mpimo** eka nhweti leyi yi nga hela.(Mpimo wa 10 wu ta kopmba ku vava loku ku tlulaka mpimo loku ku endlaka ku va u nga koti ku endla nchumu).

0 1 2 3 4 5 6 7 8 9 .1**0**
Ku hava switlhavi
Switlhavi swo vava ku tlula mpimo

8. Pima xitlhavi xa wena hi ku endla xirhendzewutana eka nomboro **yin'we** leyi yi kombetaka mpimo wa xitlhavi xa wena **lowu wu nga ehansi swinene.** (Mpimo wa 10 wu ta kopmba ku vava loku ku tlulaka mpimo loku ku endlaka ku va u nga koti ku endla nchumu).

0	1	2	3	4	5	6	7	8	9	**10**
Ku hava switlhavi										Switlhavi swo ava ku tlula mpimo

9. Pima xitlhavi xa wena hi ku endla xirhendzewutana eka nomboro **yin'we** leyi yi kombetaka mpimo wa xitlhavi xa wena eka **nkarhi wa sweswi.**

0	1	2	3	4	5	6	7	8	9	**10**
Ku hava switlhavi										Switlhavi swo vava ku tlula mpimo

10. Xana u tshunguriwa hi ndlela yini kumbe u nyikiwa murhi wihi ku susa switlhavi?

(i) ……

(ii) ……

(iii) ……

11. Xana matshungulele lawa kumbe murhi wo tshungula lowu u wu tekaka wu antswisa switlhavi xana? (hlawula u ba xirhendzewutana eka nomboroya tiphesente leti ti kombaka ku antswa loku u ku kumaka).

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	**100%**
A ndzi twi ku									Ndza Nchuncheka antswa	

12. Incini lexi xi nga va ka xi vanga xitlhavi xa wena?

(i) ……

(ii) ……

(iii) ……

13. Eka vhiki leri ri nga hela xana xiyimo xa rihanyo xa wena ku katsa ni switlhavi swi nghenelele ni ku ku tsandzisa kiu endla leswi swi landzelaka: hlawula nomboro yin'we ku suka eka 0 ku ya fika eka 4 kwalaha hansi, leyi yi hlamuselaka xiyimo xa wena u tsala eka xibokisanalexi xi faneleke (ku suka eka i ku ya fika eka vi).

0 Ni kantsongo
1 Swintsongo
2 Swi le xikarhi
3 Swinenenyana
4 Ngopfu

i. ☐ LESWI U TITWISAKA XISWONA

ii. ☐ VUXAKA BYA WENA NI VAN'WANA VANHU

iii. ☐ KU KOTA KU FAMBA

iv. ☐ ETLELA

v ☐ RHO WA WENA (nghenisa wa lomu u tithaka kona ni wa le ndyangu)

vi. ☐ KU TIPHINA HI VUTOMI

SWIN'WANA(Boxa) ……

1. INA ……
2. AWA

14. Xiyimo xa vukati: Bana xirhevutana kumbe u fungha nhlamulo leyi u yi hlawuleke.

1. U wexe
2. Mi tekanile
3. Mi thalanile ni nghamu
4. U muferiwa
5. mi hambanile ni nghamu

15. Dyondzo …….. vuhenhla lebyi fikeriweke

16. Ntirho wa muvabyi …….. (loko kuri leswaku a wu tirhi hi byel ntirho wa wena u nga se tshika ntirho)

Ntirho lowu wu tirhiwaka hi nghamu ……

17. Xana u ni nkarhi wo tanihi kwihi u tiva mbuyelo wa wena wa ndzavisiso

…….. masiku
…….. mavhiki
…….. tinhweti
…….. malembe

MPFUMELELO: Ndzi hlayile nhlamuselo leyi yi nyikiweke ya dyondzo ya “Swivutiso swo komisiwa hi swivavi” kutani ndzi ta nghenela purojeke leyi ya ndzavisiso. Naswona ndza swi twisisa leswaku swi nga endleka leswaku ndzi nga beriwa rinqingho eka nkarhi lowu wu taka kambe swi nga endleka leswaku ndzi ala ku ya emahlweni ni ndzavisiso lowu loko ndzi nga ha swi lavi.

…….. ……
Nsayino wa Muvabyi Siku

…… ……
Nsayino wa mulavisisi kumbe nsayino wa muvutiseri Siku

Mulavisis-Nkulu: Manana Noko Mphahlele

Adirese: School of Physiology, Brain Function Research Unit
University of the Witwatersrand, Medical School
7 York Road, Parktown, Johannesburg, 2193

Rinqingho: 011 717 2254/2363 **Fekisi:** 011 643 2765

Appendix H

HIV PAIN

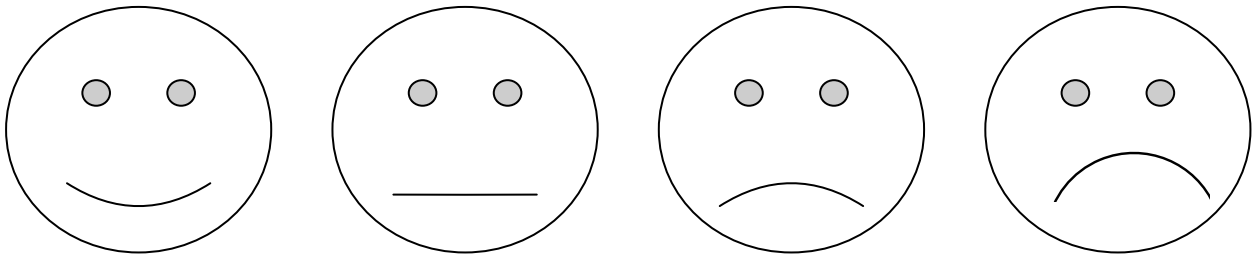
FACES PAIN SCALE

Patient Reference Number:……

Date: ……

Dear Patient,

Please choose the face that better describe how much pain you are feeling right now. You would choose the face that is on your far left if you are not feeling any pain and the pain on your far right if you are feeling very much pain.



NO PAIN

WORST PAIN POSSIBLE

Principal Investigator: Ms Noko Mphahlele

Address: School of Physiology, Brain Function Research Unit
University of the Witwatersrand, Medical School
7 York Road, Parktown, Johannesburg, 2193

Telephone: 011 717 2254/ 2363 **Fax:** 011 643 2765

HIV PAIN

KARNOFSKY PERFORMANCE INDEX

Patient Number: ……

Date: ……

Definition

Able to carry on normal activity and to work	100	Normal; no complaint; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his or her needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled, requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death not imminent
	20	Very sick; hospitalization necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

CHAPTER 7

REFERENCES

AIDSInfo. (2013). HIV/AIDS treatment Guidelines: http://aidsinfo.nih.gov/guidelines; accessed on: 02/07/2013.

Aires, E. M., and Bammann, R. H. (2005). Pain in hospitalized HIV-positive patients: clinical and therapeutical issues. *Braz J Infect Dis* **9**(3)**,** 201-8.

Aisyaturridha, A., Naing, L., and Nizar, A. J. (2006). Validation of the Malay Brief Pain Inventory questionnaire to measure cancer pain. *J Pain Symptom Manage* **31**(1)**,** 13-21.

Anand, A., Carmosino, L., and Glatt, A. E. (1994). Evaluation of recalcitrant pain in HIV-infected hospitalized patients. *J Acquir Immune Defic Syndr* **7**(1)**,** 52-6.

Arber, A. (2004). Is pain what the patient says it is? Interpreting an account of pain. *Int J Palliat Nurs* **10**(10)**,** 491-6.

Attal, N., Cruccu, G., Baron, R., Haanpaa, M., Hansson, P., Jensen, T. S., and Nurmikko, T. (2010). EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* **17**(9)**,** 1113-e88.

Ballantyne, J. C., and Shin, N. S. (2008). Efficacy of opioids for chronic pain: a review of the evidence. *Clin J Pain* **24**(6)**,** 469-78.

Barone, J. E., Wolkomir, A. F., Muakkassa, F. F., and Fares, L. G., 2nd. (1988). Abdominal pain and anorectal disease in AIDS. *Gastroenterol Clin North Am* **17**(3)**,** 631-8.

Bates, M. S., and Rankin-Hill, L. (1994). Control, culture and chronic pain. *Social Science & Medicine* **39**(5)**,** 629-645.

Bates, M. S., Rankinâ€□Hill, L., Sanchezâ€□Ayendez, M., and Mendezâ€• Bryan, R. (1994). A cross-cultural comparison of adaptation to chronic pain among Anglo-Americans and native Puerto Ricans. *Medical Anthropology* **16**(1-4)**,** 141-173.

Beck, S. L., and Falkson, G. (2001). Prevalence and management of cancer pain in South Africa. *Pain* **94**(1)**,** 75-84.

Berhe, T., Melkamu, Y., and Amare, A. (2012). The pattern and predictors of mortality of HIV/AIDS patients with neurologic manifestation in Ethiopia: a retrospective study. *AIDS Res Ther* **9,** 11.

Bhat, V. G., Ramburuth, M., Singh, M., Titi, O., Antony, A. P., Chiya, L., Irusen, E. M., Mtyapi, P. P., Mofoka, M. E., Zibeke, A., Chere-Sao, L. A., Gwadiso, N., Sethathi, N. C., Mbondwana, S. R., and Msengana, M. (2010). Factors associated with poor adherence to anti-retroviral therapy in patients attending a rural health centre in South Africa. *Eur J Clin Microbiol Infect Dis* **29**(8)**,** 947-53.

Bing, E. G., Burnam, M. A., Longshore, D., Fleishman, J. A., Sherbourne, C. D., London, A. S., Turner, B. J., Eggan, F., Beckman, R., Vitiello, B., Morton, S. C., Orlando, M., Bozzette, S. A., Ortiz-Barron, L., and Shapiro, M. (2001). Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Arch Gen Psychiatry* **58**(8)**,** 721-8.

Brechtl, J. R., Breitbart, W., Galietta, M., Krivo, S., and Rosenfeld, B. (2001). The use of highly active antiretroviral therapy (HAART) in patients with advanced HIV infection: impact on medical, palliative

care, and quality of life outcomes. *J Pain Symptom Manage* **21**(1)**,** 41-51.

Breitbart, W., Kaim, M., and Rosenfeld, B. (1999). Clinicians' perceptions of barriers to pain management in AIDS. *J Pain Symptom Manage* **18**(3)**,** 203-12.

Breitbart, W., McDonald, M. V., Rosenfeld, B., Passik, S. D., Hewitt, D., Thaler, H., and Portenoy, R. K. (1996a). Pain in ambulatory AIDS patients. I: Pain characteristics and medical correlates. *Pain* **68**(2-3)**,** 315-21.

Breitbart, W., Passik, S., McDonald, M. V., Rosenfeld, B., Smith, M., Kaim, M., and Funesti-Esch, J. (1998). Patient-related barriers to pain management in ambulatory AIDS patients. *Pain* **76**(1-2)**,** 9-16.

Breitbart, W., Rosenfeld, B., Passik, S., Kaim, M., Funesti-Esch, J., and Stein, K. (1997). A comparison of pain report and adequacy of analgesic therapy in ambulatory AIDS patients with and without a history of substance abuse. *Pain* **72**(1-2)**,** 235-43.

Breitbart, W., Rosenfeld, B. D., Passik, S. D., McDonald, M. V., Thaler, H., and Portenoy, R. K. (1996). The undertreatment of pain in ambulatory AIDS patients. *Pain* **65**(2-3)**,** 243-9.

Breitbart, W., Rosenfeld, B. D., Passik, S. D., McDonald, M. V., Thaler, H., and Portenoy, R. K. (1996b). The undertreatment of pain in ambulatory AIDS patients. *Pain* **65**(2-3)**,** 243-9.

Brodt, H. R., Kamps, B. S., Gute, P., Knupp, B., Staszewski, S., and Helm, E. B. (1997). Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. *Aids* **11**(14)**,** 1731-8.

Caraceni, A., Mendoza, T. R., Mencaglia, E., Baratella, C., Edwards, K., Forjaz, M. J., Martini, C., Serlin, R. C., de Conno, F., and Cleeland, C. S. (1996). A validation study of an Italian version of the Brief Pain Inventory (Breve Questionario per la Valutazione del Dolore). *Pain* **65**(1)**,** 87-92.

Cervia, L. D., McGowan, J. P., and Weseley, A. J. (2010). Clinical and Demographic Variables Related to Pain in HIV-Infected Individuals Treated with Effective, Combination Antiretroviral Therapy (cART). *Pain Medicine* **11**(4)**,** 498-503.

Chou, R., Fanciullo, G. J., Fine, P. G., Adler, J. A., Ballantyne, J. C., Davies, P., Donovan, M. I., Fishbain, D. A., Foley, K. M., Fudin, J., Gilson, A. M., Kelter, A., Mauskop, A., O'Connor, P. G., Passik, S. D., Pasternak, G. W., Portenoy, R. K., Rich, B. A., Roberts, R. G., Todd, K. H., and Miaskowski, C. (2009). Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* **10**(2)**,** 113-30.

Cleeland, C. S., Gonin, R., Hatfield, A. K., Edmonson, J. H., Blum, R. H., Stewart, J. A., and Pandya, K. J. (1994). Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med* **330**(9)**,** 592-6.

Cleeland, C. S., Ladinsky, J. L., Serlin, R. C., and Nugyen, C. T. (1988). Multidimensional measurement of cancer pain: comparisons of US and Vietnamese patients. *J Pain Symptom Manage* **3**(1)**,** 23-7.

Cleeland, C. S., and Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* **23**(2)**,** 129-38.

Clifford, D. B., Simpson, D. M., Brown, S., Moyle, G., Brew, B. J., Conway, B., Tobias, J. K., and Vanhove, G. F. (2012). A randomized, double-blind, controlled study of NGX-4010, a capsaicin 8% dermal patch, for the treatment of painful HIV-associated distal sensory polyneuropathy. *J Acquir Immune Defic Syndr* **59**(2)**,** 126-33.

Clucas, C., Harding, R., Lampe, F. C., Anderson, J., Date, H. L., Johnson, M., Edwards, S., Fisher, M., and Sherr, L. (2011). Doctor-patient concordance during HIV treatment switching decision-making. *HIV Med* **12**(2)**,** 87-96.

Compton, W. M., and Volkow, N. D. (2006). Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend* **81**(2)**,** 103-7.

Coughlan, M. (2004). Pain and Palliative Care for People Living with HIV/AIDS in Asia, Vol. 17, pp. 91-104.

Dalakas, M. C. (2001a). Peripheral neuropathy and antiretroviral drugs. *J Peripher Nerv Syst* **6**(1)**,** 14-20.

Dalakas, M. C., Semino-Mora, C., and Leon-Monzon, M. (2001b). Mitochondrial alterations with mitochondrial DNA depletion in the

nerves of AIDS patients with peripheral neuropathy induced by 2'3'-dideoxycytidine (ddC). *Lab Invest* **81**(11)**,** 1537-44.

Daut, R. L., Cleeland, C. S., and Flanery, R. C. (1983). Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain* **17**(2)**,** 197-210.

de Boer, I. M., Prins, J. M., Sprangers, M. A., Smit, C., and Nieuwkerk, P. T. (2011). Self-reported symptoms among HIV-Infected patients on highly active antiretroviral therapy in the ATHENA cohort in The Netherlands. *HIV Clin Trials* **12**(3)**,** 161-70.

de Boer, I. M., Sprangers, M. A. G., Prins, J. M., Smit, C., de Wolf, F., and Nieuwkerk, P. T. (2010). Health-Related Quality of Life and Survival among HIV-Infected Patients Receiving Highly Active Antiretroviral Therapy: A Study of Patients in the AIDS Therapy Evaluation in the Netherlands (ATHENA) Cohort. *Clinical Infectious Diseases* **50**(2)**,** 255-263.

Del Borgo, C., Izzi, I., Chiarotti, F., Del Forno, A., Moscati, A. M., Cornacchione, E., and Fantoni, M. (2001). Multidimensional aspects of pain in HIV-infected individuals. *AIDS Patient Care STDS* **15**(2)**,** 95-102.

Dobalian, A., Tsao, J. C., and Duncan, R. P. (2004). Pain and the use of outpatient services among persons with HIV: results from a nationally representative survey. *Med Care* **42**(2)**,** 129-38.

Douaihy, A. B., Stowell, K. R., Kohnen, S., Stoklosa, J. B., and Breitbart, W. S. (2007a). Psychiatric aspects of comorbid HIV/AIDS and pain, Part 1. *AIDS Read* **17**(6)**,** 310-4.

Douaihy, A. B., Stowell, K. R., Kohnen, S., Stoklosa, J. B., and Breitbart, W. S. (2007b). Psychiatric aspects of comorbid HIV/AIDS and pain, Part 2. *AIDS Read* **17**(7)**,** 350-2, 357-61.

Dunn, K. M., Saunders, K. W., Rutter, C. M., Banta-Green, C. J., Merrill, J. O., Sullivan, M. D., Weisner, C. M., Silverberg, M. J., Campbell, C. I., Psaty, B. M., and Von Korff, M. (2010). Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med* **152**(2)**,** 85-92.

Edmunds-Oguokiri, T. (2007). Pain management in HIV/AIDS: an update for clinicians. *HIV Clin* **19**(3)**,** 7-10.

Ellis, R. J., Rosario, D., Clifford, D. B., McArthur, J. C., Simpson, D., Alexander, T., Gelman, B. B., Vaida, F., Collier, A., Marra, C. M., Ances, B., Atkinson, J. H., Dworkin, R. H., Morgello, S., Grant, I., and for the, C. S. G. (2010). Continued High Prevalence and Adverse Clinical Impact of Human Immunodeficiency Virus-Associated Sensory Neuropathy in the Era of Combination Antiretroviral Therapy: The CHARTER Study, Vol. 67, pp. 552-558.

Ferrell, B. A. (1991). Pain management in elderly people. *J Am Geriatr Soc* **39**(1)**,** 64-73.

Fishbain, D. A. (1999). Approaches to treatment decisions for psychiatric comorbidity in the management of the chronic pain patient. *Med Clin North Am* **83**(3)**,** 737-60, vii.

Fishbain, D. A., Cole, B., Lewis, J., Rosomoff, H. L., and Rosomoff, R. S. (2008). What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med* **9**(4)**,** 444-59.

Frich, L. M., and Borgbjerg, F. M. (2000). Pain and pain treatment in AIDS patients: a longitudinal study. *J Pain Symptom Manage* **19**(5)**,** 339-47.

Furlan, A. D., Sandoval, J. A., Mailis-Gagnon, A., and Tunks, E. (2006). Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *Cmaj* **174**(11)**,** 1589-94.

Gabuzda, D. H., and Hirsch, M. S. (1987). Neurologic manifestations of infection with human immunodeficiency virus. Clinical features and pathogenesis. *Ann Intern Med* **107**(3)**,** 383-91.

Gee, R. E., and Fins, J. J. (2003). Barriers to pain and symptom management, opioids, health policy, and drug benefits. *J Pain Symptom Manage* **25**(2)**,** 101-3.

Ger, L. P., Ho, S. T., Sun, W. Z., Wang, M. S., and Cleeland, C. S. (1999). Validation of the Brief Pain Inventory in a Taiwanese population. *J Pain Symptom Manage* **18**(5)**,** 316-22.

Glare, P. A. (2001). Pain in patients with HIV infection: issues for the new millennium. *Eur J Pain* **5 Suppl A,** 43-8.

Gorbach, S. L., Knox, T. A., and Roubenoff, R. (1993). Interactions Between Nutrition and Infection with Human Immunodeficiency Virus. *Nutrition Reviews* **51**(8)**,** 226-234.

Gray, G., and Berger, P. (2007). Pain in women with HIV/AIDS. *Pain* **132 Suppl 1,** S13-21.

Grond, S., Zech, D., Schug, S. A., Lynch, J., and Lehmann, K. A. (1991). Validation of World Health Organization guidelines for cancer pain relief during the last days and hours of life. *J Pain Symptom Manage* **6**(7)**,** 411-22.

Haanpaa, M. L., Gourlay, G. K., Kent, J. L., Miaskowski, C., Raja, S. N., Schmader, K. E., and Wells, C. D. (2010). Treatment considerations for patients with neuropathic pain and other medical comorbidities. *Mayo Clin Proc* **85**(3 Suppl)**,** S15-25.

Harding, R., Molloy, T., Easterbrook, P., Frame, K., and Higginson, I. J. (2006). Is antiretroviral therapy associated with symptom prevalence and burden? *Int J STD AIDS* **17**(6)**,** 400-5.

Harding, R., Powell, R. A., Kiyange, F., Downing, J., and Mwangi-Powell, F. (2010). Provision of Pain- and Symptom-Relieving Drugs for HIV/AIDS in Sub-Saharan Africa. *Journal of Pain and Symptom Management* **40**(3)**,** 405-415.

Harding, R., Simms, V., and Selman, L. (2013). Pain Among HIV Outpatients Attending HIV Care and Support Facilities in Two East

African Countries *In*, pp. 1-68. Measure Evaluation and King's College London.

Harrison, T. B., and Smith, B. (2011). Neuromuscular manifestations of HIV/AIDS. *J Clin Neuromuscul Dis* **13**(2)**,** 68-84.

Heckman, T. G., Somlai, A. M., Peters, J., Walker, J., Otto-Salaj, L., Galdabini, C. A., and Kelly, J. A. (1998). Barriers to care among persons living with HIV/AIDS in urban and rural areas. *AIDS Care* **10**(3)**,** 365-75.

Heller, T., Goblirsch, S., Wallrauch, C., Lessells, R., and Brunetti, E. (2010). Abdominal tuberculosis: sonographic diagnosis and treatment response in HIV-positive adults in rural South Africa. *Int J Infect Dis*.

Hewitt, D. J., McDonald, M., Portenoy, R. K., Rosenfeld, B., Passik, S., and Breitbart, W. (1997). Pain syndromes and etiologies in ambulatory AIDS patients. *Pain* **70**(2-3)**,** 117-23.

Hirschfeld, S. (1998). Pain as a complication of HIV disease. *AIDS Patient Care STDS* **12**(2)**,** 91-108.

Hitchcock, S. A., Meyer, H. P., and Gwyther, E. (2008). Neuropathic pain in AIDS patients prior to antiretroviral therapy. *S Afr Med J* **98**(11)**,** 889-92.

Hovanessian, H. C. (1999). New developments in the treatment of HIV disease: An overview. *Ann Emerg Med* **33**(5)**,** 546-55.

Hughes, J., Jelsma, J., Maclean, E., Darder, M., and Tinise, X. (2004). The health-related quality of life of people living with HIV/AIDS. *Disabil Rehabil* **26**(6)**,** 371-6.

Ives, N. J., Gazzard, B. G., and Easterbrook, P. J. (2001). The Changing Pattern of AIDS-defining Illnesses with the Introduction of Highly Active Antiretroviral Therapy (HAART)in a London Clinic. *Journal of Infection* **42**(2)**,** 134-139.

Jackson, T., Iezzi, T., Gunderson, J., Nagasaka, T., and Fritch, A. (2002). Gender Differences in Pain Perception: The Mediating Role of Self-Efficacy Beliefs. *Sex Roles* **47**(11)**,** 561-568.

Jelsma, J., Maclean, E., Hughes, J., Tinise, X., and Darder, M. (2005). An investigation into the health-related quality of life of individuals living with HIV who are receiving HAART. *AIDS Care* **17**(5)**,** 579-88.

Joint United Nations Programme on HIV/AIDS (UNAIDS), and (WHO), W. H. O. (2009). "AIDS epidemic update." Geneva, UNAIDS.

Jordan, J. M. (1999). Effect of race and ethnicity on outcomes in arthritis and rheumatic conditions. *Current Opinion in Rheumatology* **11**(2)**,** 98-103.

Justice, A. C., Chang, C. H., Rabeneck, L., and Zackin, R. (2001). Clinical importance of provider-reported HIV symptoms compared with patient-report. *Med Care* **39**(4)**,** 397-408.

Kamerman, P. R., and Mitchell, D. (2011). Current perspectives on HIV-related pain and its management: insights from sub-Saharan Africa. *Pain Management* **1**(6)**,** 587-596.

Kamerman, P. R., Wadley, A. L., and Cherry, C. L. (2012). HIV-associated sensory neuropathy: risk factors and genetics. *Curr Pain Headache Rep* **16**(3)**,** 226-36.

Karus, D., Raveis, V. H., Alexander, C., Hanna, B., Selwyn, P., Marconi, K., and Higginson, I. (2005). Patient reports of symptoms and their treatment at three palliative care projects servicing individuals with HIV/AIDS. *J Pain Symptom Manage* **30**(5)**,** 408-17.

Katwere, M., Kambugu, A., Piloya, T., Wong, M., Hendel-Paterson, B., Sande, M. A., Ronald, A., Katabira, E., Were, E. M., Menten, J., and Colebunders, R. (2009). Clinical presentation and aetiologies of acute or complicated headache among HIV-seropositive patients in a Ugandan clinic. *J Int AIDS Soc* **12,** 21.

Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., and Cleeland, C. S. (2004). Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* **20**(5)**,** 309-18.

Keswani, S. C., Pardo, C. A., Cherry, C. L., Hoke, A., and McArthur, J. C. (2002). HIV-associated sensory neuropathies. *Aids* **16**(16)**,** 2105-17.

Kinsey, K., McVeigh, J., and Chantler, I. (2008). Habitual physical activity levels are positively correlated with CD4 counts in an HIV-positive South African population. *African Journal of AIDS Research* **7,** 237-242.

Klepstad, P., Loge, J. H., Borchgrevink, P. C., Mendoza, T. R., Cleeland, C. S., and Kaasa, S. (2002). The Norwegian brief pain inventory questionnaire: translation and validation in cancer pain patients. *J Pain Symptom Manage* **24**(5)**,** 517-25.

Kline, P. (1994). "An Easy Guide to Factor Analysis." Routledge.

Koeppe, J., Armon, C., Lyda, K., Nielsen, C., and Johnson, S. (2010). Ongoing pain despite aggressive opioid pain management among persons with HIV. *Clin J Pain* **26**(3)**,** 190-8.

Koeppe, J., Lichtenstein, K., Armon, C., Chmiel, J. S., Buchacz, K., Wood, K., and Brooks, J. T. (2011). Factors associated with initiation of prolonged analgesic use among patients in the HIV Outpatient Study (HOPS). *Clin J Pain* **27**(8)**,** 699-706.

Koeppe, J., Lyda, K., Johnson, S., and Armon, C. (2012). Variables associated with decreasing pain among persons living with human immunodeficiency virus: a longitudinal follow-up study. *Clin J Pain* **28**(1)**,** 32-8.

Larue, F., Fontaine, A., and Colleau, S. M. (1997). Underestimation and undertreatment of pain in HIV disease: multicentre study. *Bmj* **314**(7073)**,** 23-8.

Larue, R., Brasseur, L., Musseault, P., Demeulemeester, R., Bonifassi, L., and Bez, G. (1994). Pain and HIV infection: A French national survey. *J Palliat Care* **10,** 95.

Lebovits, A. H., Lefkowitz, M., McCarthy, D., Simon, R., Wilpon, H., Jung, R., and Fried, E. (1989). The prevalence and management of pain

in patients with AIDS: a review of 134 cases. *Clin J Pain* **5**(3)**,** 245-8.

Lebovits, A. H., Smith, G., Maignan, M., and Lefkowitz, M. (1994). Pain in hospitalized patients with AIDS: analgesic and psychotropic medications. *Clin J Pain* **10**(2)**,** 156-61.

Lewis, M. S., and Warfield, C. A. (1990). Management of pain in AIDS. *Hosp Pract (Off Ed)* **25**(10A)**,** 51-4.

Liu, C., Johnson, L., Ostrow, D., Silvestre, A., Visscher, B., and Jacobson, L. P. (2006a). Predictors for lower quality of life in the HAART era among HIV-infected men. *J Acquir Immune Defic Syndr* **42**(4)**,** 470-7.

Liu, C., Ostrow, D., Detels, R., Hu, Z., Johnson, L., Kingsley, L., and Jacobson, L. P. (2006b). Impacts of HIV infection and HAART use on quality of life. *Qual Life Res* **15**(6)**,** 941-9.

Livingstone, H. (2003). Pain relief in the developing world: the experience of hospice Africa-Uganda. *J Pain Palliat Care Pharmacother* **17**(3-4)**,** 107-18; discussion 119-20.

Logie, D. E., and Harding, R. (2005). An evaluation of a morphine public health programme for cancer and AIDS pain relief in Sub-Saharan Africa. *BMC Public Health* **5,** 82.

Lorenz, K. A., Cunningham, W. E., Spritzer, K. L., and Hays, R. D. (2006). Changes in symptoms and health-related quality of life in a nationally representative sample of adults in treatment for HIV. *Qual Life Res* **15**(6)**,** 951-8.

Lorenz, K. A., Shapiro, M. F., Asch, S. M., Bozzette, S. A., and Hays, R. D. (2001). Associations of symptoms and health-related quality of life: findings from a national study of persons with HIV infection. *Ann Intern Med* **134**(9 Pt 2)**,** 854-60.

Lum, P. J., Little, S., Botsko, M., Hersh, D., Thawley, R. E., Egan, J. E., Mitty, J., Boverman, J., and Fiellin, D. A. (2011). Opioid-prescribing practices and provider confidence recognizing opioid analgesic abuse in HIV primary care settings. *J Acquir Immune Defic Syndr* **56 Suppl 1,** S91-7.

Luma, H. N., Tchaleu, B. C., Ngahane, B. H., Temfack, E., Doualla, M. S., Halle, M. P., Joko, H. A., and Koulla-Shiro, S. (2013). Tuberculous meningitis: presentation, diagnosis and outcome in hiv-infected patients at the douala general hospital, cameroon: a cross sectional study. *AIDS Res Ther* **10**(1)**,** 16.

Makoae, L. N., Seboni, N. M., Molosiwa, K., Moleko, M., Human, S., Sukati, N. A., and Holzemer, W. L. (2005). The symptom experience of people living with HIV/AIDS in Southern Africa. *J Assoc Nurses AIDS Care* **16**(3)**,** 22-32.

Manchikanti, K. N., Manchikanti, L., Damron, K. S., Pampati, V., and Fellows, B. (2008). Increasing deaths from opioid analgesics in the United States: an evaluation in an interventional pain management practice. *J Opioid Manag* **4**(5)**,** 271-83.

Manchikanti, L., Cash, K. A., Damron, K. S., Manchukonda, R., Pampati, V., and McManus, C. D. (2006). Controlled substance abuse and

illicit drug use in chronic pain patients: An evaluation of multiple variables. *Pain Physician* **9**(3)**,** 215-25.

Marcus, K. S., Kerns, R. D., Rosenfeld, B., and Breitbart, W. (2000). HIV/AIDS-related Pain as a Chronic Pain Condition: Implications of a Biopsychosocial Model for Comprehensive Assessment and Effective Management. *Pain Medicine* **1**(3)**,** 260-273.

Maree, J. E., Dreyer Wright, S. C., and Makua, M. R. (2011). The Management of HIV- and AIDS-Related Pain in a Primary Health Clinic in Tshwane, South Africa. *Pain Management Nursing* (In press)**,** 1-8.

Maritz, J., Benatar, M., Dave, J. A., Harrison, T. B., Badri, M., Levitt, N. S., and Heckmann, J. M. (2010). HIV neuropathy in South Africans: frequency, characteristics, and risk factors. *Muscle Nerve* **41**(5)**,** 599-606.

Martin, C., Pehrsson, P., Osterberg, A., Sonnerborg, A., and Hansson, P. (1999). Pain in ambulatory HIV-infected patients with and without intravenous drug use. *Eur J Pain* **3**(2)**,** 157-164.

Martin, C., Solders, G., Sonnerborg, A., and Hansson, P. (2003). Painful and non-painful neuropathy in HIV-infected patients: an analysis of somatosensory nerve function. *Eur J Pain* **7**(1)**,** 23-31.

Mathews, W. C., McCutchan, J. A., Asch, S., Turner, B. J., Gifford, A. L., Kuromiya, K., Brown, J., Shapiro, M. F., and Bozzette, S. A. (2000). National estimates of HIV-related symptom prevalence from the HIV Cost and Services Utilization Study. *Med Care* **38**(7)**,** 750-62.

McArthur, J. C. (1987). Neurologic manifestations of AIDS. *Medicine (Baltimore)* **66**(6)**,** 407-37.

McArthur, J. C., Brew, B. J., and Nath, A. (2005). Neurological complications of HIV infection. *Lancet Neurol* **4**(9)**,** 543-55.

McCormack, J. P., Li, R., Zarowny, D., and Singer, J. (1993). Inadequate treatment of pain in ambulatory HIV patients. *Clin J Pain* **9**(4)**,** 279-83.

Merlin, J. S., Cen, L., Praestgaard, A., Turner, M., Obando, A., Alpert, C., Woolston, S., Casarett, D., Kostman, J., Gross, R., and Frank, I. (2012). Pain and Physical and Psychological Symptoms in Ambulatory HIV Patients in the Current Treatment Era. *Journal of pain and symptom management* **43**(3)**,** 638-645.

Miaskowski, C., Penko, J. M., Guzman, D., Mattson, J. E., Bangsberg, D. R., and Kushel, M. B. (2011). Occurrence and Characteristics of Chronic Pain in a Community-Based Cohort of Indigent Adults Living With HIV Infection. *The Journal of Pain* **12**(9)**,** 1004-1016.

Mocroft, A., Ledergerber, B., Katlama, C., Kirk, O., Reiss, P., d'Arminio Monforte, A., Knysz, B., Dietrich, M., Phillips, A. N., and Lundgren, J. D. (2003). Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* **362**(9377)**,** 22-9.

Morasco, B. J., Gritzner, S., Lewis, L., Oldham, R., Turk, D. C., and Dobscha, S. K. (2011). Systematic review of prevalence, correlates, and treatment outcomes for chronic non-cancer pain in patients with comorbid substance use disorder. *Pain* **152**(3)**,** 488-97.

Moss, V. (1990). Palliative care in advanced HIV disease: presentation, problems and palliation. *Aids* **4 Suppl 1,** S235-42.

Mphahlele, N., Mitchell, D., and Kamerman, P. (2008). Validation of the Wisconsin Brief Pain Questionnaire in a multilingual South African population. *J Pain Symptom Manage* **36**(4)**,** 396-412.

Mphahlele, N., Mitchell, D., and Kamerman, P. (2011). Pain in ambulatory HIV-positive South Africans. *In Press*.

Mystakidou, K., Mendoza, T., Tsilika, E., Befon, S., Parpa, E., Bellos, G., Vlahos, L., and Cleeland, C. (2001). Greek brief pain inventory: validation and utility in cancer pain. *Oncology* **60**(1)**,** 35-42.

Nair, S., Mary, T., Prarthana, S., and Harrison, P. (2009). Prevalence of pain in patients with HIV/AIDS: a cross-sectional survey in a south India state. *Indian J. Palliat. Care* **15,** 67-70.

Nakagawa, F., Lodwick, R. K., Smith, C. J., Smith, R., Cambiano, V., Lundgren, J. D., Delpech, V., and Phillips, A. N. (2012). Projected life expectancy of people with HIV according to timing of diagnosis. *Aids* **26**(3)**,** 335-43.

Namisango, E., Harding, R., Atuhaire, L., Ddungu, H., Katabira, E., Muwanika, F. R., and Powell, R. A. (2012). Pain among ambulatory HIV/AIDS patients: multicenter study of prevalence, intensity, associated factors, and effect. *J Pain* **13**(7)**,** 704-13.

Narasimooloo, C., Naidoo, S., and Gaede, B. (2011). Adequacy of pain management in HIV-positive patients. *SA Fam Pract* **53**(1)**,** 71-76.

NDOH. (2013). Revised Antiretroviral Treatment Guidelines 2013 - Presentation of the Overview http://www.sahivsoc.org/practise-guidelines/national-dept-of-health-guidelines; accessed on: 02/07/2013.

Newshan, G. (1997). Pain in human immunodeficiency virus disease. *Seminars in Oncology Nursing* **13**(1)**,** 36-41.

Newshan, G. T., and Wainapel, S. F. (1993). Pain characteristics and their management in persons with AIDS. *J Assoc Nurses AIDS Care* **4**(2)**,** 53-9.

Noble, M., Treadwell, J. R., Tregear, S. J., Coates, V. H., Wiffen, P. J., Akafomo, C., and Schoelles, K. M. (2010). Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev* (1)**,** CD006605.

Norval, D. A. (2004). Symptoms and sites of pain experienced by AIDS patients. *S Afr Med J* **94**(6)**,** 450-4.

Nunnally, J. C. (1978). "Psychometric theory." New York: McGraw-Hill.

O'Keefe, E. A., and Wood, R. (1996). The impact of human immunodeficiency virus (HIV) infection on quality of life in a multiracial South African population. *Qual Life Res* **5**(2)**,** 275-80.

O'Keefe, E. A., Wood, R., Van Zyl, A., and Cariem, A. K. (1998). Human immunodeficiency virus-related abdominal pain in South Africa. Aetiology, diagnosis and survival. *Scand J Gastroenterol* **33**(2)**,** 212-7.

O'Neill, W. M., and Sherrard, J. S. (1993). Pain in human immunodeficiency virus disease: a review. *Pain* **54**(1)**,** 3-14.

Palella, F. J., Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A., Aschman, D. J., and Holmberg, S. D. (1998). Declining Morbidity and Mortality among Patients with Advanced Human Immunodeficiency Virus Infection. *N Engl J Med* **338**(13)**,** 853-860.

Pan South, African Language, and Board (2002). "Language use and language interaction in South Africa: A national sociolinguistic survey criteria." 2. Pan South African Language Board.

Peltzer, K., and Phaswana-Mafuya, N. (2008). The symptom experience of people living with HIV and AIDS in the Eastern Cape, South Africa. *BMC Health Serv Res* **8,** 271.

Penfold, J., and Clark, A. (1992). Pain syndromes in HIV infection. *Canadian Journal of Anesthesia / Journal canadien d'anesthésie* **39**(7)**,** 724-730.

Perry, B. A., Westfall, A. O., Molony, E., Tucker, R., Ritchie, C., Saag, M. S., Mugavero, M. J., and Merlin, J. S. (2013). Characteristics of an Ambulatory Palliative Care Clinic for HIV-Infected Patients. *J Palliat Med*.

Phaladze, N. A., Human, S., Dlamini, S. B., Hulela, E. B., Hadebe, I. M., Sukati, N. A., Makoae, L. N., Seboni, N. M., Moleko, M., and Holzemer, W. L. (2005). Quality of life and the concept of "living

well" with HIV/AIDS in sub-Saharan Africa. *J Nurs Scholarsh* **37**(2)**,** 120-6.

Phillips, T. J., Cherry, C. L., Cox, S., Marshall, S. J., and Rice, A. S. (2010). Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. *PLoS One* **5**(12)**,** e14433.

Portenoy, R. K., and Lesage, P. (1999). Management of cancer pain. *Lancet* **353**(9165)**,** 1695-700.

Powers, K. A., Miller, W. C., Pilcher, C. D., Mapanje, C., Martinson, F. E., Fiscus, S. A., Chilongozi, D. A., Namakhwa, D., Price, M. A., Galvin, S. R., Hoffman, I. F., and Cohen, M. S. (2007). Improved detection of acute HIV-1 infection in sub-Saharan Africa: development of a risk score algorithm. *Aids* **21**(16)**,** 2237-42.

Pratheepawanit, N., Salek, M. S., and Finlay, I. G. (1999). The applicability of quality-of-life assessment in palliative care: comparing two quality-of-life measures. *Palliat Med* **13**(4)**,** 325-34.

Radbruch, L., Loick, G., Kiencke, P., Lindena, G., Sabatowski, R., Grond, S., Lehmann, K. A., and Cleeland, C. S. (1999). Validation of the German version of the Brief Pain Inventory. *J Pain Symptom Manage* **18**(3)**,** 180-7.

RDevelopmentCoreTeam. (2011). R: a language and environment for statistical computing (a. Vienna. R Foundation for Statistical Computing; http://www.R.project.org, ed.).

Riley, J. L., 3rd, Wade, J. B., Myers, C. D., Sheffield, D., Papas, R. K., and Price, D. D. (2002). Racial/ethnic differences in the experience of chronic pain. *Pain* **100**(3)**,** 291-8.

Rosen, S., Ketlhapile, M., Sanne, I., and Desilva, M. B. (2008). Differences in normal activities, job performance and symptom prevalence between patients not yet on antiretroviral therapy and patients initiating therapy in South Africa. *Aids* **22 Suppl 1,** S131-9.

Rosen, S., Larson, B., Brennan, A., Long, L., Fox, M., Mongwenyana, C., Ketlhapile, M., and Sanne, I. (2010). Economic outcomes of patients receiving antiretroviral therapy for HIV/AIDS in South Africa are sustained through three years on treatment. *PLoS One* **5**(9)**,** e12731.

Rosen, S., Larson, B., Brennan, A., Long, L., Fox, M., Mongwenyana, C., Ketlhapile, M., and Sanne, I. (2011). Economic Outcomes of Patients Receiving Antiretroviral Therapy for HIV/AIDS in South Africa Are Sustained through Three Years on Treatment. *PLoS ONE* **5**(9)**,** e12731.

Rosenfeld, B., Breitbart, W., McDonald, M. V., Passik, S. D., Thaler, H., and Portenoy, R. K. (1996). Pain in ambulatory AIDS patients. II: Impact of pain on psychological functioning and quality of life. *Pain* **68**(2-3)**,** 323-8.

Ruiz, M., and Cefalu, C. (2011). Palliative care program for human immunodeficiency virus-infected patients: rebuilding of an academic urban program. *Am J Hosp Palliat Care* **28**(1)**,** 16-21.

Saxena, A., Mendoza, T., and Cleeland, C. S. (1999). The assessment of cancer pain in north India: the validation of the Hindi Brief Pain Inventory--BPI-H. *J Pain Symptom Manage* **17**(1)**,** 27-41.

Schag, C. C., Heinrich, R. L., and Ganz, P. A. (1984). Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol* **2**(3)**,** 187-93.

Selwyn, P. A. (2005). Palliative care for patient with human immunodeficiency virus/acquired immune deficiency syndrome. *J Palliat Med* **8**(6)**,** 1248-68.

Seyler, C., Messou, E., Gabillard, D., Inwoley, A., Alioum, A., and Anglaret, X. (2007). Morbidity before and after HAART initiation in Sub-Saharan African HIV-infected adults: a recurrent event analysis. *AIDS Res Hum Retroviruses* **23**(11)**,** 1338-47.

Shawn, E. R., Campbell, L., Mnguni, M. B., Defilippi, K. M., and Williams, A. B. (2005). The spectrum of symptoms among rural South Africans with HIV infection. *J Assoc Nurses AIDS Care* **16**(6)**,** 12-23.

Shipton, E. (1993). "Pain: acute and chronic."

Witwatersrand University Press.

Shisana, O., Rehle, T., Simbayi, L. C., and Mbelle, N. (2005). "South African national HIV prevalence, HIV incidence, behaviour and communication survey." Cape Town: Human Sciences Research Council Press.

Sibley, L. M., and Weiner, J. P. (2011). An evaluation of access to health care services along the rural-urban continuum in Canada. *BMC Health Serv Res* **11,** 20.

Simmonds, M. J., Novy, D., and Sandoval, R. (2005). The differential influence of pain and fatigue on physical performance and health status in ambulatory patients with human immunodeficiency virus. *Clin J Pain* **21**(3)**,** 200-6.

Simpson, D. M., Schifitto, G., Clifford, D. B., Murphy, T. K., Durso-De Cruz, E., Glue, P., Whalen, E., Emir, B., Scott, G. N., and Freeman, R. (2010). Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. *Neurology* **74**(5)**,** 413-20.

Singer, E. J., Zorilla, C., Fahy-Chandon, B., Chi, S., Syndulko, K., and Tourtellotte, W. W. (1993). Painful symptoms reported by ambulatory HIV-infected men in a longitudinal study. *Pain* **54**(1)**,** 15-9.

Siziya, S., and Fylkesnes, F. (2005). Impact of HIV infection on self-rated health in a high-prevalence population with low awareness of own HIV status. *Norsk Epidemiologi* **15**(2)**,** 165-173.

Smith, M. Y., Egert, J., Winkel, G., and Jacobson, J. (2002). The impact of PTSD on pain experience in persons with HIV/AIDS. *Pain* **98**(1-2)**,** 9-17.

Smyth, K., Affandi, J. S., McArthur, J. C., Bowtell-Harris, C., Mijch, A. M., Watson, K., Costello, K., Woolley, I. J., Price, P., Wesselingh, S. L., and Cherry, C. L. (2007). Prevalence of and risk factors for HIV-

associated neuropathy in Melbourne, Australia 1993-2006. *HIV Med* **8**(6)**,** 367-73.

Solano, J. P., Gomes, B., and Higginson, I. J. (2006). A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage* **31**(1)**,** 58-69.

StatisticsSouthAfrica. (2001). Census 2001: digital census atlas (a. http://www.statssa.gov.za/census2001/digiAtlas/index.html, ed.).

Subramanian, A. K., and Morris, M. I. (2013). Mycobacterium tuberculosis infections in solid organ transplantation. *Am J Transplant* **13 Suppl 4,** 68-76.

Sukati, N. A., Mndebele, S. C., Makoa, E. T., Ramukumba, T. S., Makoae, L. N., Seboni, N. M., Human, S., and Holzemer, W. L. (2005). HIV/AIDS symptom management in Southern Africa. *J Pain Symptom Manage* **29**(2)**,** 185-92.

Tan, G., Jensen, M. P., Thornby, J. I., and Shanti, B. F. (2004). Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain* **5**(2)**,** 133-7.

Tan, I. L., Smith, B. R., von Geldern, G., Mateen, F. J., and McArthur, J. C. (2012). HIV-associated opportunistic infections of the CNS. *Lancet Neurol* **11**(7)**,** 605-17.

Tapsfield, J. B., and Bates, J. M. (2011). Hospital based palliative care in sub-Saharan Africa; a six month review from Malawi. *BMC Palliat Care* **10,** 12.

Tollefson, J., and Usher, K. (2006). Chronic pain in the rural arena. *Aust J Rural Health* **14**(3)**,** 134-5.

Tsai, Y. F., Hsiung, P. C., and Holzemer, W. L. (2002). Symptom management in Taiwanese patients with HIV/AIDS. *J Pain Symptom Manage* **23**(4)**,** 301-9.

Tsao, J. C., Dobalian, A., and Naliboff, B. D. (2004). Panic disorder and pain in a national sample of persons living with HIV. *Pain* **109**(1-2)**,** 172-80.

Tsao, J. C., Dobalian, A., and Stein, J. A. (2005). Illness burden mediates the relationship between pain and illicit drug use in persons living with HIV. *Pain* **119**(1-3)**,** 124-32.

Tsao, J. C., and Soto, T. (2009). Pain in persons living with HIV and comorbid psychologic and substance use disorders. *Clin J Pain* **25**(4)**,** 307-12.

UNAIDS (2011). "UNAIDS report on global AIDS epidemic 2010."

UNESCO (2008). "EFA global monitoring report - overcoming inequality: why governance matters. Geneva." UNESCO.

United Nations Educational, S., and (UNESCO), a. C. O. (2008). "EFA global monitoring report - overcoming inequality: why governance matters. Geneva." UNESCO.

Uwimana, J., and Struthers, P. (2007). Met and unmet palliative care needs of people living with HIV/AIDS in Rwanda. *Sahara J* **4**(1)**,** 575-85.

Van As, M., Myezwa, H., Stewart, A., Maleka, D., and Musenge, E. (2009). The International Classification of Function Disability and Health (ICF) in adults visiting the HIV outpatient clinic at a regional hospital in Johannesburg, South Africa. *AIDS Care* **21**(1)**,** 50-8.

Verma, S., Estanislao, L., Mintz, L., and Simpson, D. (2004). Controlling neuropathic pain in HIV. *Curr HIV/AIDS Rep* **1**(3)**,** 136-41.

Vogl, D., Rosenfeld, B., Breitbart, W., Thaler, H., Passik, S., McDonald, M., and Portenoy, R. K. (1999). Symptom prevalence, characteristics, and distress in AIDS outpatients. *J Pain Symptom Manage* **18**(4)**,** 253-62.

Voss, J. G., Sukati, N. A., Seboni, N. M., Makoae, L. N., Moleko, M., Human, S., Molosiwa, K., and Holzemer, W. L. (2007). Symptom burden of fatigue in men and women living with HIV/AIDS in Southern Africa. *J Assoc Nurses AIDS Care* **18**(4)**,** 22-31.

Wadley, A. L., Cherry, C. L., Price, P., and Kamerman, P. R. (2011). HIV neuropathy risk factors and symptom characterization in stavudine-exposed South Africans. *J Pain Symptom Manage* **41**(4)**,** 700-6.

Wahab, K. W., and Salami, A. K. (2011). Pain as a Symptom in Patients Living With HIV/AIDS Seen at the Outpatient Clinic of a Nigerian Tertiary Hospital. *J Int Assoc Physicians AIDS Care (Chic)* **10**(1)**,** 35-9.

Wakeham, K., Harding, R., Bamukama-Namakoola, D., Levin, J., Kissa, J., Parkes-Ratanshi, R., Muzaaya, G., Grosskurth, H., and Lalloo, D.

G. (2010). Symptom burden in HIV-infected adults at time of HIV diagnosis in rural Uganda. *J Palliat Med* **13**(4)**,** 375-80.

Wang, X. S., Mendoza, T. R., Gao, S. Z., and Cleeland, C. S. (1996). The Chinese version of the Brief Pain Inventory (BPI-C): its development and use in a study of cancer pain. *Pain* **67**(2-3)**,** 407-16.

Ward, J., Darke, S., Hall, W., and Mattick, R. (1992). Methadone maintenance and the human immunodeficiency virus: current issues in treatment and research. *Br J Addict* **87**(3)**,** 447-53.

WHO. (1987). "Analgesic ladder". *Geneva, Switz: World Health Organization*.

WHO (1990). "Cancer Pain Relief and Palliative Care." Geneva, WHO.

Wilson, L. E., Korthuis, T., Fleishman, J. A., Conviser, R., Lawrence, P. B., Moore, R. D., and Gebo, K. A. (2011). HIV-related medical service use by rural/urban residents: a multistate perspective. *AIDS Care* **23**(8)**,** 971-9.

Yoshida, D., and Caruso, J. M. (2002). Abdominal pain in the HIV infected patient. *J Emerg Med* **23**(2)**,** 111-6.