A survey of the prevalence and burden of pain and symptoms amongst HIV positive patients attending HIV treatment clinics in the University of the Witwatersrand Academic Hospital clinics.

Written by

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ii) Declaration

DECLARATION

I, LINDSAY ZEPPELINE FINDIANT, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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iii) Contents

iv) Tables, Figures and Graphs

Tables

Figures

Graphs

v) Abbreviations

AIDS	= Acquired Immune Deficiency Syndrome
ART	= Antiretroviral therapy
ARVs	= Antiretroviral medications
CDC	= Centre for Disease Control
CD4 count	= CD4 cell count
HAART	= Highly active antiretroviral therapy
HCW	= Health care worker
HIV	= Human Immunodeficiency Virus
KPS	= Karnofsky Performance Status
MDD	= Major Depressive Disorder
MSAS	= Memorial Symptom Assessment Scale
MSAS-SF	= Memorial Symptom Assessment Scale – Short Form
MSAS-GDI	= Memorial Symptom Assessment Scale - Global Distress Index
MSAS-PHYS	= Memorial Symptom Assessment Scale – Physical Symptom Subscale
MSAS-PSYCH	= Memorial Symptom Assessment Scale – Psychological Symptom Subscale
MVQOLI	= Missoula-VITAS Quality of Life Index
PI	= Principle investigator
PMI	= Pain Management Index
SSC-HIVrev	= The Revised Sign and Symptom Checklist for Persons with HIV Disease
TB	= Tuberculosis
TMSAS	= Total Memorial Symptom Assessment Scale (Short Form) score
UK	= United Kingdom
USA	= United States of America
VL	= viral load
WBPQ	= Wisconsin Brief Pain Questionnaire
WHO	= World Health Organisation

Abstract

Purpose: This study was designed to measure the symptom prevalence and symptom burden amongst patients attending three HIV treatment clinics in greater Johannesburg, and to assess the relationship of these to CD4 count, viral load, WHO stage, functional status and HAART.

Methods: Patients at the three clinics were invited, using convenience sampling, to participate in completing the interviewer administered Memorial Symptom Assessment Scale-Short Form (MSAS-SF) which assesses the 7 day prevalence and distress for 28 physical symptoms and prevalence and frequency of four psychological symptoms. Demographic and clinical data, including initial and latest CD4 counts, initial and latest viral loads and information on HAART use, were collected from the participants and from their clinic files. The Karnofsky Performance Status (KPS) scale was used to assess functional status.

Results: There were three hundred and eighty five participants with 98% on HAART. The mean symptom number was 10.24 (standard deviation [SD] = 5.7). The six most prevalent symptoms with more than 50% prevalence were: feeling sad (65%), feeling irritable (62%), numbness/tingling in hands & feet (61%), worrying (61%), problems with sexual interest or activity (52%) and pain (51%). The mean distress scores (±SD, range) were: MSAS-GDI 1.19 ± 0.89 (0-3.84), MSAS-PHYS 0.80 ± 0.71 (0-3.66), MSAS-PSYCH 1.27 ± 1.06 (0-4); and TMSAS 0.90 ± 0.63 (0.25-3.125). On regression analysis, KPS scores, WHO stages and the female gender were most consistently predictive of the subscale distress scores, while the latest CD4 count was only predictive of physical distress and viral load was not predictive of any symptom distress.

Conclusion: This study shows the high prevalence and high burden of physical symptoms amongst patients who attend outpatient HIV treatment clinics, and that this occurs at any CD4 count, all WHO stages, and with any KPS score, and among patients who are on HAART, motivating for the need for symptom control and palliative care alongside HAART in outpatient HIV treatment clinics in South Africa.

Chapter 1

Introduction

The impact of HIV on South Africa and the current situation

The Human Immunodeficiency Virus (HIV) has significantly impacted on the health status of South Africans in general. The 2010 mid-year population estimate from Statistics South Africa is 49.99 million(1). Gauteng Province, where this study that is being reported was conducted, has the largest proportion of the country's population – 22.4%(1). For all ages, the estimated HIV prevalence is considered to be around 10.5%, while for the age group with the highest incidence, those aged 15 – 49 years, the estimated HIV prevalence rate is 17%(1). The National Antenatal Sentinel HIV and Syphilis Prevalence Survey in South Africa, 2009 found the HIV prevalence in 2009 among antenatal clinic attendees aged 20-24 was 26.6%, for the age 25-29 was 37.1%, and for the age 30-34 was 41.5%(2). The National HIV prevalence study in 2008 showed that for women, the greatest prevalence was for age group 25 – 29 years, while for men, the greatest prevalence was for the ages 30 – 34, while the prevalence among women remained the highest overall prevalence(3). The estimated total number of people living in South Africa with HIV in 2009/2010, was between 5.2 and 5.63 million(1,2).

This requires that the question be answered of how many people are in need of HAART in South Africa. The answer to this question also depends on what the national guidelines are for starting HAART. The current guidelines adopted in 2010, are that HAART should be started in any patient who has a CD4 count under 350cells/mm^3(4). However, the previous guidelines were to start HAART for those patients with a CD4 count under 200cells/mm^3(5). For 2010, Statistics South Africa estimated that 1.6 million people over the age of 15 years would need HAART(1), however it is uncertain whether the 2004 or 2010 guidelines were used to calculate this figure, so this number may be significantly higher. The estimate for 2009, of the number of HIV positive people over the age of 15 who were actually on HAART, is 920 000(1). There is thus a significant shortfall on the number of South Africans needing HAART who are actually receiving it. This means that many people are starting HAART very late, with these people having a greater likelihood of significant morbidity and being at risk

for dying before starting HAART. As such, the life expectancy at birth in 2010 for the female population is 55.2 years and for the male population is 53.3 years(1). As a country managing a large scale HIV epidemic with these numbers described, we are still trying to catch up to meet the HAART needs of all South Africans with HIV.

Palliative Care in HIV Treatment clinics in South Africa

Palliative Care is defined by the WHO as 'an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering, the early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual'(6). Since the advent of antiretrovirals (ARVs) and highly active antiretroviral therapy (HAART), and the improved immunological status of patients taking these medications, mortality has decreased significantly(7), resulting in the chronicity of the disease as many people know it today. There is a misunderstanding amongst health care workers that patients with such chronic HIV disease do not need palliative care. Palliative care is considered by many to be no longer a standard need in HIV treatment clinics in 2011. However, the WHO definition of Palliative Care goes on to say that palliative care "is applicable early in the course of the illness, in conjunction with other therapies that are intended to prolong life", thus advocating for applying palliation from the early stages of disease while disease-specific management is employed(6). This is because Palliative Medicine practitioners recognise, and the WHO definition affirms, that "relief from suffering" in all its forms and at any time, including "pain and other distressing symptoms", as well as addressing quality of life issues, are integral to the management of a patient with a life-threatening illness(6). Symptom management therefore should be incorporated together with HAART in the management of HIV disease. Selwyn and Rivard write that "Rather than being 'either-or', curative and palliative approaches to HIV care need to be 'both-and', and one paradigm need never fully substitute for the other"(8). O'Neill and Barini-Garcia confirm this, writing that "Palliative Care is complementary care, not alternative care", motivating for palliation of symptoms to be an integral part of HIV care, together with HAART and disease control(9).

There are identified palliative care needs at all stages of HIV disease, with and without the use of HAART(10-14). This was highlighted in a recent correspondence to *Clinical Infectious Diseases,* commenting on the authors' findings at the recent International AIDS Society conference in relation to proposed national and multi-agency human immunodeficiency virus (HIV) quality care measures published in *Clinical Infectious Diseases*(15). Gwyther, from the Hospice Palliative Care Association of South Africa, wrote in a private communication that the goal of palliative care for patients with HIV, is the restoration of their health as the ultimate goal in the objective of improving their quality of life, and that this can be achieved through holistic care which actively addresses the care needs of the patient and their family and also necessarily assists in treatment support(16). A study conducted in Uganda, by Wakeham et al, amongst patients with a new diagnosis of HIV, found that there is a high prevalence of symptoms amongst patients, even at diagnosis and also among patients who are diagnosed in the WHO stage 1 stage of disease, not just among patients diagnosed with higher WHO stages of disease(17). Fontaine et al reported on their findings from a multi-centre cross-sectional survey conducted in France, that physicians did not reliably recognise the symptoms that their patients experienced and that this was particularly low for symptoms that do have treatments (for example nausea and vomiting) and for symptoms that may be due to drug side effects(18). Symptom recognition by physicians was best for symptoms which were measurable, such as fever and weight loss; and symptom recognition was also better for patients who were perceived to be more ill, suggesting that physicians were more vigilant in asking about symptoms in these situations(18). This particular study shows clearly that health care workers should not assume symptoms to be absent unless a clear a detailed history has been taken. It also shows that patients are often not able to make their doctors aware of the symptoms from which they are suffering, indicating communication gaps. These issues may in fact call for the use of symptom assessment tools in daily clinical practise to improve symptom assessment, as part of management protocols for patients with HIV. This study also speaks of the training needs of health care workers around the prevalence of symptoms and how burdensome symptoms may be, and also speaks to the training needs around symptom assessment and management.

This international research is relevant to the South African outpatient HIV treatment clinic, but it may be considered to be of theoretical relevance if the prevalence and burden of pain and other symptoms are not quantified in these clinic populations. If we know the symptom prevalence and the burden of those symptoms, we will be able to begin to quantify the need for, or lack of, symptom management in the South African HIV clinic setting. This study aims to quantify the prevalence and burden of pain and other symptoms in an urban clinic setting in South Africa, so that appropriate measures can be taken to address the gaps in symptom assessment and management and to motivate for adequate palliative care for patients at all stages of disease in outpatient HIV clinics and indeed in other settings of health care provision.

The prevalence of pain and symptoms experienced by patients who are HIV infected

International research has shown that patients attending HIV treatment clinics often do have symptoms(10-13). Most studies that have investigated symptoms amongst HIV patients in South Africa, were conducted before HAART was available to patients in the government health sector(19-21). These studies showed a high prevalence and burden of symptoms. However, only one of these studies used a validated symptom assessment tool(20), so the results are not easily comparable to other South Africa or international studies. Since HAART became available, a study carried out in the Eastern Cape points to a continued high prevalence of symptoms(22). International studies suggest the continued high prevalence and burden of pain and other symptoms even with the use of HAART(14,23-25). It is not appropriate to extrapolate this international data directly on to the South African population. In order to adequately assess and manage symptoms amongst a patient population attending public sector HIV treatment clinics in urban South Africa, we need to have prevalence and burden data from studies within that population. Pappas et al(26) comment that "*Estimation of the pain and symptoms in HIV infected groups and in populations in general will increase our understanding of unmet needs for palliative care*." Selwyn writes of the need to '*reacquaint*' the current medical treatment of HIV, which we are now fortunate to have better access to in South Africa (particularly HAART), with what was previously the only management available to patients with AIDS, namely palliative

care(27). He writes that we need to "*provide our patients with the benefits of both types of expertise"*(27).

The quality of life experienced by patients with HIV is complex to measure. One of the measures of quality of life is the prevalence and burden of pain and other symptoms(28-30). Other components of the measure of quality of life for patients with HIV may include physical function, social function, role function, mental/emotional health, the effect of treatment and perceptions of the patient's own health status(28-30). There is indication from research that symptoms experienced by people with HIV disease are significant in their impact on overall quality of life assessments, and that HAART does not necessarily resolve all symptom problems, although HAART does seem to stabilise quality of life over time(30). The relevance of symptoms for the patients who experience them thus go beyond the symptom experience in itself, and invade so many aspects of the patients lives, including the psychological, social, practical and spiritual dimensions. This confirms the need for clinicians and health care workers to understand the symptom prevalence and burden in the patient population we serve, so as to better understand this part of the influence of the disease on the quality of life of these patients, and in so doing, be able to treat the treatable symptoms to make improvements in patient quality of life.

The burden of pain and symptoms experienced by HIV infected patients

The prevalence of a symptom is of great importance, as it indicates how frequently the physician may expect to find the symptom in the patient group served. The presence of a symptom is however not enough for a physician to be able to adequately manage the symptom for the individual patient. For management of a symptom to be adequate, the severity or burden of the symptom needs to be known. The assessment of management success requires that the baseline burden of the symptom is known, so as to assess the change in the burden of the symptom. The international research described above suggests a high degree of burden from those symptoms that have been found to be highly prevalent(10,14,23-25). This includes psychological symptoms which have been found to be particularly burdensome to patients, even to those patients who are on HAART(10,14,23-25). To my knowledge, one South African study (including patients on HAART) and one

other Southern African study (pre-HAART), have assessed symptom burden and they have found a similar level of symptom burden amongst their study populations as has been found internationally(20,22). Burden from symptoms and psychological distress have been found to be correlated to each other and also to functional status and to quality of life measures(10). Of importance is that an increased burden from symptoms has been significantly associated with poor HAART adherence(23,31). Burdensome symptoms that are not addressed will therefore cause ongoing suffering and poorer quality of life for patients. The palliative approach aims to specifically address this suffering, so as to improve overall quality of life for the patient.

How symptoms and burden from symptom relate to disease-specific biological data and to demographic data

There is international research that suggests that pain and symptoms are prevalent at all WHO stages of HIV disease, at all CD4 count levels, and whether patients are on HAART or not(10,14,23-25). This research shows that patients with relatively 'high' CD4 counts and who are classified as WHO stage 1 or 2, do indeed have significant numbers of symptoms and do experience significant burden from those symptoms, and that the prevalence and burden of symptoms for these patient groups are not always significantly different to those patients with lower CD4 counts and who are staged as WHO stage 3 or 4 disease(10,14,23-25). This research is important for health care workers to be aware of and points to the importance of assessing each patient as an individual and to being patient-focussed, rather than being disease- and/or virus-focussed. There is very little data on these important aspects of HIV patient management recorded in an urban South African HIV treatment clinic context. Research that was done in South Africa before HAART became available, did not evaluate the relationship between symptoms and burden from symptom, with CD4 counts, viral loads, performance status, gender or age(19,20). Since the availability of HAART in the government health service, two studies have been conducted that assessed the presence of symptoms and that have, to varying degrees, compared these to biological and demographic data(22,32). One of these studies was conducted in a rural population(22) while the other does not make it clear whether it was an urban, rural or mixed population(32). The one study only used self-reported CD4 counts, which is open to

error(22), while the other study, using clinic records for accurate CD4 count collection, did not relate symptoms to any of the biological or demographic data, but compared a broader assessment of quality of life to some of these variables(32). We therefore know that symptoms could be expected to be prevalent in the urban study population proposed for this study, however the symptom prevalence and burden has not been formally researched in this environment and extrapolations from other population groups are unwise.

Without knowledge of what to expect of patient symptomatology, the health care worker's index of suspicion for symptoms may be low. Patients who do not feel able to voice their needs and who are not given a real chance and permission to do this, will not address their symptom problems with their health care worker. Such vulnerable people are those that receive care from the government HIV treatment clinics in South Africa. This means that patients who are on HAART, regardless of CD4 count, or patients receiving pre-HAART treatment at HIV treatment clinics may not be adequately screened for symptoms and burden from symptoms and there may be inadequate or absent symptom assessment and management for patients. Without knowledge of symptom prevalence and burden and how these occur at different WHO stages and CD4 count levels, health care providers may be unaware of their own training needs in the areas of symptom control and palliation for the patients they see everyday in the HIV clinic setting.

Management of health-related symptoms for HIV infected patients

Without recent data in the era of HAART on the pain and symptom prevalence and burden amongst HIV infected patients in South Africa, we are not able to comment on the need for or the adequacy of the symptomatic management of patients attending HIV treatment clinics. International studies have suggested that pain and other symptoms are undertreated(13,33,34). Palliative care is patient-focused, attending to the individual needs of individual patients. South African HIV treatment clinics tend to be very busy, with many patients requiring review each day. The focus is on immunological, virological and clinical disease control. This is often life-saving treatment for patients. The accompanying questions relating to quality of life issues, are however, often considered to be of secondary importance, and may not be addressed. It is the intention of this study to highlight what

some of these needs may be and in so doing, why these needs may actually not be of secondary importance. It is also of importance to point out that a recent study of the availability of analgesia and related medication in Sub-Saharan Africa (including South Africa) for patients with palliative care needs, including HIV patients, showed a marked discrepancy between ideal analgesic, antiemetic and anxiolytic availability and actual availability(35). This highlights the lack of understanding of pain and symptom control needs at national and local levels. An interventional study by Green et al, which used a non-randomised control trial method, with an embedded qualitative study, was begun in northern Vietnam in 2007 to assess the effectiveness of introducing palliative care into existing HIV outpatient treatment clinic services(36). The reported preliminary findings have shown that at baseline only 5% of the symptoms experienced by patients were documented by the clinicians, while after a symptom assessment tool was introduced as part of the clinic service protocol, with clinicians trained in pain and symptom management, 98% of patients had documented symptom assessment for at least one visit, and 93% of patients had symptoms documented more often(36). There has also been improved symptom management for patients with neuropathic pain and with depression, and very importantly, the qualitative part of the study showed that clinicians were very pleased at being able to assess and manage their patients' symptoms(36). This study shows that integration of palliative care assessment and management strategies into regular HIV outpatient treatment clinics in a developing country is possible and indeed very necessary for the holistic management of patients with HIV, and that palliative care does indeed improve patient outcomes.

Symptoms and Adherence to HAART

Research indicates that there is significant evidence that symptoms and the burden of symptoms experienced by patients, affect HAART adherence directly and indirectly, as well as independently affecting virological disease control(31,37). This is of great importance for the South African HIV infected patient, where stigma and poor education, among other factors, still continue to dominate the decisions of patients requiring HAART. It has been shown that pain, other physical symptoms and also psychological symptoms, especially depression and anxiety, may all contribute to inadequate adherence to HAART(31,37,38).

Another interesting finding by Sherr et al was that patients who had greater satisfaction with their doctor-patient relationship, had better HAART adherence than those who reported less satisfaction with their doctor-patient relationship(31). A good doctor-patient relationship is likely to be one in which symptoms are readily discussed and effectively managed. This research proves that it is crucial to know how and why patients with HIV in South Africa suffer, so as to manage them effectively and holistically, in an attempt to maintain HAART adherence for maintained virological suppression and HAART treatment success.

Summary

This study was conducted at three adult HIV treatment clinics in Johannesburg, South Africa. The clinics are at three academic hospitals attached to the University of the Witwatersrand's Medical School, namely the Charlotte Maxeke Johannesburg Academic Hospital, the Chris Hani Baragwanath Hospital and the Helen Joseph Hospital. At these clinics, as in the majority of other HIV treatment clinics in South Africa, anecdotal evidence is that HIV management has been provided, predominantly in the form of HAART and disease-centred management, with minimal symptom assessment and management in a patient-centred manner.

The following issues are not adequately addressed by current research: the prevalence of pain and symptoms and the burden imposed by these symptoms as experienced by urban South Africans who attend HIV treatment outpatient clinics; the relationship that symptom prevalence and burden may have with CD4 counts, viral loads, WHO stage of disease, functional status and HAART. Prior research in other settings indicates that these are important aspects of the HIV disease experience to understand, so as to manage patients more effectively, in conjunction with HAART. It is the intention of this study to document the symptom prevalence and the burden of these symptoms that are experienced by the patients attending HIV treatment clinics in the urban setting of greater Johannesburg, and to analyse the relationships that may exist between the symptoms and the burden of symptoms with the variables highlighted. In this dissertation, I describe the study conducted in order to answer some of these unanswered questions. In chapter two, I

outline and discuss the current literature on these issues, expanding on the issues raised thus far. In chapter three the aims and objectives of the study are stated and in chapter four the details of the study methods are described. The results of the study are described in chapter five. In chapter six the results are discussed and the findings are concluded in chapter seven.

Chapter 2

Literature Review

This literature review was compiled by searching MEDLINE databases through Pubmed, Ebsco and Ovid, and also using Google Scholar to extend searches. Particular references that were found through reading relevant journal articles and book chapters, were also specifically searched for through the MEDLINE database. This literature search was done over a period of time from the period of protocol development, during the time of data collection and completed during the write up of the findings in this dissertation. The words used for the searches (and used in combination) include: palliative care, HIV, symptoms, pain, depression, symptom assessment tools, symptom assessment, symptom burden, symptom distress, symptom experience, HAART, ART, quality of life, adherence, function, prognosis, antiretrovirals, AIDS, prevalence, outcome and review. All literature reviewed related to an adult study population.

South African and Southern African studies on symptoms experienced by HIV positive people

There are relatively few studies done in South Africa amongst HIV infected adults that have specifically looked at the symptom prevalence and burden in HIV positive people, particularly since HAART became available in the state health service. Symptoms are defined as "*any subjective evidence of disease or of a patient's condition, i.e. such evidence as perceived by the patient*"(39). Symptom prevalence is defined as "*the numbers of cases of (symptoms) that are present in a population at a specified time*"(39). For the purposes of this study, and in the writing of this dissertation, prevalence refers to "*point prevalence*" which is prevalence "*at a point in time"*(39). Symptom burden refers to the physical burden or load, and the emotional distress that a symptom imposes on the patient.

Norval studied the most prevalent symptoms and most common sites of pain in a cross-sectional descriptive study, in a hospice-based population in Soweto in 2002-2003, before HAART was available to patients in the state health sector(19). The study population included all the registered adult hospice patients at the time of study who were willing to participate and who fulfilled the selection criteria, reaching a reasonable study sample size(19). Patients all had advanced AIDS, WHO stage 4 disease and the group was predominantly female(19). The most prevalent symptom was pain, for 98% of participants, and 34.4% of participants identified pain as their worst symptom, with an average of 2.91 pains per patient, while the other most common symptoms identified were typical of advanced life-threatening disease, included weight loss, loss of appetite, low mood, weakness and fatigue(19). The burden of each symptom was not directly assessed and the symptom assessment tool was not a validated tool, however this study highlights the significant symptom prevalence amongst people who have advanced AIDS and who are dying of AIDS, and have for the most part not had the benefit of HAART. The mean number of pains in this study is similar to that found by a study in the USA which found an average of 2.7 pains per patient(12).

In a cross-sectional descriptive Southern Africa study done by Makoae et al in 2002, the frequency and intensity of symptoms amongst HIV positive people in South Africa, Botswana, Lesotho and Swaziland was assessed(20). This was a multi-centred study with a good sample size, including a mix of participants from urban, peri-urban and rural areas(20). In this study, no ART use was reported by participants and there was generally little availability of these drugs. The validated 64-item Revised Sign and Symptom Checklist for Persons with HIV disease was used to assess for symptom prevalence and intensity, reporting a mean total number of symptoms of 17.58 per person, with the top five symptoms not unlike those found by Norval, being fatigue, weakness, concern over weight loss, fear and worries, and painful joints(19,20). This is a valid study which achieved its objectives and found significant psychological distress on the 3 point Likert scale, and also showed a significant relationship between symptom frequency and a) financial problems and b) the presence of children to care for(20) .

A more recent cross-sectional study using convenience sampling, conducted by Peltzer and Phaswana-Mafuya in the Eastern Cape in 2007, using the same validated symptom

assessment tool as Makoae et al, found a symptom prevalence of 26.1 symptoms per person(22). In this study of good sample size, 48% of participants were on HAART and the most common symptoms found on the day of study were not unlike the symptoms found by Makoae et al and Norval, but specifically highlighted the issue of fatigue amongst their study sample(19,20,22). The data for this study was acquired by interviewing the participants and using their recall for clinical data, rather than clinic files, which is open to bias(22). Participants on HAART were found to experience more numbness or tingling of hands or fingers than those not on HAART and overall this study found that HAART was not associated with a decrease in symptom burden and in general a significant number of psychological symptoms were found(22). It appears that the majority of the aims of this study were achieved.

A longitudinal study of rather limited sample size, conducted by Bhargava and Booysen in the Free State Province of South Africa in 2004, at the beginning of the availability of HAART in South Africa, did not directly report on symptom prevalence and burden, but showed that patients who felt that they received emotional support had a significantly greater increase in CD4 cell counts following HAART initiation as well as better quality of life scores than, than patients who did not feel they received emotional support(32). The same study found that better perceived health care services resulted in better CD4 count improvements; and that better health care worker ratings and higher CD4 counts were related to improved quality of life in patients(32). The finding that the perception of better heath care service was related to better quality of life for patients shows that the quality of the health care service that is provided does appear to impact on patient outcomes(32). The findings from a United Kingdom study by Sherr et al which will be discussed in more detail further on in this chapter, clearly showed that better relationships with clear and equal communication between the patient and the health care worker result in better HAART adherence(31) and they give the findings of Bhargava and Booysen particular credence and are of importance for health care workers wishing to improve patient outcomes on HAART.

African studies on symptoms experienced by HIV positive people

An attempt was made to access the relevant studies conducted in Africa, and it appears that studies in this particular area of symptom prevalence, tend to be conducted in Uganda, Malawi, Botswana, Lesotho and Swaziland(17,20,40). An audit carried out in 2003 and 2004 over an 18 month period in Malawi by Bowie et al, was done in their pre-HAART era, in a home-based care patient group of whom 70% of patients were clinically diagnosed as WHO stage 4 disease(40). Records of initial and follow up patient assessment and management notes were audited(40). Pains were recorded by site, with 84% of participants experiencing moderate to severe pain at initial assessment visit, and with headache, fever, chest pain, shortness of breath and cough as the most prevalent symptoms(40). The functional capacity of the sample was poor, with only 44% of participants being able to care for themselves(40). This audit of a good number of patients is useful for recording the symptom prevalence over a period of time in end-stage HIV disease before HAART became available, but did not use a validated symptom assessment tool and therefore may even have under-reported on symptoms and also did not report on symptom burden.

The study by Wakeham et al in rural Uganda assessed symptom prevalence and burden, at the time of HIV diagnosis, to assess whether WHO staging and or CD4 count had any impact on symptom prevalence and burden(17). Participants of a particular double blind randomised placebo controlled trial were all invited to participate in this associated study on symptoms(17) and good participant numbers were attained. The validated Memorial Symptom Assessment Scale - Short Form (MSAS-SF) was used, and an additional 9 symptoms were added to the original 32 symptoms of the MSAS-SF(17). The sample was 59% female, and 62% of participants were in WHO stage 3 and 6% WHO stage 4(17). The mean total number of symptoms was 14 with the top 6 physical symptoms being pain, weight loss, itching, feeling drowsy/feeling tired, lack of energy, numbness or tingling of hands or feet and the two most common psychological symptoms were worry and feeling sad(17). These psychological symptoms were highly frequent if present(17). This study assessed the relationship of symptoms to biological and demographic factors and found that the number of symptoms increased for increasing disease stage by WHO staging, but even participants who were staged WHO stage 1 had a median of 9 symptoms, and 63% of these patients in WHO stage 1 had pain(17). Participants with CD4 counts less than 100 had only

slightly more symptoms than those with CD4 counts ranging from 100-200, and so there was no statistically significant difference in symptom prevalence and burden between these CD4 count groups(17). This is an important piece of research which attained their study aims and could show that for patients who are newly diagnosed with HIV, symptoms can and do occur at any stage of HIV disease, and at any CD4 count. However, it may not be correct to extrapolate these results onto patients who have already had an HIV diagnosis previously and are further along the disease trajectory.

International studies on symptoms experienced by HIV positive people

Far more study on symptom prevalence and burden has been done internationally, than in South Africa. The studies described below, show significant symptom prevalence and burden, both in the physical and psychological symptom groups.

In New York City, Vogl and colleagues conducted a large cross-sectional survey between 1992 and 1995(10). Participants were all diagnosed with AIDS (CD4 count <200, or CDC clinical category 3) and were attending an outpatient clinic(10). The researchers used the validated MSAS-SF to gather information regarding symptom prevalence and burden, and also the Karnofsky Performance Status Scale, the Brief Symptom Inventory, the Beck Depression Inventory, the Beck Hopelessness Scale, the Functional living Index – Cancer (modified for AIDS), and the Social Support Questionnaire – Short Form, thus using a comprehensive array of tools to assess the patient experience of disease(10). The mean number of symptoms per person was 16.7, out of a possible 32 MSAS-SF symptoms(10). Twelve symptoms had a prevalence of over 60%, namely worrying, lack of energy, feeling sad, pain, feeling irritable, difficulty in sleeping, feeling nervous, dry mouth, difficulty concentrating, shortness of breath, feeling drowsy and cough, showing a high prevalence of psychological symptoms and symptoms related to the psychological distress subscale(10). This study found no relationship between CD4 count and symptom prevalence or distress or any of the other MSAS-SF measures, but the authors felt this could be studied further, and that viral load results may be useful(10). The study methods employed were comprehensive and are reproducible, with good analysis of possible confounding variables.

Silverberg et al studied the prevalence of symptoms amongst women, in relation to HAART, as part of the multi-centre prospective cohort Women's Interagency HIV Study (WIHS) in the USA which included a control group of HIV negative women(11). Symptoms were assessed using an apparently non-validated questionnaire between October 1999 and April 2003(11). The most prevalent symptom was fatigue, then headaches and myalgias and the study found that the women with the highest number of symptoms were in the groups who had stopped all ART and in those who had ever changed HAART regimens(11). In their control group, women who were HIV negative did have symptoms, but had far fewer symptoms than HIV positive women(11). This study did not specify a symptom assessment tool used and did not make clear which symptoms were assessed for, making it difficult to compare with other studies.

In a cross-sectional online survey among gay HIV positive men in the United Kingdom, in 2004, Harding et al found a mean number of 12.3 symptoms (out of a possible 32 symptoms on the MSAS-SF), but that those men on HAART had more symptoms (14.0) than those not on HAART(10.3)(24). The sampling method used may have introduced selection bias, but the study population was found to be reasonably similar to samples from community sampling(24). The most prevalent symptoms were worrying, feeling sad, feeling irritable, lack of energy, feeling nervous, difficulty in sleeping, difficulty in concentrating, feeling drowsy, problems with sexual interest or activity, diarrhoea and pain, which is similar to the findings in the study in New York by Vogl et al, particularly for the frequency of psychological symptoms(10,24). The most prevalent overall symptoms were psychological symptoms, but certain physical symptoms were more prevalent amongst those on HAART(24). In contrast to Vogl et al, they found that the latest CD4 count had a very weak but significant relationship with global distress scores(10,24). The use of a validated symptom assessment tool that has been used in recent HIV symptom research, with appropriate analysis of symptoms in relation to biological and demographic data, despite being self-reported by the patient and only among gay men sampled online, makes this a useful study.

Willard et al reported on a secondary analysis of two international multi-site studies on symptom prevalence and intensity in HIV disease, each of large sample size, and concluded that CD4 count and stage of disease did not correlate with differences in symptom

experience and severity, and that those patients with CD4 counts over 350, regardless of HAART use, are not less symptomatic than those with lower CD4 counts(14). The one study reviewed was cross-sectional, and the other study was a randomised controlled trial where only the baseline data was used, meaning that the level of evidence reviewed was appropriately significant, and the validated *Revised Sign and Symptom Checklist for Persons with HIV Disease (SCC-HIVrev)* symptom assessment tool was used(14).

A cross-sectional multi-centre study, conducted in London in 2005-2006, by Harding and colleagues, of a large sample size of consecutively approached AIDS outpatients, with 67.4% of patients on HAART at the time of the study, found a high rate of burden of psychological symptoms and of pain(23). Participants completed their own questionnaires of clinical and behavioural data and also the MSAS-SF(23). Lack of energy was the most prevalent symptom at 70.8%, with the following most prevalent symptoms being feeling drowsy, difficulty sleeping, difficulty concentrating, diarrhoea, problems with sexual interest or activity, pain(23). The psychological symptoms were very common, with worrying being most prevalent, then feeling sad(23). HAART was not linked to a change in symptom prevalence, while poorer HAART adherence was related to psychological and global distress, and patients who had ever changed HAART had more symptoms and increased physical, psychological and global distress(23), similar to the findings of Silverberg et al(11). This study achieved its study aims, making it useful and valid.

A longitudinal study conducted in the USA, by Karus and colleagues, of good sample size, at three different HIV patient palliative care sites (Alabama, Baltimore and New York City), reported patient symptoms at first assessment, and found a high prevalence of physical and psychological symptoms, using the Memorial Symptom Assessment Scale (MSAS) with two modifications(34). The most common symptoms were lack of energy, pain, worrying and difficulty sleeping(34), which were similar to the findings of other studies(10,23,24). The average number of symptoms per site was 12.7, 11.9 and 10.9 and these and differences noted between the sites highlighted the need for studies to identify the specific needs of specific patient populations(34). Inadequate information of patient use of HAART was provided, making comparisons with other surveys and interpretation of the relevance of the results challenging.

Studies focusing on Pain

Pain has been defined by the International Association for the Study of Pain (IASP) as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"*(41). Pain is moderated by the patient's mood, morale and the meaning of the pain for the patient(42).

As far as pain itself is concerned, there are a number of studies that have addressed the issue of pain in HIV(12,13,33,43-46). Breitbart el al found that in the sample of AIDS outpatients in a study on the treatment of pain in New York, in the USA, that the prevalence of pain that was 'frequent or persistent', was over 60%, with a mean of 2.5 distinct pains(43). Rosenfeld et al who wrote a follow-on article to Breitbart et al, on the same study, noted that there was a definite correlation between pain and emotional distress, depression, loss of hope and quality of life factors(44). A further survey of the patient population described by Breitbart et al, was conducted by Hewitt et al, to research the pain syndromes and their causes amongst AIDS outpatients in New York, in the USA(12). In this survey which was of reasonable sample size, 61% of patients, of whom most were diagnosed with AIDS, had frequent or persistent pain(12). The mean number of pains each patient experienced in the past week was 2.7(12). Patients were clinically examined for aetiology and the breakdown according to pain type showed that 71% of the sample had one or more somatic pains, 46% had neuropathic type pain, 29% with visceral pains, and 46% experienced headaches(12). Patients who had lower CD4 counts were more likely to have a polyneuropathy and headache, and women also were more likely to have headaches than men, according to logistic regression analysis(12). Five percent of somatic pain, 5% of visceral pain and 3% of neuropathic type pain appeared to be due to treatment for HIV/AIDS(12).

Breitbart et al studied the undertreatment of pain in the same patient population described for the study by Hewitt et al above, with a sample size of 366 participants, of whom 48.7% reported their worst pain to be between 8 and 10 out of 10 (which is severe pain) and 45.6% of patients had moderate pain (4 - 7 out of10)(33). On average, 60% of patients had complete pain relief, while only 18.1% of patients with moderate pain and only 7.3% of patients with severe pain, had had opioids correctly prescribed(33). Forty eight percent of patients with severe pain had been prescribed only non-opioid analgesia, with 22.7% having

been prescribed no analgesia at all(33). According to WHO analgesic management guidelines, 84.1% of all the patients had Pain Management Index (PMI) Scores indicting inadequate analgesic treatment (namely a PMI of 0 and above), while using a more conservative cut off measure for the PMI (only patients with a PMI of -2 or -3), 49.1% of patients had inadequate analgesia(33). This shows significant under-treatment of pain. Risks for inadequate analgesic treatment were the female gender, lower levels of education, having acquired HIV through injection drug use(33). Despite the limitations of the study cited by the authors, this study highlights the general undertreatment of pain amongst the HIV positive outpatients. The reasons for this undertreatment are proposed as being due to lack of physician knowledge of pain management, the stigma of HIV disease, as well as patient related factors(33). These studies all highlight the prevalence of pain as well as its under-treatment. It is not known what the adequacy of treatment of pain is in the South African HIV outpatient setting as no formal study in this area has been done, but clinical work in the field suggests that pain is not adequately treated in HIV outpatient clinics, and the reasons may be similar to those cited by Breitbart and colleagues. As yet unpublished findings, according to a study conducted at a community HIV treatment clinic, by Parker in Cape Town among women with HIV, provide evidence for pain being markedly undertreated in this setting(47). The mean PMI score was -1.3, indicating inadequate analgesia(47). Only two patients out of 229 were found to have adequate analgesia(47). These findings support the perception that pain management is far from adequate at the level of primary HIV care.

In a longitudinal study of reasonable sample size in Copenhagen, Denmark, in 1994, Frich et al found, using semi-structured interviews, that 88% of AIDS patients experienced some form of pain at some time during the study, 69% had constant pain which interfered significantly with their function, and the prevalence of disturbing pain was 51%(13). Those patients with disturbing pain had shorter mean survival time in days than those with no pain or non-disturbing pain(13). At the time of the study, there was some advancement in anti-retroviral therapies (ART), and so 50% of patients had some form of ART, whether monotherapy or combined therapy(13). This study achieved its objectives, but did not adjust the PMI for adjuvant analgesic use(13). It is important in highlighting the importance of pain management in alleviating suffering at the end of life, and possibly also to show how adequate pain management may actually improve survival times.

Richardson et al studied the pain experience among a good sample size of women with AIDS between 1996 and 1998 as part of the Women's Interagency Health Study, by the use of an interview using recall for a 6 month period which may have introduced recall bias, but they found that 56% of the women had pain on 6 or more days in the preceding 6 months, and that CD4 counts under 200 cells/mm³ and depressive symptoms were associated with increased pain frequency and severity(45). Despite the limitations of this study, it highlights the importance of pain assessment and management and the potential relationship between pain and psychological well-being for women with AIDS.

Del Borgo et al found that using the validated Italian Pain Questionnaire (IPQ, Italian version of the McGill Pain Questionnaire), the prevalence of pain in their Italian patient sample, of whom 34% were on ART, was 60.8%(46). The most common site of pain was in the head(46). Patient staged CDC C had 60% prevalence of pain, with the group CDC A and B having 61% pain prevalence, showing that pain occurs at any stage of HIV disease(46). The sample size was reasonable and consisted of a cross-sectional group of patients admitted to the wards or to the Day Treatment Centre of one hospital in Rome and the study aims appeared to have been reached, using the pain the IPQ and a clinical examination of each patient(46).

In their article describing 'The Charter Study', a cross-sectional study using multiple assessment measures, Ellis et al write that HIV-associated sensory neuropathy and neuropathic pain continue to be problematic for patients, despite HAART, and they suggest that from their study results, preventing the CD4 count from going below 350, with HAART, could be protective against developing a sensory neuropathy and hence also neuropathic pain(48). In their study, the prevalence of HIV-associated sensory neuropathy was 57.2%, with 38% of these patients having neuropathic pain(46). The study was conducted at six academic outpatient research centres in the USA, with a very large sample size and with each participant undergoing a structured interview, a standardised examination, collection of demographic and clinical data, including blood tests, and evaluation of function, psychiatric state, and quality of life(46). It is not clear in the article whether the clinician or the patient rated the severity of the pain, however the results of this study are relevant to the body of knowledge around HIV neuropathy and neuropathic pain.

All these studies do point to a high degree of physical and psychological symptom prevalence and burden amongst people living with HIV who attend HIV outpatient treatment clinics. The international studies highlight the lack of specific evidence in the South African setting, for pain and symptom prevalence and burden.

The relevance of Palliative Care to HIV disease management

The definition of Palliative Care was discussed in the Introduction. The importance of palliative care for patients at all stages of HIV disease was discussed, because as the WHO definition states, palliative care is *"is applicable early in the course of the illness, in conjunction with other therapies that are intended to prolong life"*(6). Supporting this is the evidence from international research amongst HIV infected populations showing that symptoms are frequent among patients of all WHO stages of disease, including in WHO stage 1 disease(10-14). The research confirms the need for palliative interventions to be available for HIV infected patients at all stages of disease and *"in conjunction with other therapies that are intended to prolong life"*(6) which refers specifically to HAART in the instance of HIV disease. Extension of life without reasonable efforts to also address the patient's quality of life is not ethically justifiable, and as such palliative care aims to "*enhance quality of life, and may also positively influence the course of illness"* by using "*a team approach to address the needs of patients and their families"* and to provide treatment for the *"relief from pain and other distressing symptoms"*(6). This strongly suggests that palliative care for patients with HIV should be a part of and integrated with their ongoing HIV medical care from early on in the disease.

A study conducted in New York in 2000 and 2001, by Selwyn et al, using the validated MSAS, showed that the palliative care needs of HIV infected patients in the era of HAART-induced chronic HIV disease are becoming increasingly complex and therefore no less important than before, particularly for end-stage HIV disease in this setting(49). The article aptly describes what it set out to describe, namely the development of an integrated palliative care service for patients with AIDS who were cared for at a large hospital with inpatient and outpatient services, particularly with evidence for the need for palliative care services for

patients with end-stage HIV disease, but also recognising the increased complexity of palliative needs that are required as patients survive longer in the era of HAART(49).

The benefit that patients with HIV experience from palliation has been explored in the literature(49,50). In a systematic review conducted by Harding and colleagues, they found evidence from studies of grade 3 level evidence, to suggest that for patients with HIV and AIDS, palliative care carried out in the home and in inpatient hospice units did significantly have a positive effect on the patient pain and symptom experience(50). Despite finding predominantly grade 3 level evidence for palliative care, this review further stated that the evidence points to a significant symptom burden at all stages of HIV disease, and that palliative management is therefore warranted and required alongside the successes of HAART at prolonging life(50). It was also stressed that despite the success of HAART, there are the ongoing issues of a serious, chronic and potentially life-threatening disease to deal with – including the potential for the development of malignancies, drug toxicities and failure on HAART(50). To add to the evidence that HAART does not necessarily decrease symptom prevalence, is a subsequent study in the United Kingdom by Harding et al, which found that gay men on HAART had a greater symptom prevalence and greater distress from physical symptoms than those HIV positive gay men not on HAART(24). The evidence strongly points to the continued need for palliative care for patients with HIV, regardless of what stage of disease the patient is classified as, or what treatment the patient receives.

The relationship between clinical parameters and symptom prevalence and the burden of symptoms

There have been a number of studies attempting to link clinical parameters to symptom prevalence and burden, and there have been varying results reported. The CD4 count and viral load markers are obvious and frequently checked markers in HIV disease management. The staging methods for HIV disease, both WHO staging and CDC staging, have also been studied for their relationship with symptoms(10,17,25,46). Holzemer writes that the link between symptoms and biological markers of disease progression is not well defined(51).

Some important studies have found no relationship between symptom prevalence and burden with CD4 count(10,14,17), while Hewitt et al found that only headache and

polyneuropathy could be linked to a lower CD4 count(12). Harding et al reported a very weak but statistically significant relationship between the most recent CD4 count and the global distress rating on the MSAS-SF(24), while Lee et al found that patients with a CD4 count of less than 200 had higher physical distress scores on the MSAS-SF(25). Richardson et al found in univariate analyisis that a CD4 count of less than 200 was significantly associated with an increased pain frequency and severity, and a viral load over 50 000 was related to higher pain frequencies, in their sample of HIV positive women, although in the multivariate analysis of this study, only pain severity could be significantly related to CD4 count(45).

The Charter Study found on multivariate analysis that there was a relationship between the presence of HIV sensory neuropathy (but not neuropathic pain) and a lower lowest ever CD4 count result (<350cells/mm^3), whereas neuropathic pain was related to a higher lowest ever CD4 count and better CD4 count recovery(48). This shows the complexity of HIV neuropathy and neuropathic pain. The Charter Study found no relationship between viral load measurements and sensory neuropathy or pain(48).

A study by Ickovics et al, analysing the relationship between death, CD4 counts and depressive symptoms in women found that women with symptoms of chronic depression were more likely to have a larger decrease in CD4 count than those without such symptoms, that lower CD4 counts were correlated with greater numbers of depressive symptoms and that death was more likely in those with more HIV-related symptoms(52). Lampe et al found in their study in an HIV outpatient clinic in London that patients with symptoms of depression, anxiety and other physical symptoms were at risk for virological failure on HAART and that this was considered for the most part to be independent of a lack of adherence to HAART(37). On regression analysis of their data of a sample of which 71% of participants were on HAART, Lee et al found that the viral load was a marker for a change in symptom prevalence(25). There are a number of studies that have found a change in relationship between symptom prevalence and burden with AIDS-defining diagnoses or WHO staging(10,17,25), whereas, Del Borgo et al reported similar prevalence rates for pain in all three CDC categories(46).

The results from these various studies indicate that symptom prevalence and burden and their relationships to disease staging, AIDS-defining diagnoses past or present, CD4 count at

any stage and viral load at any stage, are not straight forward by any means. Some studies show an increasing symptom number with worsening disease stage(10,17,25), and some show no link between CD4 count levels and symptom number(10,14,17). Distress or burden from symptoms is less clearly related to disease stage, CD4 counts and viral loads. Different study methods and sample characteristics make comparisons between studies difficult. What does seem to be clear is that patients can be symptomatic from their HIV disease at any point in the disease process, and therefore, as Willard et al comment, the term "*asymptomatic*" should not be casually applied to any patient with HIV, unless the clinician has thoroughly checked that this is in fact the case(14). What is also interesting is that a study in New York found that there was no predictive value for death from CD4 counts or from viral loads, while functional status, as measured by the Karnofsky Performance Status, Mini-Mental State Examination and changes in activities of daily living, were predictive of death(49). This evidence further points to the notion of an individualised and patient-oriented assessment, rather than relying on "the numbers" of the CD4 counts and viral loads to be predictive of suffering from symptoms and even predictive of death.

The relationship between gender and age with symptom prevalence and the burden of symptoms in HIV disease

Statistics in South Africa show that women have a higher HIV infection prevalence than men, as was discussed in the introduction. The 2010 HIV prevalence estimates for women aged 15 to 49 years of age, is 19.7%, whereas the overall prevalence for the population of this age is 17.3%(1). Some studies of symptom prevalence and burden have commented that women tend to have greater symptom prevalence(25) and some studies have found this for specific symptoms, such as anxiety(19), genital problems(19), headache(12) and features of radiculopathy(12). Breitbart et al found that women with pain had a greater likelihood of having inadequately treated pain than men(33). The relationship between gender and symptom prevalence and burden is thus not clearly defined in the literature. Causality can not be determined from cross-sectional studies, and the variables at play are vast and could include social factors, financial factors, educational factors, and factors relating to health-seeking behaviours.

Not much work has been done on the influence of age on symptom prevalence and burden of symptoms in HIV disease. One study by Sherr et al found some differences between the two age groups of older than or younger than 50 years, with those older than 50 years of age having lower psychological and global distress scores than patients younger than 50 years of age, while the physical scores were no different(53). They also found that those older than 50 were more likely to be on HAART and were more likely to be adherent to HAART than the younger group(53). This is different to a study conducted in the Free State Province in South Africa found that older patients had worse CD4 count outcomes than younger patients, however, this study was small, and the CD4 count measure was not directly related to symptom prevalence(32). No conclusions can be drawn from the literature on the influence that age has on symptom prevalence and burden.

The relationship between Highly Active Anti-Retroviral Therapy (HAART) and symptoms prevalence and the burden of symptoms

Highly Active Antiretroviral Therapy (HAART) has become the standard management for HIV disease once CD4 counts reach a certain level or when disease progression includes an AIDS-defining condition. The use of HAART as apposed to dual-therapy or mono-therapy regimes has been shown to have the best virological, immunological and clinical outcomes for HIV management(54). The acceptable CD4 count cut-off level at which to start HAART, has changed over the years and has varied from country to country and by place of care. The effectiveness of HAART in its ability to improve immunological status and function and to suppress the HIV viral load is widely accepted(7), providing it is used in the recognised manner. What often happens in a busy HIV outpatient clinic is that the markers of the effectiveness of HAART (disease-focused markers, such as CD4 counts and viral loads) receive attention, rather than the patient-focused markers of disease, such as symptoms and the burden of those symptoms. This results in the neglect of the management of patient symptoms, which is not acceptable, as far as the holistic patient management requirements of the WHO definition of Palliative Care is concerned(6). In fact, as one paper on pain in AIDS patients points out, the success of HAART at improving the life expectancy of patients makes it even more important to address symptoms and the burden the symptoms are to patients(13) to enhance this improved life expectancy with a better quality of life.

Since the use of HAART, studies aimed at assessing symptoms among HIV positive patients have found that, although HAART is very effective in controlling disease progression, and reversing immunosupression to a certain degree, patients can and do still experience symptoms while on HAART(11,14,22,24,25,37,48). In fact, some studies were able to show that HIV positive patients on HAART had significantly more symptoms than those not on HAART(24,25). One study in South Africa found that taking HAART did not reduce the symptom intensity experienced by the patient(22). Two studies have found that patients who have changed HAART regimens at some point have a greater risk for having more symptoms than patients who had never changed HAART regimens(11,23).

The Charter Study found that HIV sensory neuropathy was more likely in patients currently on HAART, or who had previously been on dideoxynucleoside analogue antiretrovirals such as stavudine, didanosine, or zalcitabine (the so-called "D drugs"), while neuropathic pain occurred in 38% of those with a sensory neuropathy, with past "D drug" use being a risk factors for this pain(48). This emphasises the point that HAART drugs do have side effects. The side-effects are well known and widely published, with sensory neuropathy and neuropathic pain being one set of side effects that can occur. The symptoms that were more common among patients on HAART in the study by Peltzer and Phaswana-Mafuya were predominantly side effects that could be attributed to HAART(22). This finding is similar to those of Silverberg et al in the USA, among women who changed HAART or stopped HAART(11), however both studies also found a broader symptom prevalence than only possible HAART side effects, and also found high symptom prevalence in patients who were HIV positive but had never been on HAART, thus calling for caution that symptoms should not be entirely subscribed to HAART therapy(11,22). Harding et al also found that, although causality could not be established, certain symptoms that were more common in men on HAART were also well known side effects of HAART, however the study also found that HAART was independently linked to greater symptom prevalence and burden for most symptoms on the MSAS-SF(24). Another study conducted by Harding et al found that being on HAART was not associated with any lowering of symptom prevalence or symptom distress(23). These studies support the view that HAART does not at all negate the need for symptom assessment and management in the general HIV outpatient clinic. In fact, from the online survey in the UK, Harding et al found that the symptom prevalence of HIV

patients on HAART is comparable to patients with other advanced disease such as advanced malignancy or end stage renal disease(24).

It is for these reasons that it is important to know what the symptom prevalence and burden are among a representative sample of HIV positive patients in South Africa who attend outpatient HIV treatment clinics. We need to know what the symptom prevalence and burden are, so as to motivate the health care workers concerned to adequately assess patients who attend these treatment clinics, and as a result of assessment, provide the appropriate symptom control measures. This may require the training of health care workers and the findings of this study should inform the training needs among HIV clinicians and health care workers.

The relationship between symptoms and adherence to HAART

When considering the impact of HAART on the patient with HIV, it has potential impact on the patient's life expectancy and also their quality of life. Quality of life is a complex measure and includes many factors, but symptom prevalence and burden is an important part of the quality of life of a patient with a chronic illness(29). One of the most notable things about HAART is that the medication needs to be taken in its entirety, correctly, everyday for the rest of the patient's life, for it to be of sustained benefit. This is no small ask, and requires a patient who is motivated, well supported and also well educated about his/her disease, to be able to manage this requirement. A study published by Sherr et al discussed the difficulties in assessing adherence accurately, and this itself sheds light on the demands of HAART adherence on patients who take these drugs. Sherr at al write that adherence requires not only that each dose is taken, but that the timing should be correct and that the necessary dietary restrictions for the drugs concerned should be followed correctly(31). It is known that lack of adherence to a HAART regimen by a patient leads to failure of viral suppression and immune restoration on those particular drugs used, requiring new antiretroviral drugs to be used, and there are a limited numbers (and combinations) of these available(31). In their particular study, patients who were not adherent to their HAART regimen had higher psychological symptom burden and higher scores on the global distress score (physical and psychological symptoms) for the MSAS,

whereas patients who were considered to be fully adherent on HAART were older, had a lower psychological symptom burden and global distress scores and reported greater satisfaction with their relationship with their doctor and the outcomes from that relationship(31). Lampe et al found an association between symptoms of depression, anxiety and other physical symptoms with virological failure on HAART and that this was considered for the most part independent of a lack of adherence to HAART(37). Rodkjaer et al found that in their sample of HIV patients in Denmark, 26% had major depression and that the risk for poor HAART adherence was almost 6 times higher in depressed patients than in those not depressed(38). Lee et al concluded that *"...those on ART, regardless of current CD4 cell count or prior AIDS diagnosis, should be targeted for interventions to help manage their symptom experience and to assure adequate adherence to their medication protocols"*(55).

These studies all highlight the need for clinicians to monitor patients for physical and psychological symptoms and to manage these in a manner that is acceptable to the patient concerned as well as medically acceptable, so that HAART adherence and virological suppression remain optimal and so ensuring the best possible chance for the patient to have their disease controlled for as long as possible. The ultimate goal may be increased survival, but that has to be coupled with the goal of attaining and maintaining a desired quality of life to ensure the sustainability of the ultimate goal.

The under-treatment of symptoms

Pain is one of the most investigated individual symptoms in HIV disease. In 1996, Breitbart et al reported that a significant number of patients with AIDS in their sample in New York, who experienced pain, had inadequate analgesic treatment for their pain(33). There has been agreement among pain management specialists that adequate pain management for patients with HIV disease should employ the same WHO guidelines as for the treatment of cancer-related pain, and so, using the Pain Management Index (PMI), 84.1% of patients, in the study conducted by Breitbart et al, had pain that was unsatisfactorily treated, and even if the investigators used less strict criteria, 49.1% of patients' pain was still unsatisfactorily treated(33). The authors suggested that one of the reasons for this undertreatment of pain

was insufficient knowledge regarding pain management held by doctors involved in the care of HIV patients, and suggested that future research be conducted in this area(33). In 2001 in a study in Italy, Del Borgo et al also reported that pain was undertreated(46). In a prospective longitudinal study on pain in Denmark by Frich et al, the PMI score at the initiation of the study showed that only 25% of patients were receiving adequate analgesia, whereas by the conclusion of the study, 64% of patients had received adequate analgesia(13).

By inference, it can be said that there was found to be under-treatment of depression in patients in a Danish study on depression in HIV positive patients, as the particular study found there to be an under-diagnosis of major depression in this population(38).

The study done in the USA, by Karus et al, at three different sites also asked the question of participants whether the patient thought the individual symptoms were being treated or not(34). The results showed that although at least 50% of participants believed that pain, nausea, difficulty in swallowing and mouth sores were being treated, only a third or less of patients perceived that they were receiving treatment for a number of other symptoms, including worrying, feeling sad, feeling nervous, difficulty concentrating, dizziness and sexual problems(34). Less than 50% of patients at all sites felt that their neuropathic pain was being treated, and there was also under-treatment of gastrointestinal problems such as constipation, nausea and vomiting and diarrhoea which, as the authors point out, do have available palliative treatments(34).

As discussed in the introduction, Fontaine et al showed in their multi-centre study conducted in France, that physicians displayed a poor to moderate ability in recognising the presence of symptoms in their patients(18). The symptoms most correctly identified were those that are related to measurable physical signs(18). This shows that health care workers are poor at identifying the symptoms experienced by patients. So unless the health care worker is dedicated to taking a detailed symptom history for each patient on a regular basis, with provision of adequate time for patients to communicate this effectively and to their satisfaction with their health care worker, symptoms will be missed, to the detriment of the patient.

To be able to treat pain and the relevant symptoms experienced by patients in a satisfactory manner, the necessary medication must also be available. This may be a challenge in a resource-constrained setting. Harding et al recently published their findings of cross-sectional research into the availability of and prescribing practices for medication for pain and symptom relief in 12 Sub-Saharan African countries, including South Africa(35). They studied the availability of a range of medications available at palliative care sites, and although South Africa was among the better performing countries in the region, the findings revealed that there are still significant gaps in the provision and supply of opioid analgesia, non-opioid analgesia and other medications commonly used for symptom control, despite their being "essential drugs"(35). To be able to adequately treat pain and other symptoms, the appropriate medications, as advised by the WHO and other medical evidence, should be available for the treating doctor to prescribe, as far as is to be reasonably expected in resource constrained settings.

HIV symptom prevalence and burden as compared to that of other chronic diseases

Palliative care started out as being predominantly for people with cancer, and now the benefit of palliative care for patients with other chronic diseases, such as advanced cardiac and renal disease, is being more widely recognised. There is evidence to show that patients with chronic diseases suffer as much as cancer patients do at the end of life. Solano et al systematically searched the literature for evidence of suffering amongst patients with advanced AIDS, Cancer, Heart Disease, Chronic Obstructive Pulmonary Disease and Renal disease(56). What their literature search showed, was that from 64 studies and 18 textbook chapters, pain, fatigue and breathlessness had on average, an over 50% prevalence rate for all five of these diseases nearing the end of life(27). Insomnia, anorexia and depression were also common symptoms in all these diseases, with not too dissimilar frequencies(27). It is thus clear from this informative review of the international literature that the frequency of symptoms requiring palliation in cancer patients and indeed other advanced diseases is not very different to those symptom needs of patients with advanced HIV disease.

Vogl et al wrote that the symptom prevalence found in their study of AIDS outpatients in New York was higher than the average symptom prevalence in a comparative study for patients with cancer who were receiving outpatient treatment(10). Harding et al commented that the symptom prevalence and burden of their findings in a UK-based online survey, was comparable to patients with advanced malignant disease(24).

These findings strongly suggest that there is a need for palliation amongst ambulant patients with HIV disease, regardless of stage of disease, just as there is a need for palliation for patients with cancer and other chronic and advanced diseases.

The burden of suffering of HIV disease as seen from a Public Health perspective

In the introductory chapter, I highlighted the significant impact that HIV has had and is having on the health status of South Africans. The mortality and the symptom-related suffering of patients with HIV have also been discussed. Understanding that palliation is wider than end of life care and "*is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life*"(6) is important for understanding the need for the role of palliative care at all stages of HIV disease. Understanding this, highlights the very large need for palliation for HIV infected patients in South Africa. Disease trajectories have been specifically studied in relation to the end of life functional decline that patients experience as their disease moves closer to the end of life(57,58). However, disease trajectories for chronic disease are helpful in understanding the unpredictable course of HIV disease, pointing out that even with HAART, HIV is a chronic disease with an unpredictable course. The difficulty in predicting the course of HIV disease should encourage health care workers to involve palliation early in the course of illness, rather than delaying palliation and symptom control measures which are able to improve the quality of life for patients while they still have ample time to enjoy life, and be as active and as productive as is possible.

There are studies that show that palliative care does help to minimise the costs of health care for the provider, however there is a need for more research to assess the patient outcomes from palliative care and how these relate to cost savings(59). Palliative care

should most importantly improve patient outcomes. Resources for health care are limited in most countries in the world, but particularly so in the developing world countries, and so the temptation is there to dispense with or ignore palliative care and only focus on curative and current types of care(59-61). Harding writes that "*The unhelpful distinction between curative and palliative resources is even less useful in poorer countries"*(60), motivating that both areas actually are required to grow in developing countries, not either curative care or palliative care(60). The research providing evidence for the need for both types of care has been conducted predominantly in the developed world, but it does indicate that palliative care in HIV management does have desired and important health outcomes for patients(59-61). Krakauer highlights this issue also, and makes the crucial point that ensuring the adequacy of curative care for poor people in resource constrained settings is the fundamental basis from which palliative care should operate(62). This means that patients with cancer should have adequate access to internationally acceptable curative care and for patients with HIV, HAART should be the standard basis of medical care(62). From this basis, palliative care should operate together with primary clinical teams, or palliative care may have to be provided by the primary clinical team where necessary, to relieve suffering amongst those who need it(62).

The issues that these authors highlight are the need for good and appropriate evidence for the needs for palliative care amongst patients in the developing world, the clinical effectiveness of palliative care and the cost-effectiveness of quality palliative care in the South African setting(59-62). This study attempts to add to the evidence for the needs for palliation that exist amongst patients who attend South African HIV treatment clinics, so that more can be done to implement palliative care in this setting and to stimulate further research into this area so that the inequalities of care can be addressed in a step-wise and effective manner.

Clinical and research tools used to study symptom prevalence and the burden of symptoms and patient function

There are a number of tools available to be used in the assessment of the patient experience of illness. The use of the correct tool is important to obtain the information required. The Memorial Symptom Assessment Scale (MSAS) is a validated symptom assessment tool developed by Portenoy et al that measures patient rated severity, frequency and distress relating to 32 symptoms(63). It has been found clinically that patients find this tool difficult to use as it requires a fair amount of time and is quite complex(64). Chang et al have studied the shorter version of the MSAS, namely the Memorial Symptom Assessment Scale Short Form (MSAS-SF) among cancer patients and found it to be a valid and quick to use tool for use for symptom assessment(64). The MSAS-SF measures for the presence of 32 symptoms and their distress or frequency. Distress and frequency of these symptoms are measured on a 5 point Likert scale. From the tool can be obtained: a physical symptom subscale, a psychological symptom subscale and a global distress index(64). The global distress index (MSAS-GDI) includes 4 psychological symptoms namely – feeling worried, sad, irritable and nervous; and 6 physical symptoms namely – lack of energy, pain, lack of appetite, feeling drowsy, constipation and dry mouth(64). The physical symptom distress score (MSAS-PHYS) incorporates 12 physical symptoms namely – lack of energy, pain, loss of appetite, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated and dizziness(64). The psychological symptom distress score (MSAS-PSYCH) incorporates 6 psychological symptoms namely – worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable and difficulty concentrating(64). It was found that the MSAS-SF subscale scores were associated significantly and appropriately with the observer-rated Karnofsky Performance Status which measures performance and function(64). Importantly, this MSAS-SF has also been used to study symptoms amongst patients with AIDS: Vogl et al reported that the internal consistency among HIV patients was a high as in cancer patients(10,64). The MSAS-SF includes all the commonest symptoms that have been noted in previous studies, and is itself a commonly used symptom assessment tool for patients with HIV as shown in the literature survey in this chapter. It notes pain as a single measure. It is a suitable tool to use in this survey.

The Karnofsky Performance Status Scale (KPS) has been used in the assessment of function in patients with cancer, HIV and AIDS(10,27,65). Mor et al studied its reliability and validity for use in research amongst patients with cancer who had a KPS score of 50% or less and found good correlation between KPS scores and function and also between KPS scores and prognosis(65). Despite the fact that this study was conducted only in patients with cancer with a KPS of 50% or less, the authors concluded that this is a reliable and valid tool(65). The KPS has been widely used in clinical and research settings for patients with other chronic and life-threatening diseases, including HIV and AIDS(10,27). It is a clinician rated measure of the patient's functional status. The scale ranges from 0% (dead) to 100% (normal). Any score below 70% indicates that the patient is unable to care for him/herself without assistance(10,27). This tool is suitable for use in this study and was used as an observer rated tool of performance status.

I did look at other symptom assessment tools and these are evaluated, explaining why they were not used in this study. The Missoula-VITAS Quality of Life Index (MVQOLI) is a quality of life assessment tool, developed by Byock and Merriman, which assesses a person's experience of nearing the end of life(66). It assesses 25 items that measure adaptation to and integration of a patient's physical and functional decline, and attainment of life completion and life closure. There are 5 quality of life domains – symptom control, function, interpersonal issues, well-being and transcendence. It also measures satisfaction and importance in each domain(66). The authors Schwartz et al conclude that this tool is best used as a clinical tool rather than a psychometric research tool. This tool assesses quality of life issues and not direct symptom prevalence. It also is designed for patients facing the end of their lives which the participants of this study were not necessarily likely to be facing with imminent certainty, and for all these reasons it was not appropriate for this survey.

The Wisconsin Brief Pain Questionnaire (WBPQ) was developed by Daut et al in order to assess pain intensity and pain interference in mood-related matters and in activity-related matters, in patients with pain from cancer or other diseases(67). Mphahlele et al of the School of Physiology of the University of the Witwatersrand have produced validated translations of the WBPQ in isiZulu, Setswana and Xitsonga(67). Mphahlele et al note that certain questions were not possible to translate without a significant change in meaning,

and so were left out of the translated versions if this was the case(67). Their manner of overcoming the problem of having missing values in the answered questionnaire, was to have an interviewer administer the question to the participants, to ensure there were no missing values(67). This is a useful questionnaire to use to assess pain experienced by patients with HIV. It is more informative than the MSAS-SF is on pain – in the description of the pain experienced by the patient, and particularly on the number and type of pains, as well as the effect of the pain on mood and function(67). Its particular usefulness in South Africa is that it is already translated and validated in the above-mentioned languages(67). The aim of this survey is to establish prevalence and burden of pain and other symptoms. The MSAS-SF satisfactorily accounts for pain and the burden thereof. What the MSAS-SF does not do is differentiate different areas or types of pain. This would be useful, but this was not the aim of this study and therefore this tool was not utilized in this survey. It was also felt that it would be too burdensome for patients to answer questions from two fairly detailed tools.

Another symptom assessment tool that has been used for HIV in Southern Africa, is The Revised Sign and Symptom Checklist for Persons with HIV Disease (SSC-HIVrev)(68). It has 72 symptoms, physical and psychological, with eight gynaecological questions, so there are 64 symptoms which relate to both men and women(68). This was translated into seven languages for the study by Makoae et al, namely Sesotho, Setswana, Siswati, Tswana, Venda, Xhosa, and Zulu(20), but these translations were not validated. The presence of the symptoms on the day of the study is enquired about and the intensity of the symptoms (also on the day of study) is also enquired about, with the intensity scored as mild moderate or severe, therefore on a 3 point Likert scale(68). Validity and reliability of the original version has been studied in a sample in the USA, by Holzemer et al 2001(68). This symptom assessment tool was not used in this study as it is less frequently used in the literature than the Memorial Symptom Assessment Short Form (MSAS-SF), thus making it less useful for comparison with other studies.

Rationale for the study

The aim of this research study was to survey the prevalence of symptoms and the burden these symptoms pose to the patients attending large HIV treatment clinics in the urban greater Johannesburg, Gauteng Province, South Africa. These patients receive appropriate disease-specific care for their HIV disease, however not as much is known about the palliative care needs of these patients with this life-threatening illness in this particular setting. Understanding the pain and symptom prevalence and the burden from these symptoms among these patients will assist in addressing these needs and in so doing, improve the quality of life of patients with HIV who attend outpatient treatment clinics. This type of patient-focused management may also possibly improve patient adherence to anti-retroviral therapy (HAART), as other studies have suggested. It is also the hope that this study will stimulate further research into the palliative care needs that these patients have and how these can best be addressed.

Chapter 3

Aims and Objectives

AIM

To survey the prevalence and burden of pain and other symptoms in HIV positive people who attend outpatient HIV treatment clinics at Johannesburg's three adult academic hospital complexes, namely the Charlotte Maxeke Johannesburg Academic Hospital, the Chris Hani Baragwanath Hospital and the Helen Joseph Hospital.

OBJECTIVES

1. To survey the prevalence and burden of pain and other symptoms.
2. To determine the prevalence and burden of symptoms in relation to the WHO stage of illness, CD 4 count, viral load, functional status of the patient (as assessed by the Karnofsky Performance Status), and in relation to HAART.
3. To determine if the prevalence and burden of symptoms is associated with gender and age.

Chapter 4

Methodology

Study Design

This is a cross-sectional survey with descriptive analysis.

Study Site

The research was conducted in the outpatient adult HIV treatment clinics at the academic hospitals associated with the University of the Witwatersrand, namely the Charlotte Maxeke Johannesburg Academic Hospital, the Chris Hani Baragwanath Hospital and the Helen Joseph Hospital.

Study Population

The study population was all of the adult patients who are registered at the above three hospitals' outpatient adult HIV treatment clinics from 21 September 2009 to 14 April 2010.

Selection Criteria

The following were the inclusion criteria for the selection of participants:

- Confirmed HIV positive patients attending one of these mentioned outpatient adult HIV treatment clinics
- Patients over the age of 18 years on the day of participation in the study
- Both male and female patients
- Patients of any WHO stage of disease
- Patients who were able to and did consent to take part in the study

The following were the exclusion criteria for the selection of participants:

- Patients who were in extreme distress or were very ill on the day, were not invited to participate in the study
- Patients not cognitively able to consent to participation in the study
- Patients under the age of 18 years on the day of the study

Study sample

The study sample was taken from the patients attending the stated adult HIV treatment clinics.

Simple random sampling was used. To reduce selection bias associated with this method, every fifth eligible patient in the queue waiting to see a clinic doctor was invited to participate in the study. The days on which the sampling was done at each clinic was spread out over the study time according to the schedule of the clinic and that of the two research nurses.

Sample size

Sample size calculations were based on the primary aim of assessing symptom prevalence as a proportion. The assumptions were that if the estimate of prevalence was to be of a precision of within 5% of the true value, so that the prevalence can be reported with 95% confidence, the largest sample size of 385 participants was obtained for the assumption of an initial prevalence of 50%. Thus, the number of participants required for a confidence interval of 95% (5% precision) and for a proportion of 50% prevalence, was calculated to be 384.16, and this was rounded up to 385 participants.

This table illustrates the above explanation:

	p	n_p
1.	.01	15.21274
2.	.05	72.9904
3.	.1	138.2976
4.	.2	245.8624
5.	.3	322.6944
6.	.4	368.7936
7.	.5	384.16
8.	.6	368.7936
9.	.7	322.6944
10.	.8	245.8624
11.	.9	138.2976
12.	.95	72.99042
13.	.99	15.21272

Study period

Sampling was begun on 21 September 2009. The last participant was recruited on 14 April 2010.

Data collection

Data Collection Tools

The Memorial Symptom Assessment Scale Short Form (MSAS-SF) was used to document symptoms that the participants had experienced in the last one week, as well as the burden for the physical symptoms or the frequency for the psychological symptoms. This tool is validated, as was described in the literature review. The participants were asked to answer yes to any symptom they had had in the past week, and if the symptom was present to answer how much it had distressed or bothered them (that is, the burden of the symptom), on a five point Lickert scale. The five point scale ranged from 0, "not at all", to 4, "very much". The MSAS-SF was translated into isiZulu and Sesotho, which are the two main languages spoken by inhabitants of the Johannesburg region. The Wits Palliative Care unit had previously done these translations of the MSAS-SF. The method of translation used was the method of 'back translation'. By this method, one forward translation was conducted by first language isiZulu and Sesotho speakers respectively and then a back translation into English by separate first language speakers in isiZulu and Sesotho respectively. These translations had already been checked, piloted and used successfully. These translated versions were re-checked for meaning, which was found to be satisfactory. It was decided to administer the MSAS-SF as an interviewer-administered tool to assist patients who are not adequately literate, and so to keep the method of MSAS-SF administration as uniform as possible for all participants.

The Karnofsky Performance Status tool was used to assess functional status on an 11 point scale from 0% to 100%, with 0% being dead and 100% being normal function. The research nurse interviewing the participant assessed their functional status through observation and questioning and assigned a value accordingly.

A Participant Data Sheet was used to record the demographic details of each participant, and relevant clinical details obtained from the clinic file of each participant. The Participant Data Sheet was developed by the Principle Investigator (PI), in collaboration with her supervisors and in particular with a colleague who heads up one of the HIV treatment clinics

at which the study was conducted, with the aim and objectives of the study in mind. It was designed to be simple to use while also collecting the necessary information. The demographic details recorded were: age at last birthday, gender, self-determined ethnicity, latest CD4 count with date, latest viral load with date, latest albumin level with date, initial CD4 count before starting HAART with date, initial viral load before starting HAART with date, WHO staging, HIV-related diagnoses, diagnoses unrelated to HIV, whether the participant was on HAART and if so the date of starting, any change in HAART including the date/s and previous regimen/s and reason/s for change. This form also included a space to record the participant's Karnofsky Performance Status score which was assessed once the MSAS-SF and clinical information was completed, as above. It included a subjective question for the participant to answer once the MSAS-SF had been administered: "Do you think that any of your symptoms are because of your ARVs? If yes, which symptoms?"

Data Collection Method

The number of participants at each site was obtained by dividing the total number required, namely 385 participants, by three. Thus, two sites would have 128 participants and one site would have 129 participants.

Nurses with research experience were required. The department of Wits Palliative Care where I worked at the time of the study had two experienced research nurses, Sr Keletso Mmoledi and Sr Ntombi Hatta. The PI acquainted the research nurses with the research protocol and trained them in the administration of the MSAS-SF original version and acquainted them with the translated versions. The Karnofsky Performance Status tool and the Data Collection sheet were explained and the use thereof assessed. Sr Mmoledi and Sr Hatta had both received formal training in the ethics of research and so were also conversant with the ethical norms required. Ethical research methods with regards to this study were reviewed by the PI with the research nurses. In September 2009, Sr Mmoledi then started to recruit participants at Helen Joseph Hospital's HIV clinic, and then also concurrently recruited participants at Chris Hani Baragwanath Hospital's HIV clinic. At each hospital, the PI introduced her to the HIV Clinic staff and we explained the research aims and protocol.

In January 2010, the team's other nurse with research experience, Sr Ntombi Hatta, was able to take over from Sr Mmoledi with participant recruitment and data collection. The PI acquainted Sr Hatta with the research protocol and she was trained in the use of the MSAS-SF and the Karnofsky Performance Status tool. The Data Collection Sheet was also explained. Her understanding and use of these tools was assessed. After being introduced to the HIV clinic staff by Sr Mmoledi, she continued the recruitment of participants at Chris Hani Baragwanath Hospital and then concurrently also recruited participants and collected data at the Charlotte Maxeke Johannesburg Academic Hospital's HIV clinic, after being introduced to that HIV clinic's staff by the PI. Sr Hatta then completed the recruitment of participants at Helen Joseph Hospital.

The procedure followed with each participant

Participants were recruited while waiting to see the doctor on the morning of their clinic visit. The research nurse would inform the patients in the waiting area about the study and what involvement would mean. She would then invite each fifth person in the queue to consider participation on a purely voluntary basis. It would be explained that this would not interfere with the person's visit to the doctor. Those who wished to participate then took turns to sit with the research nurse, in a private room or area away from other patients to ensure confidentiality. The research nurse explained the patient information document and the informed consent document in the language of choice of the participant – either in English, isiZulu or Sesotho. The language chosen would be used throughout that participant's interview. If the participant chose to participate, he or she would sign the informed consent document.

The research nurse would then use the participant's clinic file to extract the data required on the Participant Data Sheet. Once this was done, the research nurse would then use the MSAS-SF in the participant's chosen language. This involved explaining the purpose of the MSAS-SF and what the question was for each symptom. The MSAS-SF was used as an interviewer administered tool, so the research nurse would ask the questions and fill in the answers as given by the patient. The participant was asked if he or she had had the symptom in the past one week. If the symptom was present, they were asked how much

the symptom distressed or bothered them, on a scale of 0 to 4. This was done for each of the physical symptoms. The last four symptoms are psychological and if they were present, the participant was asked how often the symptom occurred, also on a scale of 0 to 4.

Once this was completed, the research nurse would rate the participant on the Karnofsky Performance Scale and note this on the Participant Data Sheet. The research nurse would then ask the participant the question on the bottom of the Participant Data Sheet which asked if the participant thought that any of these MSAS-SF symptoms were due to their ARV's, and if so, which symptoms.

Once this was completed, the participant was thanked and that was the end of the interview. The participant left with their copy of the patient information sheet.

The Data was and is stored in the Wits Palliative Care Offices in a locked area. The informed consent documents are stored in a separate file from the data forms and questionnaires, to ensure anonymity. No identifying details of the participants were written onto the data forms and MSAS-SF questionnaires.

Data analysis

Data was entered by the PI, the research assistant working at Wits Palliative Care, Miss Nozipho Zwane, and by the research nurse Sr Hatta. The Participant Data was entered into Microsoft Access 2007 on a database created by Miss Zwane as guided by the PI. The MSAS-SF data was entered into Microsoft Excel 2007 onto a spreadsheet created by Miss Zwane, as guided by the PI.

During data capturing, the PI did random checks to assess the completeness of the data. After completion of the data collection, the PI obtained a random 10% sample of the numbers 1 to 385 which was generated using STATA by the Statistician, Edmore Marinda, from the University of the Witwatersrand School of Public Health. These study numbers' data sets were fully double entered by the PI alone, to check the consistency and accuracy of the three different data capturers. There was found to be no marked discrepancy in the data entered on first data entry. There was no significant missing data.

The Participant Data was transferred to a Microsoft Excel 2007 document. All the Participant Data and the MSAS-SF data were assessed in Microsoft Excel 2007 for outliers by the PI. Frequency pivot tables were created for each variable. No significant outliers were found. Frequencies are reported as percentages. Formal statistical analysis was begun using STATA by the statistician, from the University of the Witwatersrand School of Public Health. The analysis was however not completed because the statistician experienced time constraints and the PI relocated before statistical analysis was adequately completed, making it difficult for the statistician and the PI to meet to continue to work on the analyisis. Therefore, the analyisis was repeated and completed by Anneli Hardy of the University of Cape Town's Statistical Consulting Service, again using STATA. The results of the frequencies obtained in Excel correlated with those in STATA. Cronbach's coefficient alpha was used to assess reliability of the MSAS-SF subscales. One way analysis of variance (ANOVA) was used to assess the relationships between the demographic and clinical variables (for example the WHO stage) with the MSAS-SF subscale scores. This was correlated with the Kruskal-Wallis equality-of-populations rank test for each correlation of the non-parametric data. SPSS was used to calculate the effect size for the significant comparisons found in these analyses. In STATA, Multiple regression analysis was performed to determine those clinical and demographic variables that were predictive of the MSAS-SF subscale distress scores. STATA version 10.1 and PASW Statistics (SPSS) version 18 were used.

Ethical considerations

This study obtained permission from the Research Ethics Committee of the University of Cape Town, and from the Committee for Research in Human Subjects (Medical) at the University of the Witwatersrand. See appendix.

Agreement from the Hospital management and the heads of the HIV clinics concerned was obtained once both Research Ethics Committees had granted their approval.

The research nurse provided an information sheet to each participant, explaining the study procedure and aims and the anonymity and confidentiality of each participant. Consent for the study was written and verbal and completely voluntary. Verbal clarification was

available for the participants from the research nurses. The patient hospital number was entered only onto the consent form, along with the participant name, only for the purposes of allowing extraction of missing laboratory data where this was required if the patient record was incomplete on the day of study. The study number was used for the data set. This was been done to ensure patient confidentiality and anonymity which is of paramount importance. The participants were free to exit from study participation at any point. All effort was made to ensure understanding and appreciation of the study, confidentiality and the fact of voluntary informed consent. The participants received on their participant information form, the means with which to make contact with the researcher, should the participant have had or still has any questions or would like to know the results of the survey.

This survey investigated the symptoms of a medically vulnerable group. A vulnerable person is someone who has limited means of protecting his or her own interests or rights, by virtue of lack of power, resources, intellectual or educational abilities. A vulnerable group has members with such qualities. Financial, educational, cultural, health care treatment availability and choice options are issues that play a role in making groups vulnerable to research injustices(69). The medically vulnerable group of HIV positive people who do not have many choices or options for obtaining treatment due to their financial constraints as well as perhaps educational and cultural constraints, is the group this study surveyed. There were no overt risks to the participants as the survey involved no study intervention. The benefits to the group of HIV positive patients in general will be greater health care worker appreciation of the prevalence and burden of symptoms within this population, thus it is hoped this will leading to greater vigilance and improved treatment of these symptoms in the future. It was emphasized that neither participation, nor non participation would lead to a change in the level care for the individual patient. The benefits of understanding the symptom prevalence amongst a South African urban HIV positive population, both on and off Highly Active Antiretroviral Therapy (HAART) who attend an HIV treatment clinic, will enable better understanding of the population group we serve and it is hoped by the researcher that this will lead to better patient care across these clinics as well as in other HIV treatment clinics in South Africa.

No children were included in the study. All individuals were 18 years or older. Individuals suffering from dementia, mental illness or mental retardation were excluded from the study to protect the cognitively vulnerable and to ensure that all symptoms found were the experience of the individuals concerned. The researcher was not and is not a member of staff of these clinics and so it was not anticipated that there would be undue pressure due to such deference. This survey was a study of a population that is often financially vulnerable, but no compensation was awarded as the study occurred on a day that the patient would normally have attended their clinic.

If and when the research nurses uncovered medical problems during the interviews, they referred these patients back to the clinic doctor, or to the palliative care service, or to another speciality, as indicated, and with a written referral as needed. This was not found to be a problem and any referrals that were made, were never regarding severe matters.

Chapter 5

Results

Participant Data – Demographics

The Participant Data Sheet is in the Appendix.

The sample size was 385 participants. (n = 385)

Table 1: Demographic Information

Factor	N (%)
Gender	
Male	93 (24.16)
Female	292 (75.84)
Ethnicity	
Black	378 (98.18)
Other	7 (1.82)
WHO staging	
1	98 (25.45)
2	251 (65.19)
3	30 (7.79)
4	6 (1.56)
HAART	
Yes	379 (98.44)
No	6 (1.56)
Age mean (std)	40.31 (9.1)
Median (Q1-Q3)	40 (33 - 46)
Range	24 - 79
Initial CD4 count mean(std)	115.10 (103)
Median (Q1-Q3)	94 (41 - 160)
Range	2 - 616
Latest CD4 count mean (std)	355.06 (219)
Median (Q1-Q3)	322 (206 - 452)
Range	4 - 1403
KPS Mean (std)	80 (6.8)
Median (Q1-Q3)	90 (90 - 90)
Range	70 - 100
Albumin mean(std)	33.1 (8.5)
Median (Q1-Q3)	33 (29 - 39)
Range	14 – 48

Age

The ages of the participants ranged from 22 to 79 years of age. The mean age was 40.3 years. See also Table 1.

Graph 1: Age distribution of the participants

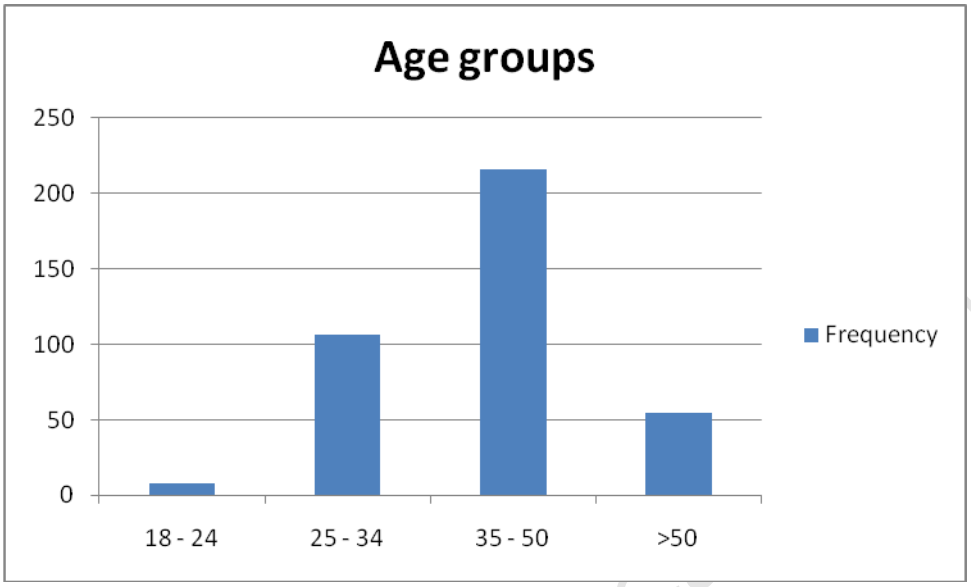


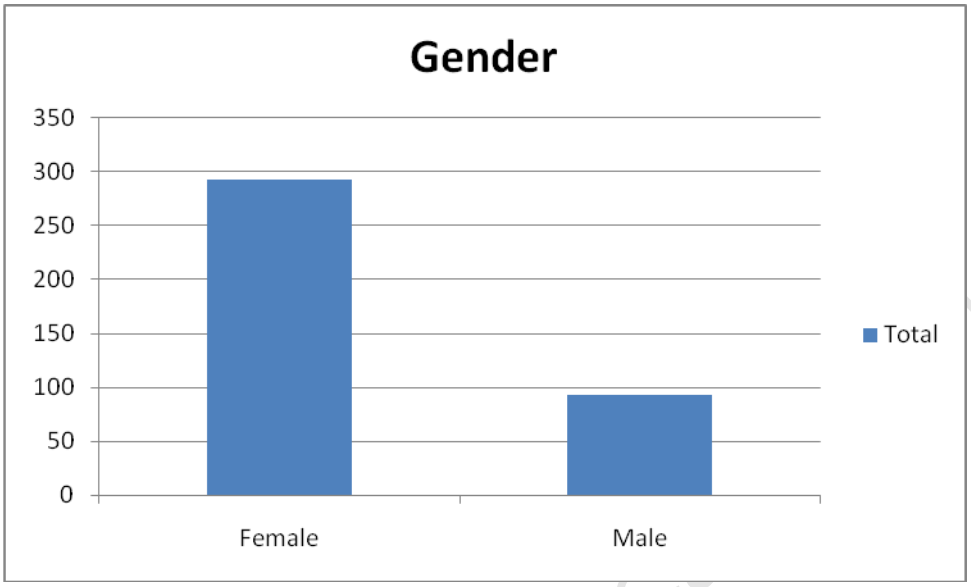
Table 2: Age distribution for statistical analysis

Age	Frequency	Percent	Cum.
1. 18-30	52	13.51	13.51
2. 31-44	219	56.88	70.39
3. 45+	114	29.61	100.00
Total	385	100.00	

Gender

Of the 385 participants, 292 (75.84%) were female and 93 (24.16%) were male, as depicted in the graph. See also Table 1.

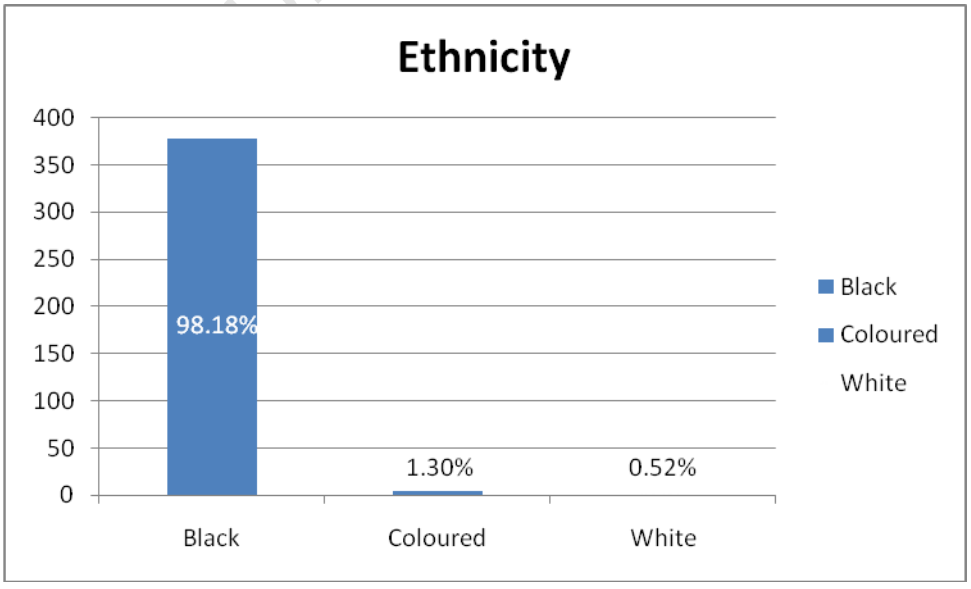
Graph 2: Distribution of Gender



Self-Determined Ethnicity

Three hundred and seventy eight (98.18%) of the 385 participants were black, five (1.30%) were coloured and two (0.52%) were white, as depicted in the graph below. See Table 1.

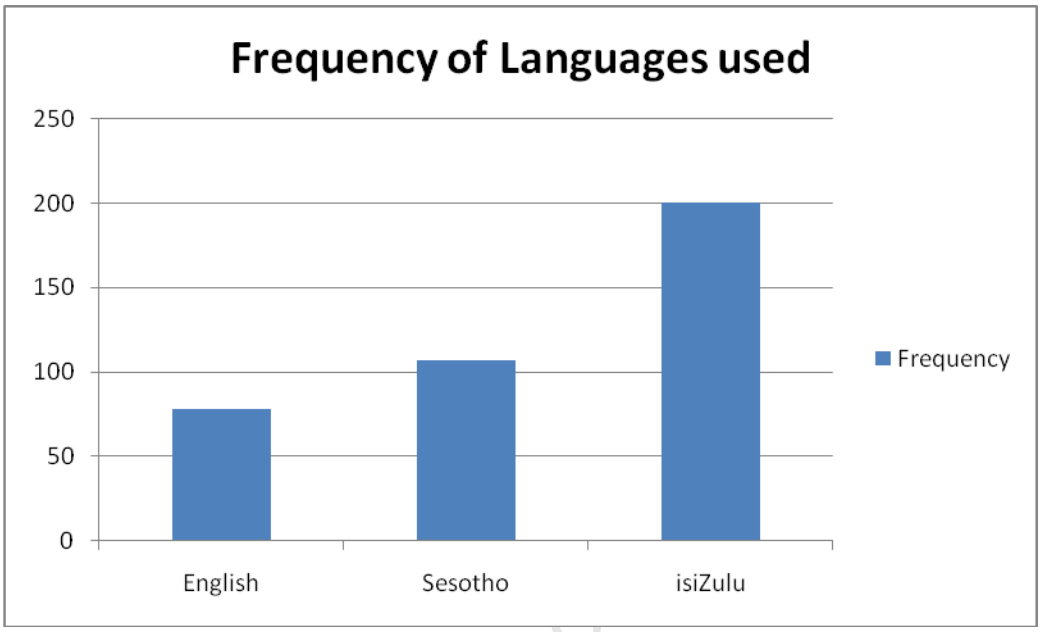
Graph 3: Self-determined ethnicity



Language used for the interview

According to each participant's choice of language used, two hundred (51.95%) of the interviews were done in isiZulu; 107 (27.79%) were done in Sesotho, and 78 (22.59%) of the interviews were done in English. This distribution is depicted in the graph below.

Graph 4: Distribution of languages used by participants for the study interview



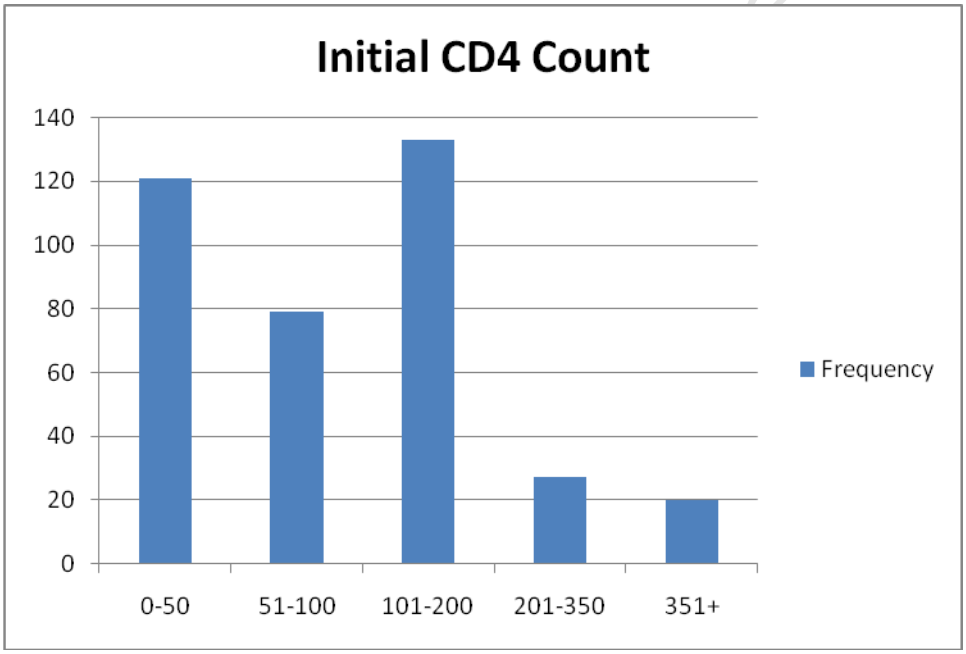
Participant's Clinical Data

Initial CD4 Count before starting HAART

Three hundred and eighty (98.70%) of the 385 participants had an initial CD4 Count. This ranged from <1 – 616 cells/mm³. The mean CD4 count before starting HAART was 115.1cells/mm³. See also Table 1.

This graph shows the Initial CD4 Counts in groups of: 0-50, 51-100, 101-200, 201-350, 351+: This grouping was done after reading the literature(10,17) and using the recent 2010 SA DOH HAART guidelines(4).

Graph 5: Initial CD4 counts of participants before HAART was started

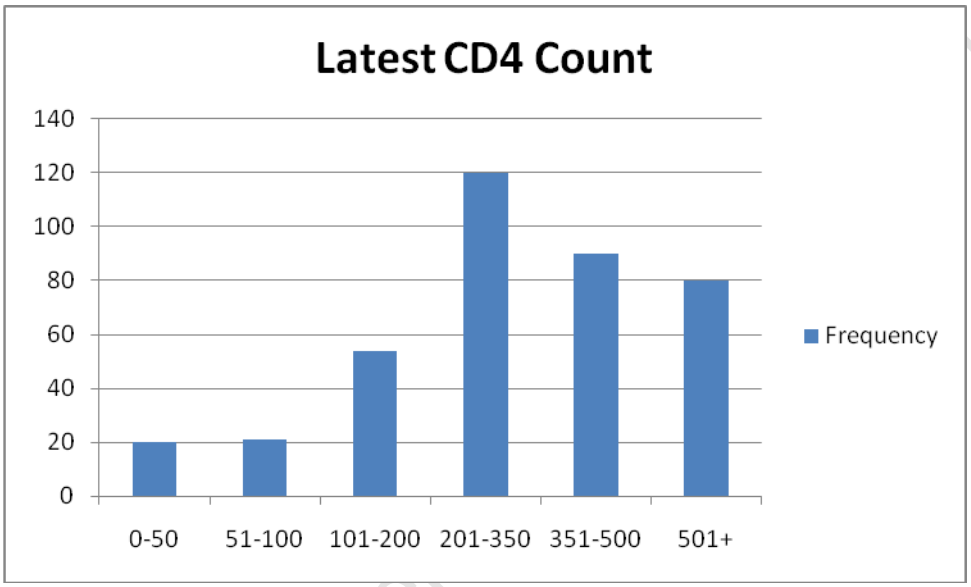


Latest CD4 Count

All patients had a latest CD4 count. The latest CD4 Count ranged from 2 to 1403 cells/mm³. The mean CD4 Count value was 355.06 cells/mm³. See Table 1.

This graph shows the Latest CD4 Counts in groups of: 0-50, 51-100, 101-200, 201-350, 351-500, 501+. The addition of the groups 351-500 and 501+ instead of only 350+ was to accommodate for the participants with CD4 counts higher than 500, to differentiate the CD4 count groups further.

Graph 6: Distribution of the participants' latest CD4 counts



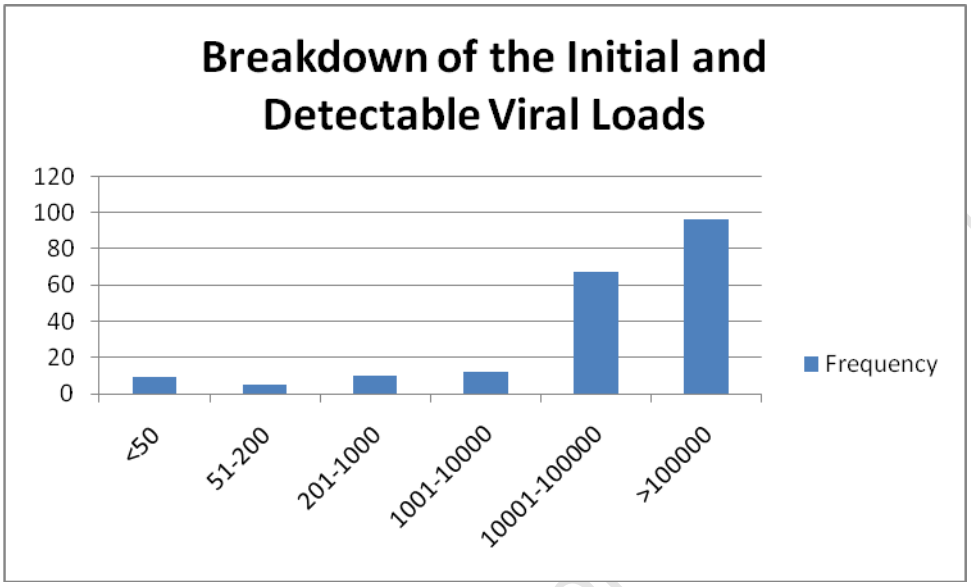
Initial Viral Load before starting HAART

Two hundred and thirty six (63.90%) of the 385 participants had a viral load recording before HAART was started. The range was from <25 to 21 million copies/ml. Viral suppression was taken to be any viral load not detected by that laboratory doing the test, and any viral loads detected from 0 to 40 copies/ml by the laboratory were taken to be undetectable, so as to make the data less confounding as some laboratories could detect a viral copies of above 25 copies/ml, while others could only detect viral copies over 40 copies/ml. Using this cut-off of 40 copies/ml, there were 42 measurements that were undetectable before HAART was started. One hundred and forty nine participants had no viral load measurement before starting HAART. The mean initial viral load before starting

HAART for those with a viral load measurement that was detectable, was 373 209 copies/ml.

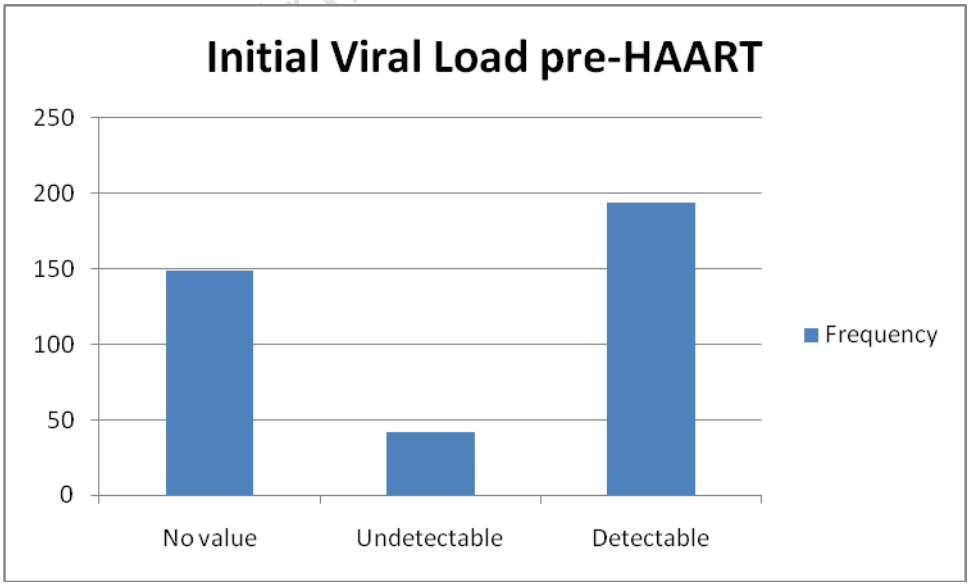
This graph shows the breakdown of Initial Detectable Viral Load in groups of <50; 51-200, 201-1000, 1001-10 000; 10 001-100 000; >100 000 copies/ml.

Graph 7: Breakdown of initial detectable viral load values



This graph shows the simpler breakdown of the Initial viral load (VL taken before HAART was commenced) for all participants.

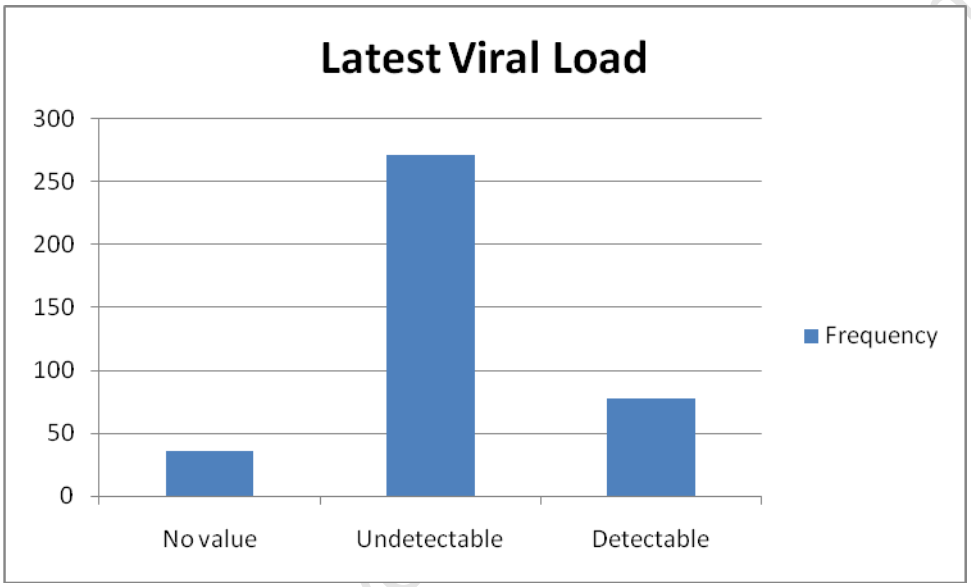
Graph 8: Breakdown of all initial viral load values



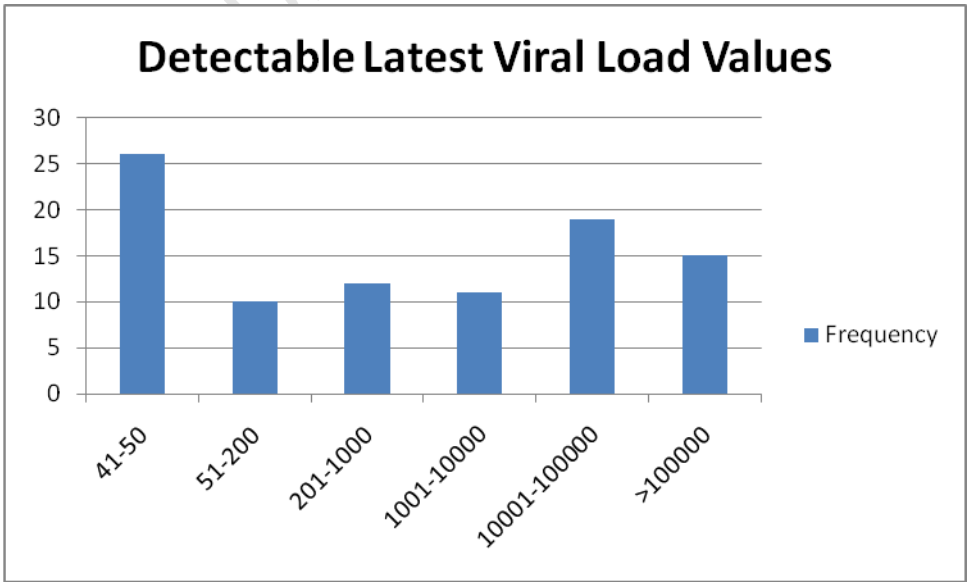
Latest Viral Load

Not all participants had a latest viral load – only 349 (90.65%) of the 385 participants. The number of patients who had viral suppression is 271, while 78 participants had a detectable viral load. The mean latest viral load was 90 932.59 copies/ml for those 76 patients with a detectable viral load. As for the initial viral load, viral suppression was taken to be any viral load not detected by that laboratory, and any viral loads detected from 0 to 40 copies/ml by the laboratory were taken to be undetectable. This graph shows the latest viral load results for all the participants as either no value, undetectable, or detectable.

Graph 9: Distribution of all latest viral load values



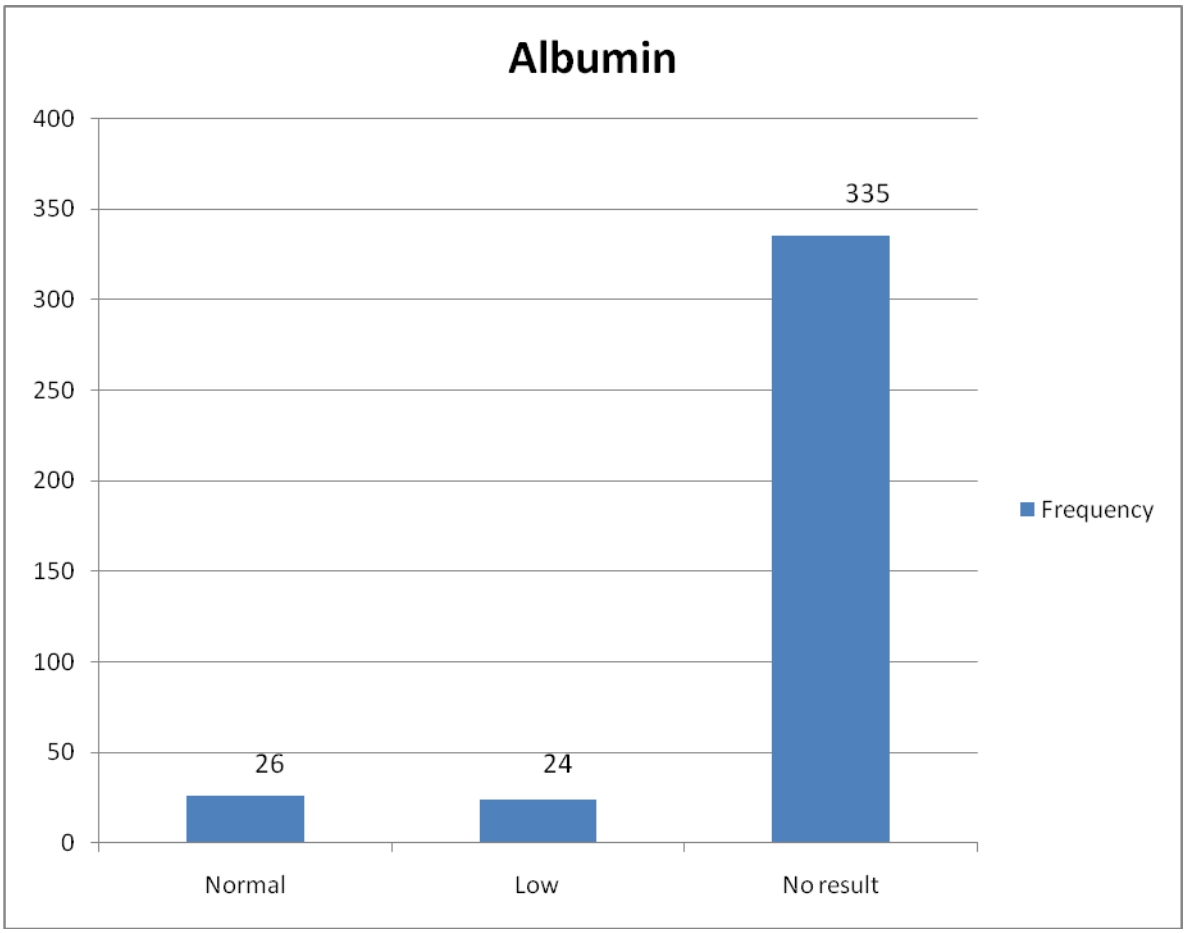
Graph 10: Distribution of detectable latest viral load values



Latest Albumin Level

Only 50 of the 385 participants had an albumin level checked according to their clinic file. The range was from 14 – 48 g/l. The mean albumin level was 33.1 g/l. The National Health Laboratory Service (NHLS) reference value for adult normal albumin is 35-52g/l(70). For those participants with an albumin level, 26 had a normal albumin level of equal to or greater than 35g/l, and 24 had a low albumin (<35g/l). No participants had greater than normal values. The graph below represents these findings. See also Table 1.

Graph 11: Distribution of the recorded albumin values



WHO Staging

The WHO stage of disease, as staged at diagnosis was obtained from the participant files for each of the 385 participants. See also Table 1.

WHO stage 1 - 98 (25.45%)

WHO stage 2 – 251 (65.19%)

WHO stage 3 – 30 (7.79%)

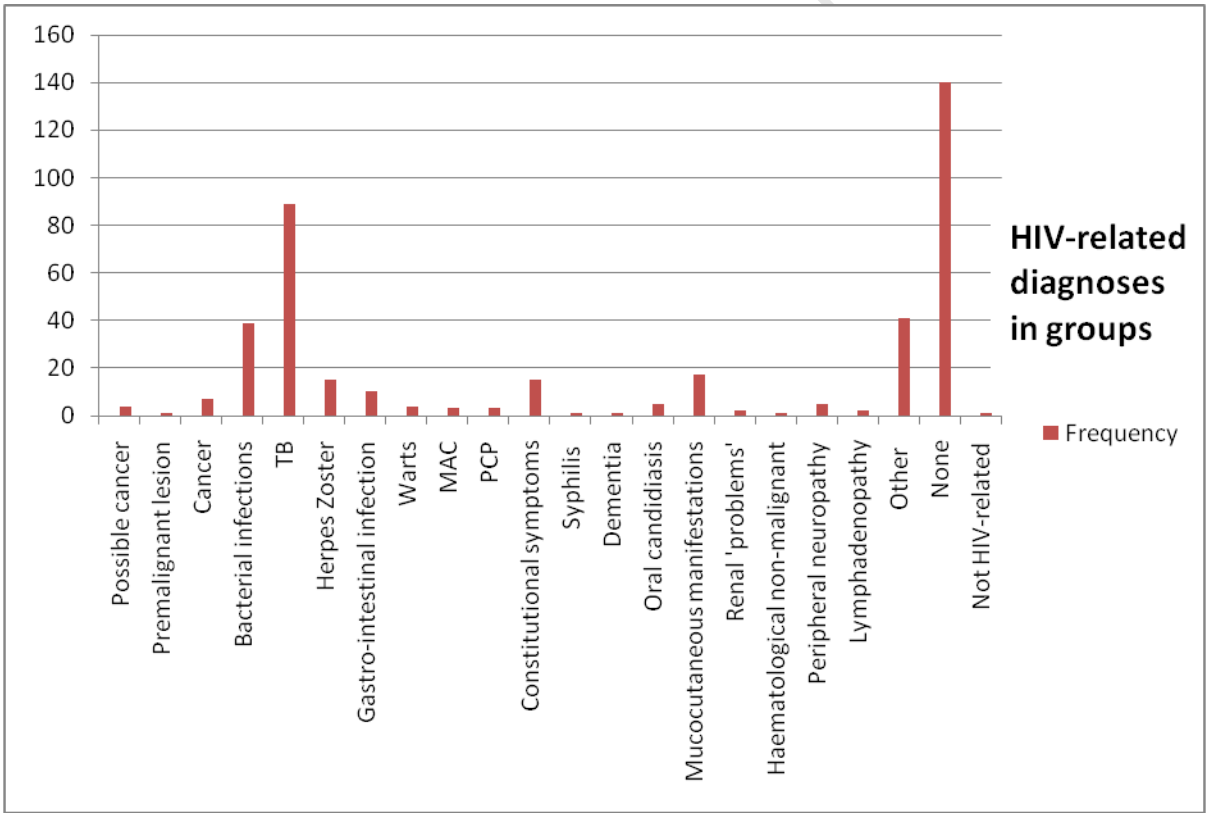
WHO stage 4 – 6 (1.56%)

For statistical analysis, WHO stages 3 and 4 were combined into one group.

HIV Related Diagnoses

HIV related diagnoses were collected from the files for 245 (63.64%) of the 385 participants. 140 of the participants had no recorded HIV related diagnoses. There were a total of 406 HIV related diagnoses. One diagnosis was considered by the PI as not HIV related. The diagnoses were grouped by the PI as follows: Possible Cancer (being investigated), Premalignant lesion, Cancer, Bacterial Infections, TB, Herpes Zoster, Gastro-Intestinal Infection, Warts, MAC, PCP, Constitutional Symptoms, Syphilis, Dementia, Oral Candidiasis, Mucocutaneous manifestations (other than Candidiasis), Renal 'problems', Non-malignant Haematological, Peripheral neuropathy, Lymphadenopathy and other. The graph below shows the frequency of each of these.

Graph 12: HIV related diagnoses as grouped by the PI



The number of those patients who were recorded as never having a diagnosis of Tuberculosis (TB) was 295, whereas 89 (23.18%) had had TB diagnosed at some point in the past.

Patients taking HAART

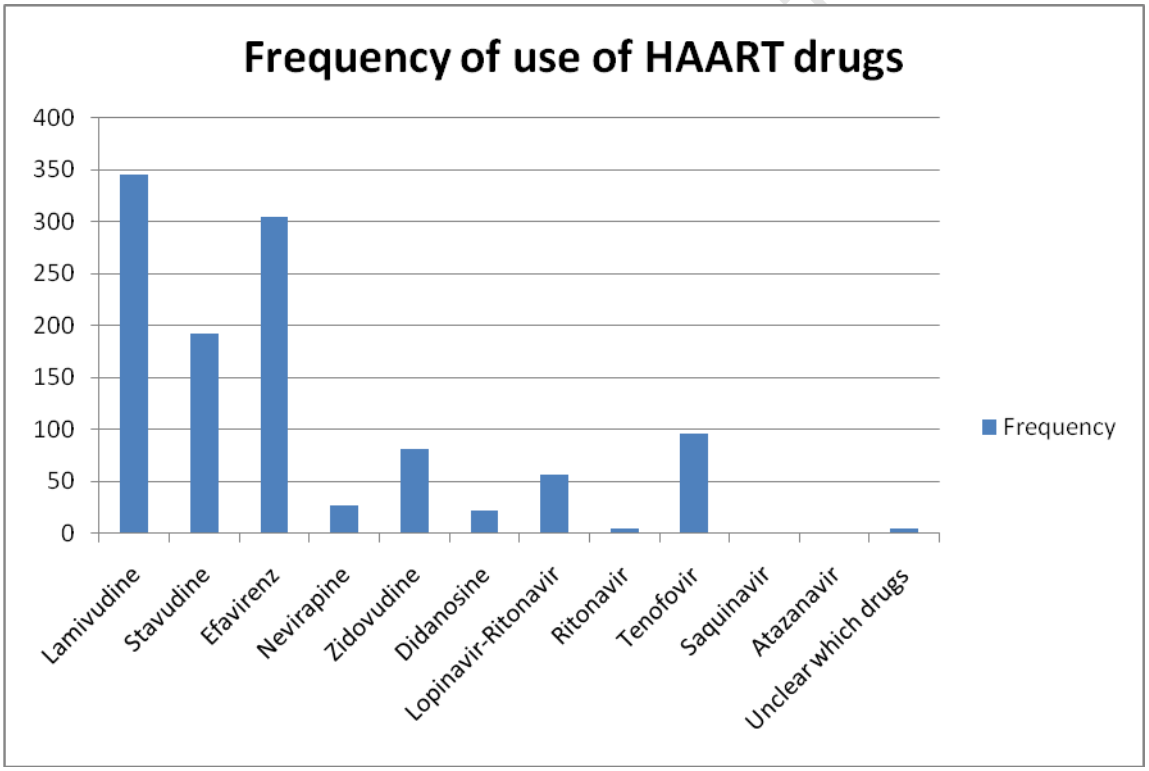
Of the 385 participants, 379 (98.44%) were taking HAART at the time of the interview. Six participants (1.56%) were not on HAART at the time of the interview. See also Table 1.

HAART Drugs used

The drugs that the participants of the study were taking are as follows: Lamivudine, Stavudine, Efavirenz, Nevirapine, Zidovudine, Didanosine, Lopinavir-Ritonavir, Ritonavir, Tenofovir, Saquinavir, Atazanavir.

The graph below depicts the frequency with which each of the drugs was used in the study.

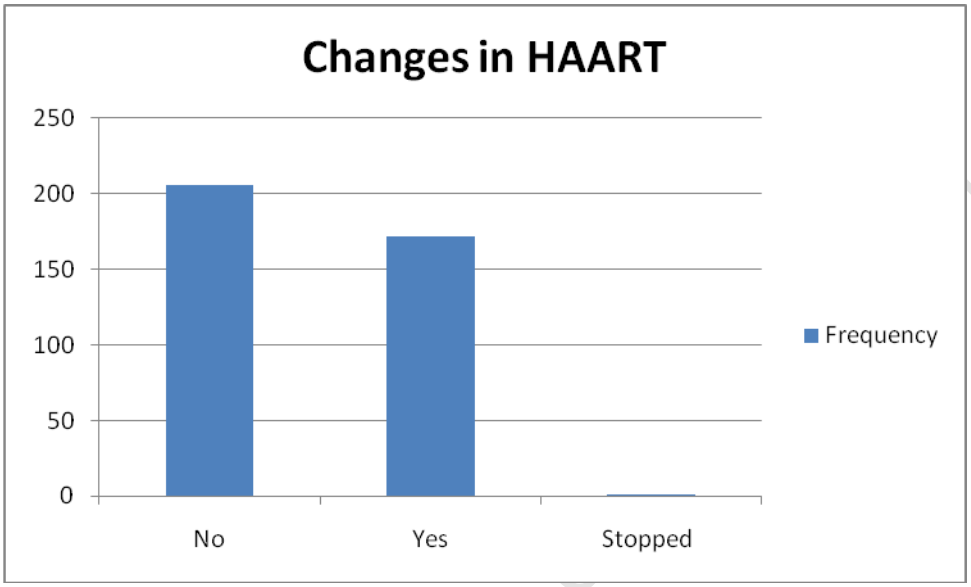
Graph 13: HAART drugs taken by participants



Changes in HAART

Of the 379 participants who were on HAART, 207 (54.62%) had never changed HAART. They had been stable on HAART since its initiation, 172 (44.68%) had changed HAART regimens at least once. One participant (0.26%) had stopped HAART treatment. The graph below depicts this information.

Graph 14: Frequency with which participants had ever changed HAART regimes



Reasons for change in HAART

The reasons for a change in HAART were grouped into the following categories.

Table 3: Reasons for change in HAART

Reason	Frequency
Lipodystrophy	75
Neuropathic pain	45
Raised Lactic Acid or Lactic Acidosis	23
Virological Failure	16
Clinical symptoms of failure	12
Defaulted treatment	8
Possibility of pregnancy	4
Hepatitis B infection	4
Drug Toxicity	3
Drug resistance	3
Gyanecomastia	3
Dyslipidaemia	3
Non-Specific Clinical Symptoms	3
Immunological Failure	3
Anaemia	3
Liver Abnormalities	3
Adverse Drug Reaction	2
Skin Rash	2
Pancreatitis	1
Renal Dysfunction	1
Structured Treatment interruption	1
Treatment failure	1
Insomnia	1
Nausea & Vomiting	1
Psychiatric Symptoms	1
Angioedema	1

Current Karnofsky Performance Status (KPS)

Of the 385 participants,

59 (15.32%) had KPS of 100%,

269 (69.85%) had KPS of 90%,

44 (11.43%) had KPS of 80%,

6 (1.56%) had KPS of 70%,

1 (0.26%) had KPS of 60%,

1 (0.26%) had KPS of 50%,

1 (0.26%) had KPS of 40%, and

4 (1.04%) had no KPS assigned.

The mean KPS score was 80. No participant had a KPS score of less than 40%.

See also Table 1.

To make **statistical analysis** of the data easier, the KPS scores were grouped as follows:

KPS	40% to 80%	53	(13.91%)
KPS	90%	269	(70.60%)
KPS	100%	59	(15.49%)

The subjective question: "Do you think any of your symptoms are because of your ARVs?"

Of the 385 participants, 236 (61.3%) answered "yes" to this question, and 145 (37.66%) answered "no". Two participants (0.52%) answered that it was not applicable. Two more had no answer recorded.

The symptoms indicated as being thought to be due to HAART by the participants

The most common MSAS-SF symptoms that participants said were due to their HAART were Body Fat Distribution Changes (46.19%) and Numbness/Tingling of hands & feet (37.73%). This table indicates the correlation between MSAS-SF symptoms and the symptoms attributed to HAART use by the participants.

Table 4: Symptoms perceived as due to HAART by the participants

Symptoms	Frequency
Body fat distribution changes	109
Numbness/tingling of hands & feet	89
Other	24
Changes in skin	15
All of the symptoms	8
Weight loss	8
Itching	8
Dizziness	6
Lack of energy	6
Pain	5
Swelling of arms & legs	5
Diarrhoea	4
Feeling bloated	3
Shortness of breath	2
Problems with sexual interest or activity	2
Feeling drowsy	2
Lack of appetite	2
Mouth Sores	1
"I don't look like myself"	1
Difficulty in swallowing	1
Change in the way food tastes	1
Hair loss	0
Constipation	0
Feeling Sad	0
Worrying	0
Feeling irritable	0
Feeling nervous	0
Dry mouth	0
Nausea	0
Difficulty concentrating	0
Sweats	0
Difficulty sleeping	0
Cough	0
Problems with urination	0
Vomiting	0

Memorial Symptom Assessment Scale –Short Form (MSAS-SF)

A copy of the MSAS-SF is found in the Appendix.

Symptom prevalence and burden

The prevalence of all the symptoms is shown in Table 2.

Table 5: Prevalence of all symptoms by MSAS-SF

Symptom	Prevalence n (%)
Feeling sad	249 (64.68%)
Feeling irritable	239 (62.08%)
Numbness/tingling in hands & feet	235 (61.04%)
Worrying	235 (61.04%)
Problems with sexual interest or activity	200 (51.95%)
Pain	197 (51.17%)
"I don't look like myself"	188 (48.83%)
Feeling nervous	156 (40.52%)
Lack of Energy	155 (40.26%)
Sweats	150 (38.96%)
Weight loss	150 (38.96%)
Feeling bloated	147 (38.98%)
Feeling drowsy	139 (36.10%)
Changes in skin	136 (35.32%)
Difficulty concentrating	131 (34.03%)
Constipation	121 (31.43%)
Itching	116 (30.13%)
Lack of appetite	100 (25.97%)
Cough	98 (25.45%)
Dizziness	94 (24.42%)
Swelling of arms or legs	92 (23.90%)
Difficulty sleeping	89 (23.12%)
Dry mouth	89 (23.12%)
Shortness of breath	71 (18.44%)
Nausea	67 (17.40%)
Diarrhoea	59 (15.32%)
Problems with urination	55 (14.29%)
Mouth sores	55 (14.29%)
Change in the way food tastes	52 (13.51%)
Hair loss	35 (9.09%)
Vomiting	23 (5.97%)
Difficulty swallowing	18 (4.68%)

All participants had at least one symptom. The mean number of symptoms (±SD, range), of the 32 symptoms on the MSAS-SF, that participants experienced was 10.24 (± 5.71, 1-28).

All four psychological symptoms (feeling sad, feeling irritable, worrying and feeling nervous) were in the top ten most prevalent symptoms, with feeling sad being the most prevalent symptom overall. The top ten symptoms are, in order from most prevalent: feeling sad, feeling irritable, numbness/tingling in hands and feet, worrying, problems with sexual interest or activity, pain, "I don't look like myself", feeling nervous, lack of energy and sweats.

Six symptoms had more than 50% prevalence, with four having more than 60% prevalence. They are: feeling sad (65%), feeling irritable (62%), numbness/tingling in hands & feet (61%), worrying (61%), problems with sexual interest or activity (52%) and pain (51%).

High frequency for the psychological symptoms is taken as those occurring frequently or almost constantly. High distress for physicals symptoms is taken as any symptom distress described as quite a bit or very much. This has been done in other studies, by Vogl et al and Wakeham et al(10,17).

Table 6 shows the distress ratings for the physical symptoms.

Table 6: Burden/Distress for Physical symptom: including High Distress (%) for Physical Symptoms*

Symptom	**Not at all n (%)**	**A little bit n (%)**	**Somewhat n (%)**	**Quite a bit n (%)**	**Very much n (%)**	**High distress (%)***
Numbness/tingling in hands & feet	18 (7.69%)	28 (11.97%)	42 (17.95%)	38 (16.24%)	108 (46.15%)	62.39
Problems with Sexual interest or activity	14 (7.04%)	18 (9.05%)	31 (15.50%)	28 (14.00%)	108 (54.27%)	68.27
Pain	15 (7.61%)	29 (14.80%)	36 (18.27%)	28 (14.29%)	88 (44.90%)	59.19
"I don't look like myself"	6 (3.19%)	19 (10.11%)	29 (15.43%)	21 (11.17%)	113 (60.11%)	71.28
Lack of Energy	8 (5.16%)	25 (16.13%)	46 (29.68%)	21 (13.55%)	55 (35.48%)	49.03
Sweats	8 (5.37%)	22 (14.77%)	32 (21.48%)	27 (18.12%)	60 (40.27%)	58.39

Symptom	Not at all n (%)	A little bit n (%)	Somewhat n (%)	Quite a bit n (%)	Very much n (%)	High distress (%)*
Weight loss	6 (4.05%)	24 (16.22%)	24 (16.22%)	18 (12.16%)	77 (52.03%)	64.19
Feeling bloated	10 (6.80%)	39 (26.53%)	25 (17.01%)	36 (24.49%)	37 (25.17%)	49.66
Feeling drowsy	15 (10.87%)	42 (30.43%)	22 (15.94%)	23 (16.67%)	36 (26.09%)	42.76
Changes in skin	13 (9.56%)	27 (19.85%)	26 (19.12%)	16 (11.76%)	54 (39.71%)	51.47
Difficult concentrating	9 (6.87%)	30 (22.90%)	28 (21.37%)	23 (17.56%)	40 (30.53%)	48.09
Constipation	9 (7.44%)	29 (23.97%)	27 (22.31%)	25 (20.66%)	31 (25.62%)	46.28
Itching	8 (6.90%)	25 (21.55%)	23 (19.83%)	22 (18.97%)	37 (31.90%)	50.87
Lack of appetite	6 (6.00%)	12 (12.00%)	23 (23.00%)	21 (21.00%)	38 (38.00%)	59.00
Cough	21 (21.43%)	30 (30.61%)	15 (15.31%)	8 (8.16%)	24 (24.49%)	32.65
Dizziness	8 (8.51%)	24 (25.53%)	17 (18.09%)	12 (12.77%)	33 (35.11%)	47.88
Swelling of arms/legs	4 (4.40%)	21 (23.08%)	22 (24.18%)	11 (12.09%)	33 (36.26%)	48.35
Difficulty in sleeping	7 (7.87%)	13 (14.61%)	13 (14.61%)	14 (15.73%)	42 (47.19%)	62.92
Dry mouth	9 (10.23%)	19 (21.60%)	15 (17.05%)	20 (22.73%)	25 (28.41%)	51.14
Shortness of breath	3 (4.29%)	12 (17.14%)	14 (20.00%)	12 (17.14%)	29 (41.43%)	58.57
Nausea	6 (8.96%)	22 (32.84%)	12 (17.91%)	8 (11.94%)	19 (28.36%)	40.30
Diarrhoea	7 (11.86%)	16 (27.12%)	10 (16.95%)	11 (18.64%)	15 (25.42%)	44.06
Change in the way food tastes	5 (9.43%)	8 (15.09%)	7 (13.46%)	11 (21.15%)	21 (39.62%)	60.77
Mouth Sores	0 (0)	20 (37.04%)	15 (27.78%)	5 (9.26%)	14 (25.93%)	35.19
Problems with Urination	0 (0)	12 (21.82%)	11 (20.00%)	8 (14.55%)	24 (43.64%)	58.19
Hair loss	4 (11.43%)	8 (22.86%)	5 (14.29%)	3 (8.57%)	15 (42.86%)	51.43
Vomiting	4 (17.39%)	11 (47.83%)	1 (4.35%)	3 (13.04%)	4 (17.39%)	30.43
Difficulty swallowing	1 (5.56%)	5 (27.78%)	1 (5.56%)	5 (27.78%)	6 (33.33%)	61.11

***High distress for physical symptoms = Quite a bit and Very much**

Table 7 shows the frequency ratings for the psychological symptoms.

Table 7: Frequency of Psychological Symptoms: including High Frequency (%) for Psychological Symptoms *

Psychological symptom	Rarely n (%)	Occasionally n (%)	Frequently n (%)	Almost constantly n (%)	High Frequency (%)*
Feeling sad	62 (24.90%)	67 (26.91%)	33 (13.25%)	87 (34.94%)	48.19
Feeling irritable	40 (16.81%)	55 (23.01%)	41 (17.15%)	102 (42.86%)	60.01
Worrying	57 (24.15%)	47 (19.92%)	37 (15.68%)	95 (40.25%)	55.93
Feeling nervous	40 (25.64%)	33 (21.15%)	24 (15.38%)	59 (37.82%)	53.20

***High Frequency of psychological symptoms = Frequently and Almost constantly**

The high frequency of the psychological symptoms was over 48% for each of the four psychological symptoms, with the symptom with the highest frequency being feeling irritable, at 60%.

The highest "high distress" generated by the physical symptoms was for "I don't look like myself", at 71%. 'Problems with sexual interest or activity' was the second most highly distressing symptom if it occurred, at 68% high distress. The high distress for numbness or tingling of hands or feet was 62%, and for pain was 59%.

MSAS-SF Subscales

Subscales are generated from the MSAS-SF, as described in the literature review. The subscales are the Global Distress Index (MSAS-GDI), the Physical Symptom Subscale score (MSAS-PHYS), the Psychological Symptom Subscale score (MSAS-PSYCH) and the Total Memorial Symptom Assessment Score (TMSAS). The subscale scores for this study are read as the mean MSAS-GDI, mean MSAS-PHYS, mean MSAS-PSYCH and the mean TMSAS. A constitutional symptom constellation was formed, using five constitutional symptoms, namely lack of energy, sweats, weight loss, lack of appetite, and feeling drowsy.

The Cronbach's coefficient alpha for MSAS-GDI was 0.7939; for MSAS-PHYS was 0.7657; for MSAS-PSYCH was 0.7873. The Cronbach's alpha coefficient for TMSAS was 0.8784. The Cronbach's alpha coefficient for the constitutional symptom subscale was 0.5931.

The mean (±SD, range) MSAS-GDI score was 1.19 ± 0.89 (0-3.84).

The mean (±SD, range) MSAS-PHYS score was 0.80 ± 0.71 (0-3.66).

The mean (±SD, range) MSAS-PSYCH score was 1.27 ± 1.06 (0-4).

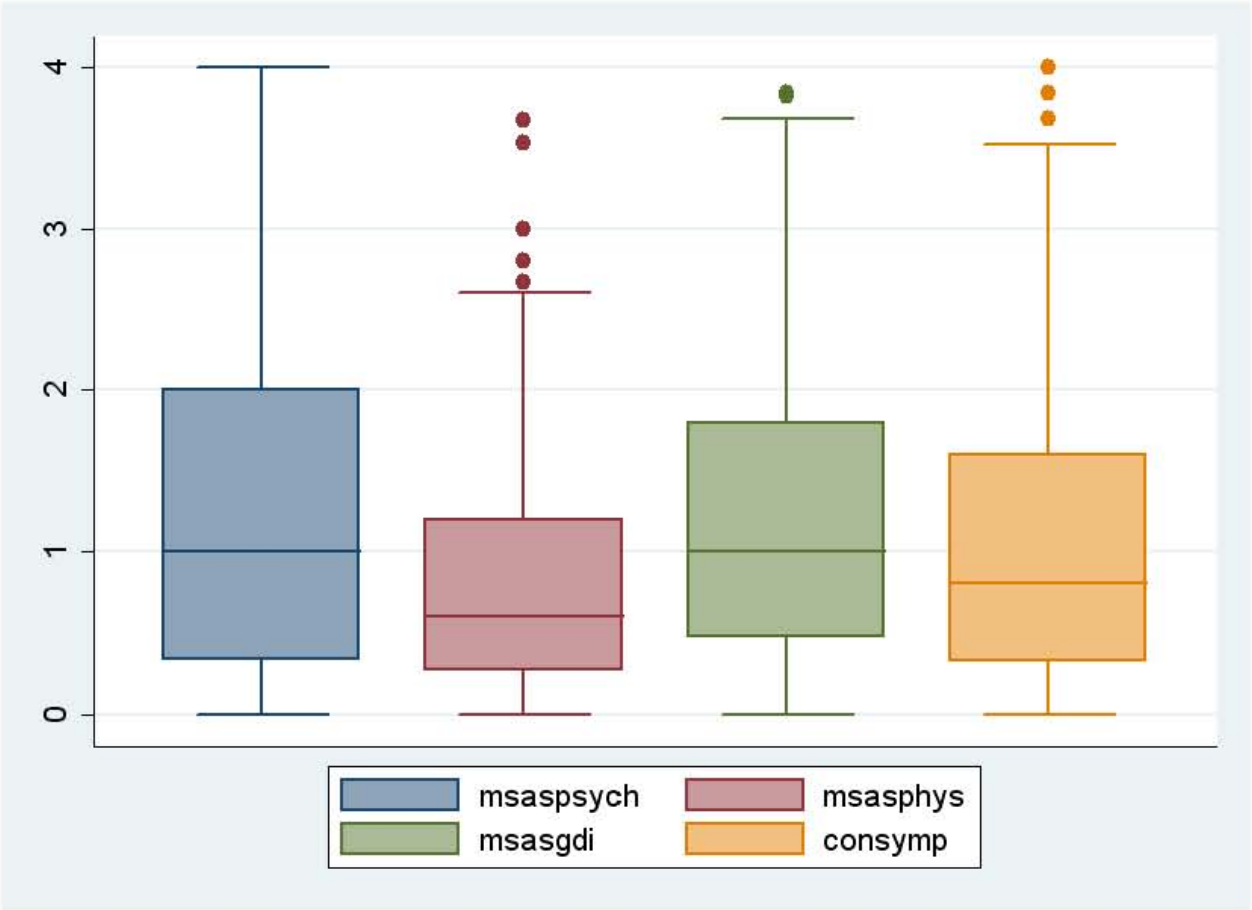
The mean (±SD, range) TMSAS score was 0.90 ± 0.63 (0.25-3.125).

The mean (±SD, range) Constitutional symptom score was 1.04 ± 0.94 (0-4). The use of this subscale is new and was not validated.

The mean number of psychological symptoms experienced, out of a possible six symptoms (worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating) was 2.85 symptoms. The mean number of physical symptoms experienced, out of a possible 12 (lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness) was 3.46.

See Figure 1 below for the Boxplot distributions of the scores for MSAS-GDI, MSAS-PHYS, MSAS-PSYCH and the constitutional symptom subscale.

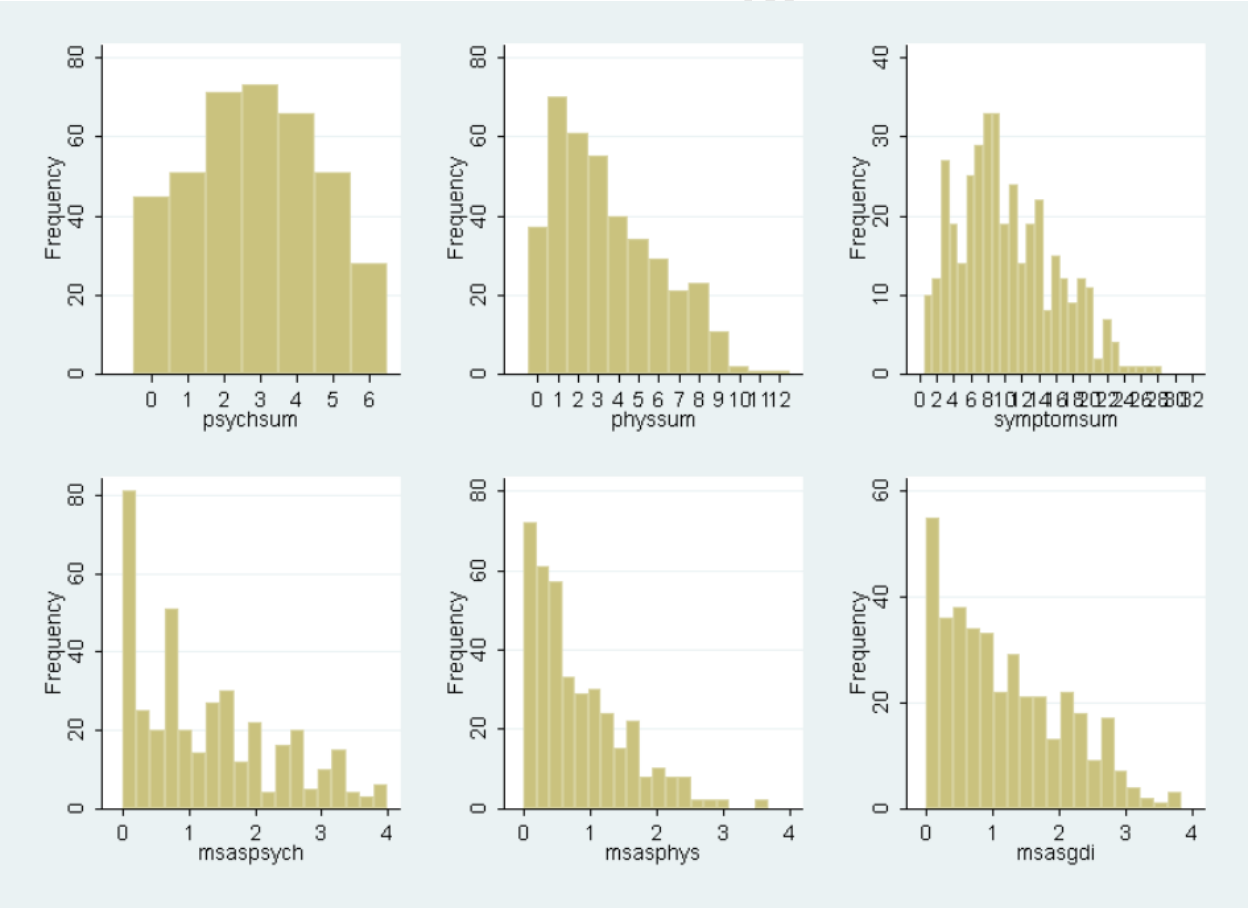
<u>Figure 1</u>: This Boxplot shows the distributions of the scores on the subscales MSAS-GDI, MSAS-PHYS, MSAS-PSYCH and the constitutional symptom subscale:



Normality/Distribution of the data

The Shapiro-Francia W' test for normal data was applied to test the normality of the data. The results show that the sum of the psychological symptoms (psychsum) has a near normal distribution, but the physical symptom sum (physsum) is not normally distributed with few patients experiencing a very large number of symptoms, and the sum of all the symptoms (symptomsum) has a near normal distribution, but with relatively few patients experiencing a very large number of symptoms. The MSAS-PSYCH score and the MSAS-PHYS score are not normally distributed, with a logarithmic type curve, showing that relatively few patients had very high psychological and physical distress respectively. The MSAS-GDI score is also not normally distributed, but with a flatter curve, but also showing that relatively few patients had very high global distress. See Figure 2 below.

Figure 2: Histograms of the distribution of the data for these six calculations:

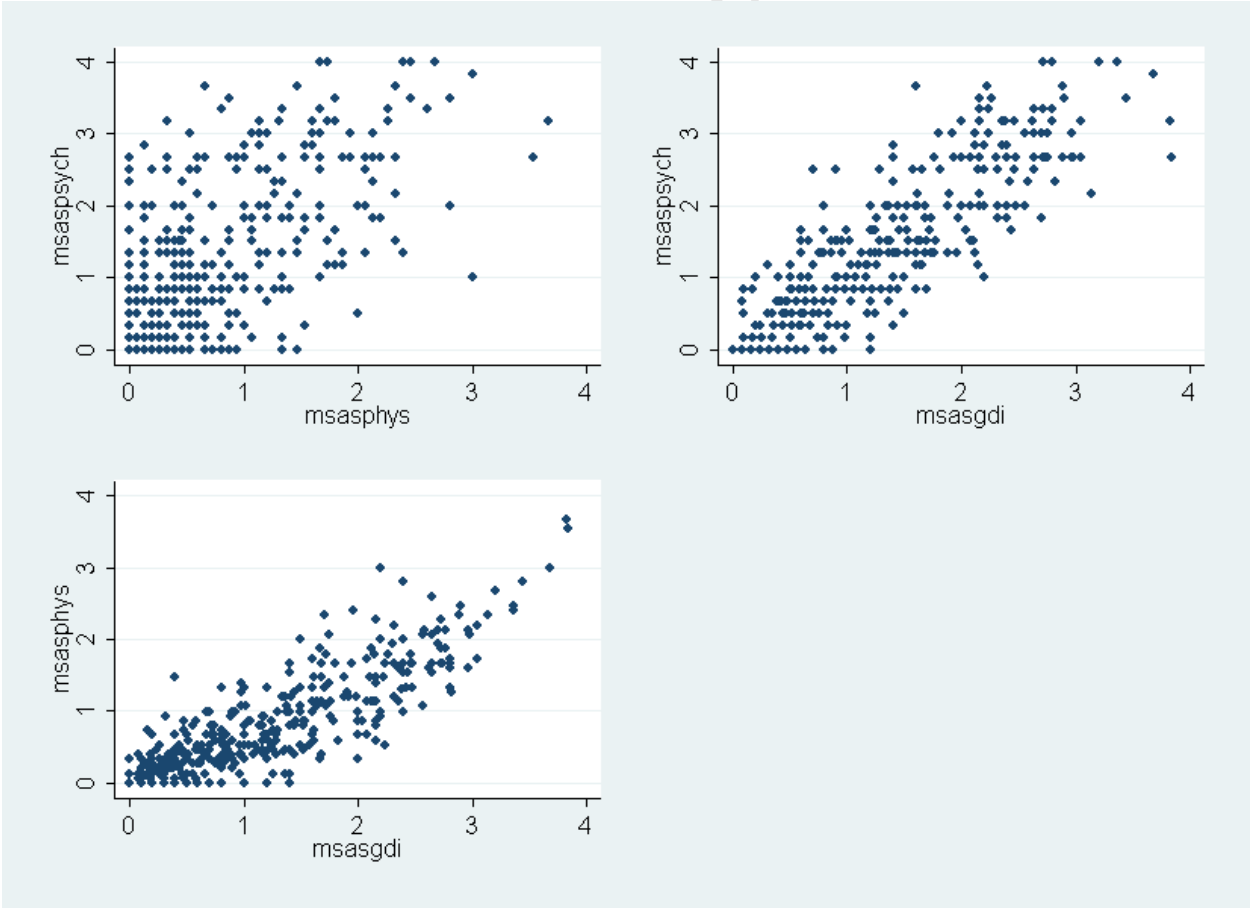


Correlation of MSAS-SF with demographic and clinical factors

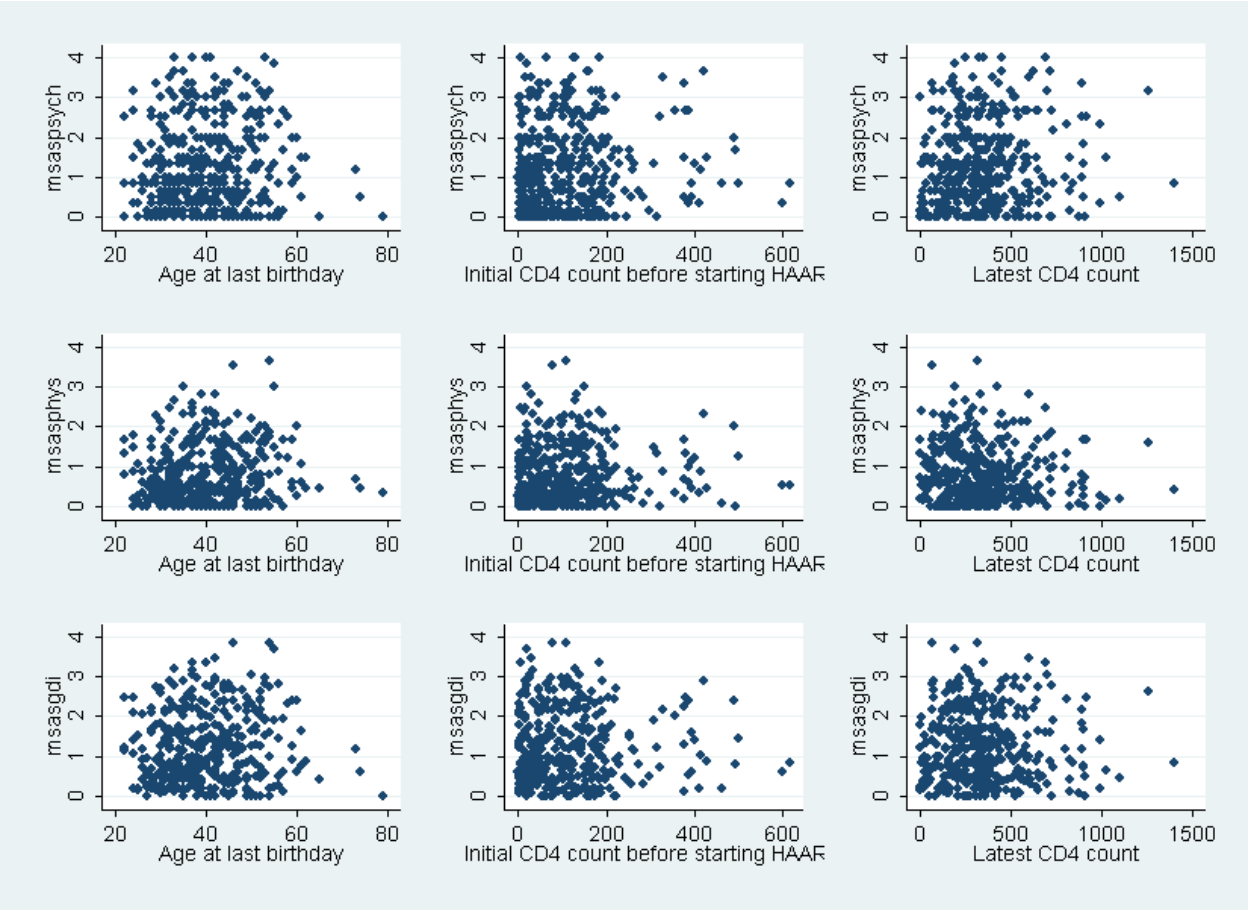
The p value was set at 5% ($p<0.05$) for significance.

The Spearman correlation found that there was a large and significant correlation between MSAS-PSYCH and MSAS-PHYS; there was a very large and significant correlation between MSAS-GDI and MSAS-PHYS and also between MSAS-GDI and MSAS-PSYCH. See Figure 3. There was a very small but significant correlation between age and MSAS-PHYS. There was no correlation between the initial CD4 count and any of the MSAS-SF subscales, nor between the latest CD4 count and any of the MSAS-SF subscales. See Figure 4. There was also no correlation between the latest viral load and any of the MSAS-SF subscales. Further statistical correlations were performed and will now be discussed individually.

Figure 3: The Scatter plots show the correlation of the MSAS-SF subscales with each other:



<u>Figure 4</u>: The Scatter plots show the relationships between the three MSAS-SF subscales and age, initial CD4 count and latest CD4 count:



Initial CD 4 count versus MSAS-SF Subscales

The comparisons between the initial CD4 counts and the MSAS-SF subscales showed no significant differences between the CD4 count groups (<50, 51-100, 101-200, >200) with any of the subscales, namely MSAS-GDI, -PHYS, -PSYCH. The p values were all > 0.05 for the Kruskal-Wallis equality-of-populations rank test.

Latest CD 4 count versus MSAS-SF Subscales

The Kruskal-Wallis equality-of-populations rank test for the nonparametric data, suggests no difference in distribution across the categories of the latest CD4 groups (<50, 51-100, 101-200, 201-350, 351-500, 500+) in any of the three MSAS-SF subscales, MSAS-GDI, -PHYS, or -PSYCH. The p values were all greater than 0.05

Latest Viral Load versus MSAS-SF Subscales

The Pearson correlation showed no correlation between latest viral load and MSAS-PSYCH, a small correlation between latest viral load and MSAS-PHYS, and an even smaller correlation between latest viral load and MSAS-GDI. However, no significance was found for the correlations between the latest viral load and the MSAS-PHYS and the MSAS-GDI.

Latest Viral Load versus Constitutional Symptoms

The latest viral load, either detectable or not, was compared to the grouping of constitutional symptoms, namely lack of energy, sweats, weight loss, lack of appetite, and feeling drowsy, and no significant difference in these symptoms was found between those with a detectable viral load and those whose viral lad was undetectable. This was according to the Two-sample t test with equal variances, and confirmed with the Two-sample Wilcoxon rank-sum (Mann-Whitney) test.

Latest Viral Load versus Perception that symptoms were due to HAART

The latest viral load, either detectable or not, was compared to the perception that symptoms were due to HAART, either yes, or no. This was tested using a chi-square test of independence. The results show that 180 participants with an undetectable viral load (66.18% of participants with an undetectable viral load) responded 'Yes' to the question of whether they thought their symptoms were because of their HAART, compared to 40 participants with a detectable viral load (52.63% of participants who had a detectable viral load). The chi-square=4.6868, and p=0.030. The effect size for the relationship between the latest viral load and the perception that symptoms were due to HAART, was measured, with a *Phi* value of -0.116.

Latest Albumin level versus MSAS-SF subscales

To asses the relationship of the albumin level to the MSAS-SF subscales, two groups of albumin level were compared: a) low albumin - less than 35g/l or b) normal albumin - greater than or equal to 35g/l. There was no significant difference between albumin groups according to the sum of all symptoms, as calculated by the Two-sample t test with equal variances. The low albumin group seemed to show a greater mean symptom prevalence (9.333333 vs 8.961538) but this was not significant. The Two-sample Wilcoxon rank-sum (Mann-Whitney) test showed that there was no significant difference between the albumin groups for the sum of the physical symptoms or the sum of the psychological symptoms.

When comparing the albumin groups with the MSAS-GDI, MSAS-PHYS and MSAS-PSYCH, the Two-sample t test with equal variances and the Two-sample Wilcoxon rank-sum (Mann-Whitney) tests were used, and there was no statistically significant difference for the MSAS-SF subscales by the albumin groups. The group with a normal albumin level had a greater mean MSAS-PSYCH score (1.25641) than those with a low albumin level (0.7777778), but the difference was not significant.

WHO stage versus MSAS-SF Subscales

The WHO stages as grouped for statistical purposes were compared to the MSAS-PSYCH, MSAS-PHYS and MSAS-GDI using one way ANOVA but because the data was not normally distributed and there was unequal variance, the Kruskal-Wallis equality-of-populations rank test was used to confirm the findings and is the statistic used to report the findings. There are significant differences for MSAS-PSYCH and MSAS-GDI and there are also differences for MSAS-PHYS.

For MSAS-GDI, one way ANOVA does show a significant difference, which is confirmed by the Kruskal-Wallis equality-of-populations rank test, where the chi-squared is 32.148 with 2 d.f. with a probability of 0.0001. For MSAS-GDI, WHO stage 1 and 2 and are significantly different (p=0.0001), as are stages 3&4 compared to stage 1 (p=0.0001), but stage 2 is not significantly different to stages 3&4 (p=0.363).

The Kruskal-Wallis equality-of-populations rank test with chi-squared = 8.135 with 2 d.f. and probability = 0.0171, suggests that the distribution of MSAS-PHYS is not the same across the WHO stage groups, but with no statistical significance, with p>0.1 for each of the comparisons on the Scheffe test.

For MSAS-PSYCH, WHO stage 1 compared to WHO stage 2, there was a significant difference with WHO stage 2 participants experiencing more frequent psychological symptoms than participants who were staged WHO 1 (p=0.0001). For MSAS-PSYCH, this was also true for WHO stages 3 & 4 compared to stage 1 (p=0.0001), but the relationship was not significant when comparing WHO stage 3&4 to stage 2 (p=0.429). The Kruskal-Wallis equality-of-

populations rank test confirmed that this was correct for the non-parametric data used, chi-squared = 37.891 with 2 d.f with the probability = 0.0001.

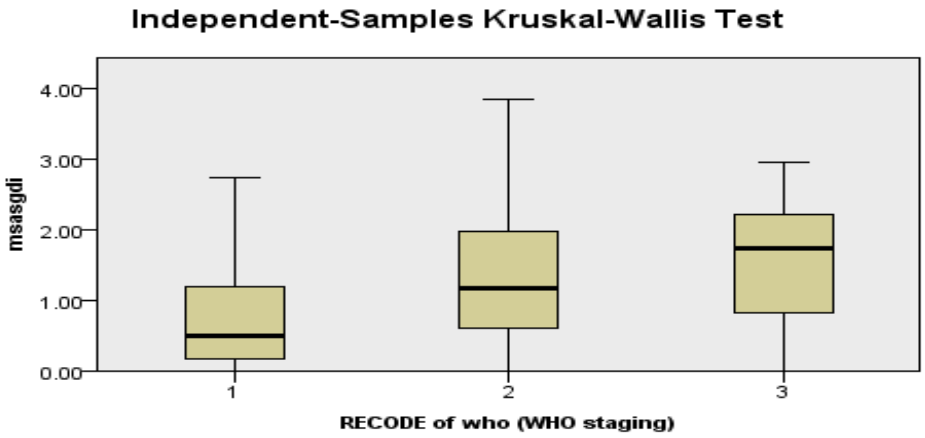
See Figures 5, 6 and 7: The Boxplots for each of these three relationships are found on the subsequent pages.

'1' denotes WHO group 1

'2' denotes WHO group 2

'3' denotes WHO groups 3 and 4

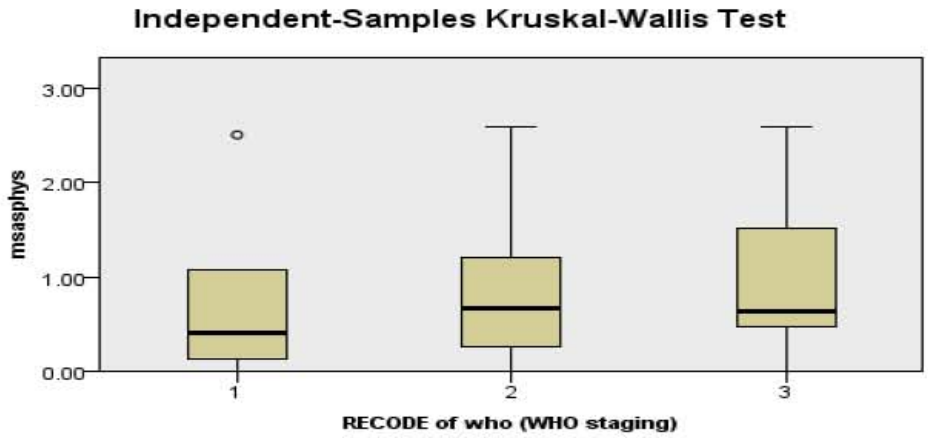
<u>Figure 5</u>: This is the boxplot distribution of MSAS-GDI scores according to WHO groups:



Total N	385
Test Statistic	32.158
Degrees of Freedom	2
Asymptotic Sig. (2-sided test)	.000

1. The test statistic is adjusted for ties.

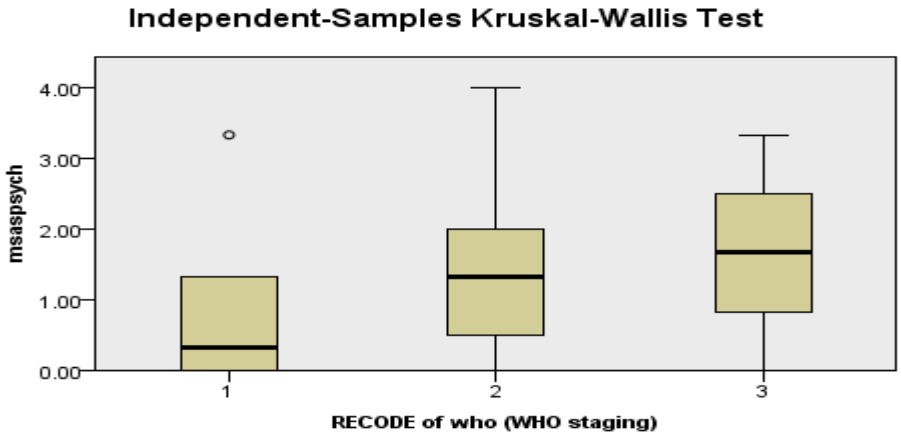
<u>Figure 6</u>: This is the boxplot distribution of MSAS-PHYS scores according to WHO groups:



Total N	385
Test Statistic	8.154
Degrees of Freedom	2
Asymptotic Sig. (2-sided test)	.017

1. The test statistic is adjusted for ties.

<u>Figure 7</u>: This is the boxplot distribution of MSAS-PSYCH scores according to WHO groups:



Total N	385
Test Statistic	38.078
Degrees of Freedom	2
Asymptotic Sig. (2-sided test)	.000

1. The test statistic is adjusted for ties.

The effect sizes for the relationships between WHO groups and the MSAS-SF subscales were tested using SPSS. The effect size for the relationship between the WHO stage and MSAS-GDI was measured by an *eta* value of 0.258. The effect size for the relationship between WHO stage and MSAS-PHYS was measured by an *eta* value of 0.102. The effect size for the relationship between WHO stage and MSAS-PSYCH was measured by an *eta* value of 0.269.

Karnofsky Performance Status (KPS) versus MSAS-SF Subscales

The KPS groups for statistical analysis and comparisons are: KPS 40-80%; KPS 90% and KPS 100%. The Kruskal-Wallis equality-of-populations rank test was applied due to the unequal variance.

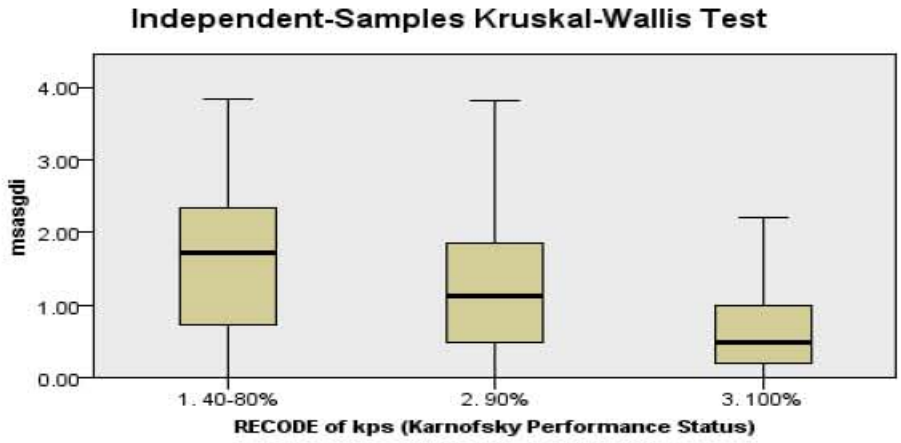
For MSAS-GDI, the differences by KPS groups were significant, especially for the comparison between the groups with KPS 100% and those with KPS < 100%. Kruskal-Wallis equality-of-populations rank test reported a chi-squared value of 26.602 with 2 d.f. and a probability of 0.0001. The difference between the groups KPS 40-80% and KPS 90% was only just significant (p=0.042). The difference between the groups KPS 40-80% and KPS 100% was significant with p<0.001, as for the difference between the groups KPS 90% and KPS 100%.

For MSAS-PHYS, the differences by KPS groups were significant for all the group comparisons, and especially for the comparison between the groups with KPS 100% and those with KPS <100%. Kruskal-Wallis equality-of-populations rank test reported a chi-squared value of 27.343 with 2 d.f. with probability of 0.001. The difference between groups KPS 40-80% and KPS 90% was significant with p=0.19. The difference between groups KPS 40-90% and KPS 100% was also significant with p<0.001. The difference between groups KPS 90% and KPS 100% was significant with p=0.001.

A comparison of the KPS scores to the MSAS-PSYCH subscale seemed to suggest that the relationship between those with KPS 40-80% compared to those with KPS 100% (p<0.001), and KPS 90% compared to KPS 100% (p=0.001) were significant, but they need to be reported with caution. There was no significant relationship between the group with KPS 40-80% and the group with KPS 90% (p=0.220). The Kruskal-Wallis equality of populations rank test reported a chi-squared of 21.816 with 2 d.f. and probability of 0.0001, showing that the distribution of MSAS-PSYCH was not the same across the groupings of KPS.

See Figures 8, 9 and 10 for the boxplots of each of these three relationships.

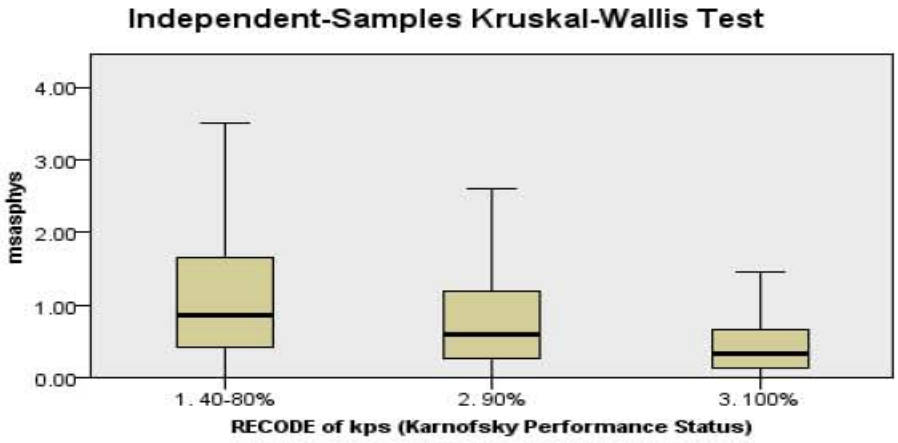
<u>Figure 8</u>: This is the boxplot distribution of the MSAS-GDI scores according to KPS groups:



Total N	381
Test Statistic	26.609
Degrees of Freedom	2
Asymptotic Sig. (2-sided test)	.000

1. The test statistic is adjusted for ties.

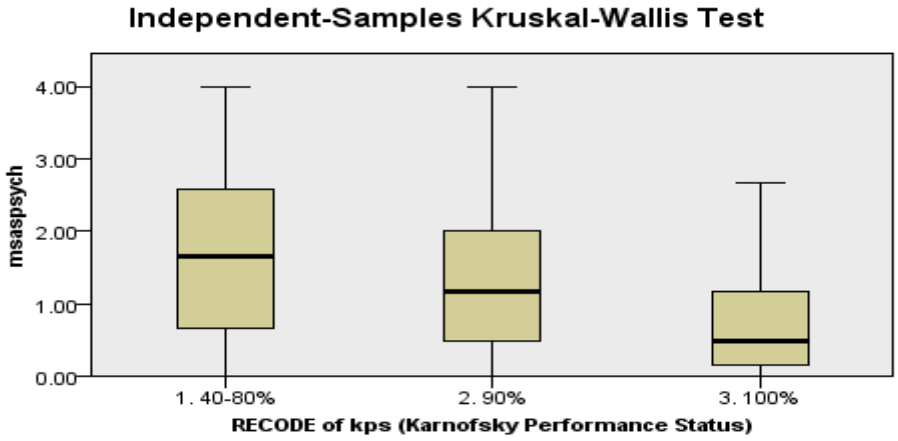
<u>Figure 9</u>: This is the boxplot distribution of MSAS-PHYS scores according to KPS groups:



Total N	381
Test Statistic	27.407
Degrees of Freedom	2
Asymptotic Sig. (2-sided test)	.000

1. The test statistic is adjusted for ties.

<u>Figure 10</u>: This is the boxplot distribution of MSAS-PSYCH scores according to KPS groups:



Total N	381
Test Statistic	21.920
Degrees of Freedom	2
Asymptotic Sig. (2-sided test)	.000

1. The test statistic is adjusted for ties.

The effect sizes for the relationships between the KPS groups and the MSAS-SF subscales were tested in SPSS. The effect size for the relationship between the KPS groups according to MSAS-GDI was measured by an *eta* value of 0.259. The effect size for the relationship between the KPS groups according to MSAS-PHYS was measured by an *eta* value of 0.255. The effect size for the relationship between the KPS groups according to MSAS-PSYCH was measured by an *eta* value of 0.228.

Age versus MSAS-SF Subscales

Although the Spearman correlation found a very small but significant correlation between MSAS-PHYS and age, when comparing the age categories with MSAS-PSYCH, -PHYS, -GDI subscales, according to the Kruskal-Wallis equality-of-populations rank test for each subscale, there was no significant difference for any of the subscales by age group

Gender versus MSAS-SF Subscales

The comparison of gender groups versus the MSAS-SF subscales did reveal differences.

For **MSAS-GDI**, according to the two-tailed result on the Two-sample t test with equal variances, the p value is 0.0207, which shows significance. The mean MSAS-GDI for females is 1.259231, while the mean MSAS-GDI for males is 1.013763.

For **MSAS-PHYS**, according to the two-tailed result on the Two-sample t test with equal variances, the p value is 0.0424, which is just significant. The mean MSAS-PHYS for females is 0.8484433, while the mean MSAS-PHYS for males is 0.6767025.

For **MSAS-PSYCH**, according to the two-tailed result on the Two-sample t test with equal variances, the p value is 0.0400, which is just significant. The mean MSAS-PSYCH for females is 1.336187, while the mean MSAS-PSYCH for males is 1.077061.

The effect sizes for the relationships between gender and the MSAS-SF subscales were tested using SPSS. The effect size for the relationship between gender and MSAS-GDI had an *eta* value of 0.118. The effect size for the relationship between gender and MSAS-PHYS had an *eta* value of 0.104. The effect size for the relationship between gender and MSAS-PSYCH had an *eta* value of 0.105.

Pain versus MSAS-PSYCH

The presence of pain (as reported yes or no on the MSAS-SF questionnaire) was compared to the psychological distress rated by the MSAS-PSYCH. The findings show that patients who report the presence of pain, regardless of distress rating, had greater MSAS-PSYCH scores. The variances were not equal between the two groups, and so the Two Sample T test for unequal variances was used and suggested that the difference in mean scores on the MSAS-PSYCH is statistically significant on the one tailed test with t = -5.4228 and Pr(T < t) = 0.0000. The group with no pain had a lower mean MSAS-PSYCH score (0.9849291) than that for the group with pain (1.549069). This was confirmed by the Two-sample Wilcoxon rank-sum (Mann-Whitney) test with a probability of 0.0000. The effect size for the relationship between pain and the MSAS-PSYCH subscale was tested in SPSS, finding an *eta* of 0.266.

Previous Change in HAART versus Symptom Prevalence and MSAS-PHYS

When comparing any previous change in HAART regimen (either a change or no change) to symptom prevalence, there was no significant difference found in symptom prevalence between the two groups. The group who had had HAART changed did have a slightly higher mean number of symptoms (10.60694) than the group who had not had a change in HAART (9.757282) but this was not significant. When comparing any previous change in HAART regimen to MSAS-PHYS, the group that had changed HAART had a slightly higher MSAS-PHYS distress score (0.8535646), than those who had not changed HAART (0.7450427), but this was not a significant difference.

Months on HAART versus Symptom Prevalence

The number of months on HAART was compared to the sum of all the symptoms (symptom sum). The correlation coefficient between the two variables is -0.0061 which suggests that there was no correlation between the length of time on HAART and the symptom sum.

Past or Present Tuberculosis versus Symptom Prevalence

A past history of tuberculosis (TB) or present TB was related to symptom prevalence, showing that compared to those who had never had TB, those who had had a diagnosis of TB had a greater mean number of symptoms (11.225 symptoms) than those who had never had TB (9.922 symptoms). Two-sample t test with equal variances suggested significance with a probability of 0.0295, but this was not confirmed by the Two-sample Wilcoxon rank-sum (Mann-Whitney) test, although it approached significance with a probability of 0.0561.

The effect size for the relationship between past or present TB and symptom prevalence was measured, producing an *eta* value of 0.96.

Regression Analysis

Multiple regression analyses were performed in STATA, with each of the four MSAS-SF subscales as the dependent (or response) variables. The list of predictors (independent variables) in the models were as follows:

WHO stage, with WHO stage1 as the reference category

KPS, with KPS group3 (=KPS 100%) as the reference category

Gender, with female gender as the reference category

Past or present Tuberculosis, with this diagnosis absent as the reference category

Change in HAART, with no change as the reference category

Latest CD4 count

Initial CD4 count

Latest viral load

The models excluded 6 patients as there were 6 patients who were not taking HAART at the time of the study, but this was not deemed a large number and so would not affect the result or applicability of the model.

For **MSAS-GDI**, the F value is 5.02 with a probability of 0.0000. The R-squared value is 0.1318 with an Adjusted R-squared value of 0.1055, indicating that this model explains 10.55% of MSAS-GDI. The significant contributors were KPS 40-80%, KPS 90%, WHO stages 2, 3 and 4, and female gender. KPS 40-80% had the largest Beta value, indicating that this group gave the largest contribution to the model.

Table 8: Regression analysis statistics for MSAS-GDI

MSAS-GDI	Coef.	Std. Err.	t	P>|t|	Beta
Gender_2	-.3107558	.1147813	-2.71	0.007	-.147456
TB	-.0496682	.1137387	-0.44	0.663	-.0234668
WHO2_2	.4188622	.1137882	3.68	0.000	.2178426
WHO2_3	.4843509	.2014533	2.40	0.017	.1482123
KPS2_1	.8326838	.191629	4.35	0.000	.3081274
KPS2_2	.4131511	.1356941	3.04	0.003	.2044811
Changed HAART	.1292097	.0959767	1.35	0.179	.0720752
Latest CD4	-.0001834	.0002312	-0.79	0.428	-.0447956
Initial CD4	-.0000984	.0004511	-0.22	0.827	-.0113267
Latest viral Load	-.1417831	.116466	-1.22	0.224	-.0654773
Constitutional	.6274269	.1888556	3.32	0.001	

For **MSAS-PHYS**, the F value is 3.58, with a probability of 0.0002. The R-squared value is 0.0976, with an Adjusted R-squared value of 0.0704 indicating that this model explains 7.04% of MSAS-PHYS. The significant contributors were KPS score 40-80% , KPS 90%, female gender and latest CD4 count, with KPS 40-80% obtaining the largest Beta value and so showing that this group gave the largest contribution to the model.

Table 9: Regression analysis statistics for MSAS-PHYS

MSAS-PHYS	Coef.	Std. Err.	t	P>|t|	Beta
Gender_2	-.2564952	.0927321	-2.77	0.006	-.1535795
TB	-.0372929	.0918897	-0.41	0.685	-.0222338
WHO2_2	.0736877	.0919297	0.80	0.423	.048359
WHO2_3	-.0514441	.1627546	-0.32	0.752	-.0198642
KPS2_1	.7078632	.1548175	4.57	0.000	.3305296
KPS2_2	.3259508	.1096276	2.97	0.003	.2035669
Changed HAART	.1329433	.0775398	1.71	0.087	.0935768
Latest CD4	-.0003871	.0001868	-2.07	0.039	-.1193471
Initial CD4	.0001268	.0003645	0.35	0.728	.0184133
Latest viral Load	-.0620163	.0940932	-0.66	0.510	-.0361396
Constitutional	.5866991	.1525768	3.85	0.000	

For **MSAS-PSYCH**, the F value is 4.69, with a probability of 0.0000. The R-squared value is 0.1242, with an Adjusted R-squared value of 0.0977 indicating that this model explains 9.77% of MSAS-PSYCH. The significant contributors were KPS 40-80%, KPS 90%, WHO stage 2, 3 and 4, and female gender. Again KPS 40-80% had the largest Beta value, indicating this group was the largest contributor to the model.

Table 10: Regression analysis statistics for MSAS-PSYCH

MSAS-PSYCH	Coef.	Std. Err.	t	P>|t|	Beta
Gender_2	-.2748675	.1375191	-2.00	0.046	-.1093356
TB	-.1005091	.1362699	-0.74	0.461	-.0398085
WHO2_2	.5208049	.1363292	3.82	0.000	.2270606
WHO2_3	.6887124	.2413605	2.85	0.005	.1766677
KPS2_1	.9075492	.2295901	3.95	0.000	.281524
KPS2_2	.4713213	.1625746	2.90	0.004	.1955494
Changed HAART	.1577696	.1149894	1.37	0.171	.073775
Latest CD4	.0000258	.0002771	0.09	0.926	.0052833
Initial CD4	-.0001058	.0005405	-0.20	0.845	-.0102076
Latest viral load	-.1870735	.1395375	-1.34	0.181	-.0724226
Constitutional	.4962892	.2262672	2.19	0.029	

For **TMSAS**, the F value is 5.65, with a probability of 0.0000. The R-squared value is 0.1459, with an Adjusted R-squared value of 0.1201, indicating that this model explains 12.01% of TMSAS. The significant contributors were KPS 40-80%, KPS 90%, WHO stages 2, 3&4, female gender and a change in HAART. The contributor with the largest Beta value was KPS 40-80%, indicating that this group conferred the largest contribution to the model.

Table 11: Regression anaylsis statistics for TMSAS

TMSAS	Coef.	Std. Err.	t	P>|t|	Beta
Gender_2	-.1846685	.0797602	-2.32	0.021	-.1250726
TB	-.0082346	.0790356	-0.10	0.917	-.0055532
WHO2_2	.2444412	.07907	3.09	0.002	.1814563
WHO2_3	.2967827	.1399875	2.12	0.035	.129625
KPS2_1	.693013	.1331607	5.20	0.000	.3660308
KPS2_2	.3428021	.0942922	3.64	0.000	.2421664
Changed HAART	.1422743	.0666931	2.13	0.034	.1132774
Latest CD4	-.0001713	.0001607	-1.07	0.287	-.059753
Initial CD4	.0000307	.0003135	0.10	0.922	.0050484
Latest viral load	-.0796979	.0809308	-0.98	0.325	-.0525339
Constitutional	.4303062	.1312335	3.28	0.001	

The diagnostics were checked and no serious violation of the assumptions was found. The heteroskedacity and multicollinearity were acceptable, as was the scatter plot of residuals. The model specification values suggest that the model is acceptable.

Chapter 6

Discussion

This cross-sectional survey was conducted in order to evaluate the prevalence and burden of pain and other symptoms amongst the HIV clinic attendees of the three HIV treatment clinics in Johannesburg, Gauteng, which formed the population group of the study. The prevalence and symptom burden was then related to the various demographic and clinical factors to be able to determine relevant and significant relationships which could inform clinical work in the field of HIV Medicine and Palliative Medicine in South Africa. International research has shown that palliative care should be integrated into routine HIV care, as symptoms have been found to be under-reported and under-treated in outpatient HIV treatment clinics(10,24,49,50,60,62).

Demographics

The demographics of age, gender and ethnicity among the participants of this study are consistent with the 2008 National HIV Prevalence, Incidence, Behaviour and Communication Survey(3), and with the 2009 National Antenatal Sentinel HIV and Syphilis Prevalence Survey(2). Three other Southern African HIV symptom prevalence studies have found similar percentages of females and males(19,20,22). The difference in symptom prevalence and burden between males and females has been found previously in the literature. Vogl et al found that for certain symptoms (eight in total), men reported higher distress while for other symptoms (two), women reported higher distress, but overall they found that men and women had a similar symptom prevalence(10). A study in San Francisco found that women were significantly more likely than men to have more symptoms and greater symptom burden(25). In South Africa, in a hospice population, it was found that women reported more anxiety than men(19). A study on pain in AIDS patients in New York found that women more often had headaches and radiculopathy than men(12). However, Southern African studies have found no significant differences between men and women for symptom prevalence(20) or intensity(22). Health seeking behaviour in men and women may be different, and therefore reporting of symptom presence and its burden may also be

different between the genders and this may very well be skewing the data findings. It is not possible to ascribe a causal relationship to the differences found in this study and in other studies, but the differences may be clinically important. This may be particularly so, in relation to the poor family, social and economic contexts in which many HIV infected women in South Africa find themselves. These findings may however, not be of clinical assistance, as both men and women do have symptoms and do experience suffering as a result of their symptoms. Health care workers should not exclude men from screening for symptoms as a result of the findings of this study. This area requires further research to clarify the findings of various studies that show differences in symptom prevalence and burden between males and females, and also to search for the reasons for these differences, if they are confirmed to be significant differences.

This study found no significant difference for any of the MSAS-SF subscales of symptom distress by age group. The age grouping for statistical purposes may have had a role to play in the fact that no differences were found. The important finding here is that adult patients of all ages appear to experience symptoms and burden from symptoms.

The number of participants choosing to conduct their interview in English may represent literacy and educational level, with a comfortable level of English comprehension. The choice of conducting the interview in English was entirely the patient's own decision as the questionnaire was available in isiZulu and Sesotho. The choice to conduct the interview in English may have been because the participants had a first language other than isiZulu and Sesotho and were more comfortable in English than either of these two languages. Another reason may be that health care workers in South Africa predominantly do communicate in English and so the participants may have felt more used to this language for discussing medical matters. Whatever the primary language used the research nurses were able to speak with the participants in English, isiZulu and Sesotho, so the meaning of questions would have been clarified if there was uncertainty.

Symptom Prevalence and Symptom Burden

The high prevalence of symptoms and the high symptom burden experienced by the participants of this study indicate a high degree of unmet symptom control and underline the palliative care needs amongst the patients of the three HIV treatment clinics which were surveyed. These findings suggests that either patients under-report their symptoms to their doctors, or that their doctors do not ask their patients about symptoms and therefore are unaware of the symptoms needs, or that the doctors are unaware of treatment and management options for these symptoms and palliative care needs. All of these possibilities may be present and are reported in international literature as barriers to meeting patients' needs with regard to symptom control(10,18,23,24). These findings raise the questions of whether patients are empowered to report symptoms, or whether doctors are ignoring symptoms and the distress associated with these symptoms? The mean number of symptoms experienced by this cohort of patients is similar to the mean number of MSAS-SF symptoms experienced by the men in the UK-based online survey, of whom over half were on HAART(24), while it is lower than the mean symptom number of other international studies which have used the same symptom assessment tool(10,17,23). A study of the symptoms experienced by advanced AIDS patients in Soweto, South Africa, found a lower mean number of symptoms(19), however the assessment tool in the Soweto study had fewer symptoms than the MSAS-SF, indicating that unless the clinician specifically asks about specific symptoms, the presence of symptoms may be under-estimated and under-assessed and the patient will be under-treated. Clinicians need to actively seek symptoms rather than rely on symptoms being reported by patients. The findings points to a high symptom prevalence amongst this study population, regardless of disease stage or the use HAART. A study assessing symptom prevalence and burden amongst cancer patients who were already receiving palliative care in South Africa and Uganda, found more symptoms among the advanced cancer patients than among the participants of the current study(71). There are however, common symptoms described in both studies, showing that the symptoms of patients with HIV who receive outpatient HIV care are comparable to the symptoms of patients with incurable cancer who are receiving palliative care. The question must be asked – why do the patients with advanced cancer receive palliation for their symptoms, while patients with HIV do not receive palliation for the same symptoms? Is this because palliative care developed out of cancer care and the medical fraternity has not yet

recognised the applicability of palliative care to other disease entities? Clinicians may also be unaware of the applicability of palliative care "*early in the course of*" chronic disease(6), including for patients with HIV who attend outpatient HIV treatment clinics.

Six symptoms had more than 50% prevalence in this study. They are: feeling sad, feeling irritable, numbness/tingling in hands & feet, worrying, problems with sexual interest or activity and pain. The next most common symptoms are "I don't look like myself", feeling nervous and lack of energy. In their online survey in the UK, Harding et al found a very similar profile of top symptoms, with the only marked difference between these samples, being that their participants had a greater frequency of difficulty sleeping, difficulty concentrating and feeling drowsy(24). The outpatient population study conducted in London had a very similar symptom prevalence profile to the online survey although sadness, worry and irritability seemed to be more prevalent amongst the participants of the online survey(23,24). It is significant that there is a distribution of symptoms across emotional, psychological and physical domains. This highlights the importance of the comprehensive response of palliative care described in the WHO definition of palliative care as *"assessment and treatment of pain and other distressing problems, physical, psychosocial and spiritual*"(6). The participants of the study conducted in the outpatient HIV treatment clinics in the academic hospitals associated with the University of the Witwatersrand, more frequently complained of numbness or tingling in their hands or feet and more often felt "I don't look like myself" than the online survey in the UK(24). Pain is a common symptom for this study and for other studies(10,17,19,23,24,40). These and other symptoms all require adequate acknowledgement and assessment from the treating doctors, and then they require appropriate, acceptable and effective treatment. Without such support and treatment, patients will continue to suffer from these symptoms. Symptoms such as nociceptive pain, neuropathic pain, sadness and worry can escalate if untreated, leading to far greater morbidity for the patient, and a far more difficult clinical situation to manage.

All four psychological symptoms (feeling sad, feeling irritable, worrying and feeling nervous) are in the top ten most prevalent symptoms in this study, with feeling sad being the most prevalent symptom overall. The study in New York had very similar findings with regards these psychological symptoms(10), as did the studies in the UK(23,24). The study in Uganda amongst newly diagnosed patients found that worrying was the 9th most prevalent

symptom and feeling sad was the 11th most prevalent symptom(17). For the participants in the study in Soweto, a low mood was the fourth most common symptom, with 69.9% of participants experiencing low mood(19). Makoae et al found in their study in sub-Saharan Africa that "fear and worries" as a symptom was in the top five symptoms in their study(20). These studies all highlight the high prevalence of psychological symptoms amongst patients with HIV which this study confirms. It appears that these symptoms are under-recognised by health care workers in HIV treatment clinics and that there is inadequate holistice assessment for psychological symptoms, leading to poor psychological support and under-treatment of psychiatric conditions and an ongoing cycle of psychological suffering.

The high prevalence and high rating of high frequency for the psychological symptoms is one of the most notable findings on first looking at the prevalence and burden data. The most prevalent symptom was feeling sad, with a high frequency. Many other studies of HIV positive patients, some of which were mentioned above, have also reported a high psychological symptom prevalence and symptom burden(10,20,22-25,37). Lampe reported from a study in London, that nearly half of their cohort of patients reported either anxiety or depression, with these patients having a significantly greater risk for rebound of the viral load, than those patients without anxiety or depression and that this risk was not adequately explained by poor adherence to HAART(72). Can sadness be extrapolated to depression, and if so, should we be screening our patients for depression more routinely? Perhaps sadness, in conjunction with other symptoms such as worry, irritability, and even physical symptoms in otherwise HAART-responsive patients, can be linked to depression which should be treated? There is of course the ever-present difficulty in using physical symptoms as markers for depression in patients with a general medical condition such as HIV. How relevant is this for a clinically, virologically and immunologically controlled patient on HAART? Rodkjaer et al remind us that patient self report of symptoms of depression is not adequate to diagnose a Major Depressive Disorder (MDD) and that a psychiatric consultation is the optimal manner in which to diagnose MDD(38). However, their study also found that depression was underdiagnosed in their setting in Denmark with 38% of participant experiencing symptoms of depression and 26% being diagnosed with MDD(38). They also found that patients who had MDD (but had not been diagnosed or treated for this) had a significantly increased rate of poor adherence to HAART(38). Lampe et al write

that their study points to a link between depressive and physical symptoms and potential virological failure in the future, for patients who are currently virally-suppressed on HAART(37). A study conducted by Sherr et al among an outpatient sample of patients in the UK found a concerning prevalence of suicidal ideation(73). Suicidal ideation was found to be more frequent among patients with higher physical symptom distress and higher psychological symptom distress(73), showing more evidence for the need for the management of all symptoms and how this is highly important for the mental health of patients. Suicidal ideation is understood to be a very important medical issue to manage timeously, effectively and to follow up adequately. These studies show that it is vitally important to screen patients for any psychological symptoms, for depression and for suicidality, so as to manage these symptoms effectively and assist in the overall holistic HIV management for patients, particularly to prevent poor adherence or non-adherence to HAART and even virological rebound despite adherence. The findings of these other studies add to the evidence found in this study that points to a real need for health care workers, and doctors specifically, to recognise that psychological symptoms are common and that psychological support and or medical treatment is often needed but not often openly requested by patients.

The prevalence and distress associated with these four high prevalence psychological symptoms shows that even patients on HAART have significant psychological symptom burden and that, regardless of whether the patients can be classified as clinically depressed and in need of anti-depressant medication, they do need significant and ongoing psychological support. This is particularly important for patients on HAART as this could potentially relate to adherence to HAART, a fact that is considered when initiating patients on HAART. All four psychological symptoms can impact on daily functioning. They can also all impact on the sense of hope, or lack thereof. Hopelessness was not assessed in this study, but Vogl et al found that the degree of hopelessness was an independent contributor to the overall distress caused by symptoms, as measured by the MSAS-Global Distress Index(10).

Numbness or tingling of hands and feet is the classical symptom for neuropathic pain due to peripheral neuropathy. In this study, this symptom was highly prevalent and highly burdensome if present. Compared to other studies of symptom prevalence, this is a high

prevalence of neuropathic pain(12-14,17,20,22,24,25,33,48). Vogl et al found a similar prevalence of neuropathic pain to this study, but with a somewhat lower rate of high distress(10). HIV itself is known to cause peripheral neuropathies, as do many of the drugs used to treat HAART. Stavudine is the most likely drug of the commonly used ARVs to cause peripheral neuropathy and neuropathic pain(74) which was the second most frequent symptom to be perceived as due to HAART by the participants and also the second most common reason for a change in HAART. Lamivudine and didanosine are the other drugs most likely to cause peripheral neuropathy(74).

Many patients subjectively felt that their peripheral neuropathy was due to their HAART which may be correct as it is a known side-effect of certain antiretrovirals. As this is a subjective view, the objectivity of this view may be questioned but it is interesting to note that there may possibly be a great deal of negative emotion towards HAART which may be seen as causing problems. This could relate to inadequate initial and ongoing education around HIV, AIDS and HAART. Very importantly it could also point towards inadequate support and management of symptoms, once HAART is started and patients are more clinically stable. These issues could all result in poor treatment adherence. Causality can not be established on the basis of this subjective question and the specific answers which participants gave, but it is an important principle of communication that the health care worker should listen to their patient and specifically address the concerns the patient may have and also the symptoms they are experiencing. Shared decision making is the most favourable method of conducting the decision making process in a consultation, as it enables the patient to voice their opinions, feelings and beliefs; and for these to be heard and acknowledged and appropriately addressed by their health care worker(75). This leads to the patient understanding more about their medical management and so feeling more satisfied with their medical care(75) and therefore supporting adherence on the part of the patient.

The lack of symptom control for the neuropathic pain experienced by the participants in this study suggests that there is under-treatment of neuropathic pain in these treatment clinics. This is surprising, given the recognition that neuropathic pain is a complication of HIV disease and a side effect of some ARVs. It suggests that patients are not adequately assessed for neuropathic pain, or that physicians are not adequately conversant with the

accepted treatments for neuropathic pain which also require regular review of the adequacy of the pain management. The findings point to the need for HIV clinicians to have more training in the assessment and management of neuropathic pain.

Harding et al found that in their sample of online patients in the UK, patients who were on HAART had a significantly greater prevalence of numbness or tingling than those who were not on HAART(24). A reason that the prevalence of neuropathic type pain is so high amongst the participants of this study of the three outpatient HIV treatment clinics, could be that vast majority of the sample were on HAART and just less than half had changed HAART regimens at least once. The drugs that participants were taking reflect the guidelines for HAART treatment in the South African public health sector(4,5). Some authors have discussed that once patients have changed HAART regimes, there appears to be a higher prevalence of overall symptoms, including of neuropathic type pain(11,24). Neuropathic pain is a frequent reason for the change of a HAART regime so it is of concern that patients who have already changed HAART, may continue to experience neuropathic pain despite the change in HAART. Clinicians working at HIV treatment clinics need to be aware of this so that the necessary vigilance for the symptom can be employed, to ensure that patients do not go un-treated or under-treated.

The prevalence of nociceptive pain in these study participants was also high, with a symptom burden showing a large proportion of participants experiencing high distress from their pain. One London-based outpatient study found a very similar prevalence for pain(23). Pain amongst patients with HIV has been widely studied and described. There are many possible pain syndromes that can be encountered among patients who are HIV positive(12). In our study, no distinction was made on sites or type of pain, as the main aim was to first assess prevalence and overall burden of pain in general in this population. In a study of AIDS outpatients in New York City before 1996, using the MSAS-SF together with other tools, the prevalence of pain was even higher(10). Wakeham et al found the prevalence of pain amongst newly diagnosed HIV positive patients to be similar to the study in New York(17). Both these studies had different study populations to our study but both used the MSAS-SF. In a study of patients with very advanced AIDS at a hospice in Johannesburg, the majority of patients experienced pain(19). This population is also different to our study as all patients were admitted to a hospice and had advanced HIV disease and only very few of

all those patients had had access to HAART. In the current study of the patients attending three HIV treatment clinics in Johannesburg, the majority of study participants were on HAART as an outpatient at the time of study. It may therefore appear that HAART can facilitate a reduction in the development of pain as a part of the prevention of progression of disease. However, no comparisons can be drawn between the studies. This needs to be studied formally in a longitudinal manner because an online cross-sectional survey conducted in the United Kingdom, amongst HIV positive gay men, found the opposite to be the case – namely that the prevalence of pain amongst those patients on HAART was very similar to the prevalence of pain in this current study, but the prevalence of pain in those not currently on HAART was lower, suggesting that HAART may be responsible for an increasing pain prevalence(24). Norval et al in the Pain Management chapter, of A Clinical Guide to Supportive and Palliative Care for HIV/AIDS in Sub-Saharan Africa, summarize some of the findings from previous studies, pointing out that the pain experienced is diverse and can commonly be linked to marked psychological symptomotology, as well as functional changes(76). The findings from this study show that patients who reported the presence of pain, regardless of the pain distress rating, had statistically significant greater psychological distress (as per the MSAS-PSYCH scores). It is interesting to note that the top 6 most prevalent symptoms found in this study include pain, numbness or tingling in hands and feet, feeling sad, feeling irritable and worrying. These symptoms also have all been shown to have high distress or high frequency in this study, so the overlap is possibly more than co-incidental. This warrants further future study in this particular context as previous international studies have shown a relationship between the presence of pain and depressive symptoms(44,77). The symptom that occurs first is uncertain, but it seems likely that uncontrolled pain can result in psychological distress, including symptoms of depression. The IASP definition of pain makes it clear that pain is a symptom that involves the physical as well as the psychological in its expression and experience(41), so it is also possible, that patients who have symptoms of depression are likely to experience any pain they may have, as more severe than patients who do not have symptoms of depression. These findings again point to the need for the "*impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*" according to the WHO definition of palliative care(6). Dame Cecily Saunders introduced the concept of total pain to the understanding of the pain experience(76). Through this concept of total pain, she

described the all-encompassing nature of the pain experience – pain is experienced in the physical, emotional, social and spiritual spheres and pain is influenced by all four of these areas(76). Therefore, it is not unexpected to find that in this patient group, patients who experienced pain also had higher rates of psychological distress. Palliative care advocates that for this kind of pain to be effectively managed, the physical component of the pain should be adequately managed and that following this, the psychological sources and aggravators of pain should all be addressed(76), and management should be provided in a holistic and individualised manner. Total pain also requires that social and spiritual sources and aggravators of pain be sought, assessed and managed appropriately, to complete the holistic management of the patient's pain experience. This management of total pain requires knowledge of the physical pain assessment, as well as an adequate knowledge regarding the prescribing of analgesic drugs and how to titrate these drugs effectively, according to pain levels.

These study findings suggest that pain is generally poorly assessed and also poorly managed amongst these patients receiving outpatient HIV management. The prevalence of pain of high distress suggests that clinicians are not aware of the possibility that their patients may be suffering from pain, or if they are, that they do not have the skills and training required to assess and to treat pain adequately. This suggests the need for training of HIV clinicians in pain management and in palliative care so that their patients can benefit from adequate and durable pain control.

The symptom "I don't look like myself" was also prevalent and interestingly it was the most highly distressing symptom overall, if it was present. The study did not ask for any further detail from participants, regarding what they meant by this phrase. Therefore the meaning of this symptom for the participants can only theoretically explored. It could be extrapolated that for some patients this could involve lipodystophy or fat redistribution changes, which was commonly named by patients as a symptom that they felt was due to HAART. Stavudine, Zidovudine and Lopinavir-Ritonavir (as well as other protease inhibitors) cause lipodystrophy (fat redistribution from face, buttocks, legs and arms to the back of the neck, abdomen and breasts)(74) which was the most common 'symptom' due to HAART of which the participants complained and also the most common reason for a change in HAART. Skin changes and itching were fairly prevalent and both had high distress ratings.

Skin changes are often seen in HIV positive patients, and can be the first signs of disease. They may be held as very significant by patients in the way their bodies change due to the disease. Rashes causing skin changes occur with efavirenz, atazanavir and particularly with nevirapine(74). Skin changes were the fourth most common symptom attributed to HAART by the participants, and can clearly also be a drug side effect. However, more patients identified the symptom of "I don't look like myself" than those who identified skin changes, and so it appears that skin changes are not the only means by which patients judge their change in appearance. Swelling of arms and legs was not markedly prevalent, but if it was present, it had a high distress rating, and so appears that it could be a contributing factor to the feeling of "I don't look like myself". Weight loss was a fairly prevalent symptom with a high distress rating, and so is quite likely to have contributed to the feeling that the participant does not look like him or herself. It is interesting to note that patients describe weight loss, despite many of them being on HAART. Hair loss was not a prevalent symptom, but it did have high distress if it was present. All of these symptoms could contribute to the participants feeling that they did not look like themselves. A person's self-image is highly personal and maybe be vulnerable to changes in internal and external factors. Whatever the reason for the patients feeling that they did not look like themselves, the effects of this symptom can be far reaching and very debilitating to the individual. Does this feeling relate to a confusion in the person's identity? Do they act differently as a result of feeling this way? Is this feeling associated with the societal stigma they may experience in relation to the diagnosis of HIV? Does this feeling relate to the overall disease and symptom experience that these patients experience internally on a daily basis? If any of these issues do stem from the symptom "I don't look like myself", it appears likely that this overtly physical symptom does have direct links to psychological symptoms, translating into feelings of "I don't *feel* like myself", opening up many doors of vulnerability and creating reasons for debilitating emotional distress. The inter-relatedness of the physical and the psychological aspects of a person's being are widely acknowledged and accepted by palliative care practitioners(6), and training in assessing and managing problems in both of these areas would benefit HIV clinicians and their patients alike.

"Problems with sexual interest or activity" was a highly prevalent and highly distressing symptom. Only two participants indicated that they thought this symptom was due to

HAART. Two UK-based studies found very similar prevalence of this symptom(23,24), as did the New York study(10), while the while the study in San Francisco found a smaller prevalence(25). This symptom highlights how invasive this disease is into the relational lives of patients. Sexual intercourse is the most frequent transmission route for HIV in South Africa(3). This fact of transmission may be a potential cause for the HIV positive person to suffer psychologically in relation to the area of sexual intercourse, and thus have psychological problems with sexual interest or activity. HIV is associated with other sexually transmitted diseases and so there may also be associated physical factors for the individual that are involved in the symptom of problems with sexual interest or activity. In the Soweto Hospice study, women had more genital sores and more genital pain than men(19). The study in the three HIV outpatient clinics at the academic hospitals attached to the University of the Witwatersrand did not stratify between men and women in this area of problems with sexual interest or activity. If sexual activity is impaired there may be relationship problems and hence more psychological symptom prevalence and distress. Wilson et al reported that women with HIV had less satisfaction with sexual function than those who were not HIV infected, and that symptoms of depression, and CD4 counts under 200 were also related to poorer sexual function(78). Body image has been shown to be altered, as the symptom "I don't look like myself" is highly prevalent and distressing to patients. This could also affect the patients own view of their gender role and so affect intimacy and physical sexual expression. Patients have particular needs in this area of their lives, requiring far more support and even treatment than they do currently receive but what kind of support would be appropriate requires further research.

The constitutional symptoms such as lack of energy, sweats, weight loss and feeling drowsy are all fairly prevalent and have high distress ratings. Albumin has been found to be good indicator of morbidity in advanced disease in general, but not necessarily specifically in HIV disease(79,80). Morbidity relates to the suffering experienced by the patient, and so could include symptoms and the burden of symptoms experienced by patients. Albumin has also been found to be a predictor of mortality, with a low albumin predicting decreased survival/poorer prognosis and increased risk of complications(79,80), which also relates to symptom prevalence and the burden from symptoms. Albumin itself has been found not to be an indicator of nutritional status(79,80), so no conclusions can be drawn with regards the

nutritional status of patients from the albumin results obtained from the participant files. In this study albumin levels did not correlate with symptom prevalence or distress. So the use of albumin as a prognostic indicator for symptoms does not appear to be of any value according to this small sample. The relationship between albumin levels and the symptom profile would have to be formally researched for more generalisable conclusions to be drawn. These findings further add weight to the notion that laboratory values are not indicators of the disease experience of patients with HIV, reminding us that a good history enquiring about symptoms and their burden is of pivotal importance in managing all patients with HIV disease.

Bekker and Adams point out that, although constitutional symptoms "are not usually life threatening in themselves, they may be significant factors eroding a patient's comfort and quality of life"(81). Feeling drowsy and difficulty concentrating had fairly similar rates of prevalence and difficulty in concentrating had only a marginally higher percentage of high distress. These symptoms may well be linked to each other, and to difficulty in sleeping(25). Difficulty in concentrating is included in the MSAS-SF Psychological Symptom subscale so this symptom could also be related to the psychological symptoms, and if depression is present, this may also of course impact on the symptoms of feeling drowsy, lack of energy and lack of appetite. Lee at al emphasise the importance of sleep and its relationship to energy levels and symptoms in general(25). In Palliative Medicine, patients are always seen as a whole – physically, psychologically, socially and spiritually(6). The interplay between these symptoms is therefore highly relevant. Cause and effect can only be speculated upon, as this was not the focus of this particular study, however it seems likely that HIV clinicians would benefit from training in the palliative approach of assessing the patient holistically so as to identify the physical and psychological symptoms as well as the social and spiritual problems that may exist and be impacting on the patient's overall disease experience. This would result in more holistic and comprehensive management plans for patients and as such benefit their overall quality of life.

Constitutional symptoms may be related to HAART side-effects, such as hyperlactaemia which is known to be caused by abacavir, didanosine, lamivudine, stavudine, zidovudine, tenofovir(74). Metabolic changes, such as hypercholesterolaemia, hypertriglyceridaemia and insulin resistance can occur with the protease inhibitor class in general(74). The HAART

drugs used can cause some of the symptoms found to be a problem for participants, but HAART can not account for all the symptoms, and even if it could, there would still be every reason to treat the symptoms symptomatically for patient relief from suffering and for their quality of life. Clinicians should be aware of the effects of the drugs they are prescribing, so as to adequately manage these side effects, including the palliation of those symptoms that are not easily avoidable.

It is known that TB is a significant and frequent opportunistic infection amongst HIV infected people in South Africa. It was of interest to assess whether TB has any influence on symptom prevalence or burden, however not enough information was gathered regarding the timing and nature of the TB diagnosis to be able to make adequate associations, and the only information we had available to use did not show any association of the influence of TB on the illness experience. Active TB infection does produce significant symptoms, and these should be treated by first treating the cause, with the appropriate antibiotic regimen for TB, while simultaneously actively managing the unpleasant associated symptoms that the patient may experience, such as coughing, fevers, chest pain and dyspnoea(82). It is not sufficient to just treat the cause and hope that the symptoms disappear fast enough to improve the patient's problems. Active palliation of the symptoms caused by active TB should be a part of the management plan of the patient.

The gastro-intestinal symptoms of feeling bloated and constipation were more prevalent than diarrhoea. The two studies based on patients in the UK found more diarrhoea than constipation and diarrhoea had a reasonably high prevalence rate in each of those studies(23,24). Historically, and in the pre-HAART patient, diarrhoea was a significant symptom for HIV positive patients, and so it appears that HAART may do more than just protect against diarrhoea but may be related to constipation in some way. However, bloating and constipation are usually multi-factorial and may be more related to diet and lifestyle than to HAART. These symptoms are all readily managed by clinicians trained in symptom control and palliative care, motivating again for the need for HIV clinicians to be trained in palliative care.

These results suggest that symptoms are prevalent and should be extensively and actively sought by the clinician. No patient with HIV can be assumed to be asymptomatic based

purely on the CD4 count, WHO stage, presence of opportunistic infections and whether or not HAART is being taken(14). The very important area of HAART adherence is a focus for HIV outpatient treatment clinics in the management of their patients. The findings of the symptom prevalence and burden of the participants in the three clinics sampled for this study, together with the evidence from the literature that points to the integral link between symptom experience and HAART adherence(31,37,38) and are evidence for the need for the holistic management of patients with HIV in outpatient HIV treatment clinics. This holistic management must include specific palliation of symptoms during each scheduled clinic assessment, requiring HIV clinicians to be adequately trained in palliative care and actively delivering appropriate symptom control. In their review of the state of palliative care in sub-Saharan Africa, Harding and Higginson comment that there is little or no involvement of palliative care directly within and with HAART treatment clinics, and that should this happen, it would offer significant benefit for patients and providers alike, as there is much evidence from the developed world that HAART and palliative care are not and should not be mutually exclusive(83).

MSAS-SF Subscales

The Cronbach's coefficient alpha for MSAS-GDI, MSAS-PHYS, MSAS-PSYCH and for the TMSAS prove the reliability of the subscale scores in this study. The Cronbach's alpha coefficient for the constitutional symptom subscale showed that this is an unreliable subscale. The constitutional symptom subscale is new and was not validated, and as the Cronbach's coefficient alpha shows it is not reliable, no significance that can be attributed to this score, other than to say that it appears to be invalid.

The mean global distress (MSAS-GDI) score is similar to that of the study conducted among HIV positive outpatients in London(23), showing a somewhat lower global distress than in a few of the already mentioned international studies which used the MSAS-SF tool(10,17,24), but it is higher than the MSAS-GDI score in a study done in San Francisco in the USA(25). Never the less, the score indicates a high degree of untreated global distress, which incorporates both physical and psychological symptom distress. This distress rating shows that psychological symptom distress heightens the physical symptom burden that patients

experience, motivating for a greater emphasis on the holistic management of the patient, as indicated by the definition of palliative care(6).

The mean physical distress (MSAS-PHYS) score was again very similar to that found for the study of the outpatient population in London(23). Two of the other studies compared, had higher mean physical symptom distress scores than this(10,17), while two had only slightly lower mean physical distress scores(24,25). Of the two studies with higher scores, one was conducted on a sample of patients at diagnosis, pre-HAART in Uganda(17), and for the other, little information was given on antiretroviral use by the patients, and it was done before protease inhibitors were available(10). This shows that the cohort for this study experienced what is considered in the literature to be high degrees of physical distress. Measureable physical symptoms have been shown to be more commonly recognised by the physician(18), but even so, the findings of this study suggest that physical symptoms are not adequately recognised, assessed, or managed in these HIV treatment clinics, leaving the patient with unmanaged physical suffering.

The mean psychological distress (MSAS-PSYCH) score was again very similar to the score for the study on the outpatient population in London(23), showing that a large amount of psychological distress was experienced by the participants of this study. Like the MSAS-PHYS score, this MSAS-PSYCH score is higher than two other studies(17,25) and lower than the score for the online survey done in the UK(24) and for the study done in New York(10), concluding that the psychological symptom distress is unacceptably high and even higher than the physical symptom distress. Clinicians at the HIV treatment clinics surveyed appear not to be assessing psychological symptoms or if they are assessing them, it appears that they do not have the tools with which to manage psychological symptoms, resulting in the patients experiencing high degrees of distress in this area.

The mean total symptom distress (TMSAS) was not often reported in the literature but for the one study that did report this score it was lower(25) than this current study conducted in the three HIV treatment clinics in Johannesburg, showing that the participants in this study experienced large distress from their total number of symptoms. This again suggests inadequate assessment and management of symptoms at these HIV treatment clinics, resulting in ongoing suffering amongst the patients.

These symptom distress scale correlations with the biological markers of HIV disease, namely CD4 count and viral load, and with the WHO stages of disease and the KPS score, show some trends to guide clinicians. Symptom prevalence and distress was not found to correlate with viral load results, nor with CD count groups. The viral load was not found to be predictive of any of the symptom distress subscales. Similar to the findings of Lee et al(25), this study did show that on multiple regression analysis, the latest CD4 count was predictive of physical symptom distress as rated by the MSAS-PHYS. However there was not a lot of weight assigned to the latest CD4 count as a predictor in this regard. The finding that viral load results are not related to symptom prevalence, is consistent with the findings from at least one other study(24). Lee et al found that global symptom measures were not related to viral load results but that in overall regression analysis, a detectable viral load did contribute to the change in symptom number(25).

WHO staging is the indication of how advanced the HIV disease was at diagnosis and is clinically important for the management of HIV disease, and gives the clinician a quick roadmap of what may have preceded a particular patient's disease pathway. The WHO staging was delineated when CD4 counts were not readily available in resource constrained settings, enabling clinicians to manage their patients in a clinical framework where no laboratory results were available. This current study found that there are significant differences for MSAS-PSYCH and MSAS-GDI and there are also differences for MSAS-PHYS when WHO stage 1 is compared to any other WHO stage. There was no significant difference between WHO stage 2, 3 or 4 for the MSAS-SF subscales. This shows that symptom distress is a greater problem for patients who are staged as WHO stage 2, 3 and 4 as compared to those staged WHO stage 1. However, patients in WHO stage 1 do experience symptom distress. These findings for WHO stage in relation to symptom distress were confirmed in multiple regression analyses. Wakeham et al found that in their sample of newly diagnosed patients in Uganda that the WHO staging was not an indicator of symptom prevalence or burden(17). Two other international studies did find that those patients with AIDS-defining conditions (which is the same as WHO stage 4 disease) did have more symptoms and greater symptom distress than those without AIDS-defining conditions(10,25). As for the findings for viral load levels and CD4 ounts, symptoms are prevalent and burdensome for any WHO staging and show that no patient should be

presumed to be without symptoms based purely on the laboratory markers or WHO stage. This calls for a patient centred, palliative care approach to be employed by all health care workers who are involved in any management of HIV positive patients. Palliative care can be provided by the trained health care worker in the HIV treatment clinic where the patient receives their HIV care thereby reducing the need for the patient to attend another clinic which would only add an extra burden to the patient who already has many problems to face. For palliative care to be effectively provided by HIV treatment clinics, all health care workers, but particularly the doctors at the clinic, need to have the necessary accredited training to equip them to palliate their patients effectively.

This study has also found that symptom distress is correlated with functional status as measured by KPS. All symptom distress measures (global, physical and psychological symptom distress) were significantly higher for patients with KPS scores below 100%. The majority of participants had a KPS score of 90% which is a relatively high functional status and means that these participants were able to carry out normal activity but according to the findings of this study, these patients had significantly greater symptom distress than patients with a normal KPS of 100%. Multiple regression analyses showed that the KPS score and particularly KPS 40-80% was predictive of physical, psychological and global symptom distress. Vogl et al also found a relatively high functional status for their sample of patients, with 80% of their sample functioning at KPS 70% or above(10), while Del Borgo et al found a mean KPS of 70% in their sample(46). In validating the MSAS-SF, Chang et al found that KPS functional levels correlated well with changes in the MSAS-SF subscales for cancer patients and said that: “The KPS is valuable for prognosis, but does not indicate what steps the practitioner can take to help patients with poor performance status”(64). They suggested therefore that symptom assessment tools are clinically useful together with the KPS, so as to assist the clinician in how to symptomatically manage and assist a patient with a poor functional status(64). The findings of this study re-affirm the link between a poor functional status and symptoms and the need for symptomatic intervention. However, what is also clear is that patients at all levels of functionality have symptoms and also that function may be affected to a relatively small degree (for example, with a KPS of 90%) with a significant increase in symptom distress. This calls for the clinician to have a low threshold of suspicion for the presence of symptoms, both physical and psychological, amongst all

patients, regardless of how well they may appear to be functioning. A high KPS does not rule out the possibility of the presence of symptoms for the patient, and as Chang et al point out(64), the information from symptom assessment tools is of more practical value for the palliation of the patient's symptoms that the functional status itself.

The initial CD4 count was obtained for the majority of participants. The mean CD4 count before starting HAART reflects the South African national guidelines prior to 2010, for HAART to be started once a CD4 count went below 200 cells/mm³(5). However, initial CD4 count was well under 200 cells/mm³ reflecting a tendency amongst South Africans to present quite late in the progression of HIV disease. Voluntary counselling and testing (VCT) is available but many patients have found the barriers to the use of VCT sites to large to overcome so that they will just wait until they may get sick before getting tested for HIV(3). This is an important challenge to address now that HAART treatment is recommended once the CD4 count drops below 350 cells/mm³(4).

All patients had a latest CD4 count with a mean CD4 count value that reflects the improved immunological status of the patient on HAART, as the majority of the participants were taking HAART. The relevance of the viral load result or the CD4 count result on the patient experience of their daily life is not as obvious to them as the frequency of their symptoms and the burden their symptoms impose each day. If this is what affects our patients' daily lives, surely our focus as health care workers should be on the patient and their disease experience, rather than their laboratory results, as important as these may be for their management. This should be the case, as the findings from this study show that patients experience symptoms with a high degree of distress, regardless of their CD4 count or viral load level. This finding is echoed by other studies, showing that patients can have significant symptoms and symptom distress, at any CD4 count level(10,17) although Harding et al found that the latest CD4 count did relate to the MSAS-GDI score(24) and Lee et al found that although the CD4 count was not directly linked to symptoms, patients with a CD4 count of under 200 did have higher MSAS-PHYS scores(25). These findings highlight the importance of assessing for symptoms and the burden and distress caused by these symptom, regardless of the CD4 count, as the CD4 count has been shown to be generally a poor marker for symptom prevalence and burden. Palliative care is able to address these symptoms by accurately assessing the patient physically, psychologically, socially and

spiritually(6) and so being able to make a management plan that is patient-focused, with excellent symptom control and psychosocial and spiritual support as is required by each patient.

The findings of this study indicate that while HAART is very effective in controlling the virus and allowing restoration of immune function and thus clinical improvement for the patient, HAART does not prevent symptoms from occurring in large numbers and does not prevent high degrees of burden of physical symptoms, nor high frequency of psychological symptoms. This shows the large and ongoing need for symptom management and palliative care in HIV treatment clinics even in, and especially in, the era of HAART. As discussed in the literature review, a number of studies have shown that symptoms and distress from symptoms are correlated with decreased HAART adherence(31,38,55) and even with virological failure on HAART that is largely independent of adherence to HAART(37). This shows the large and pressing need for routine, appropriate, accessible and adequate symptom management and palliative care in the HIV treatment clinic for all patients who are on HAART. Approximately three quarters of the participants with a latest viral load exhibited viral suppression at last check. In the light of evidence from the literature(31,38,55), it is possible that this finding of inadequate viral suppression on HAART is related to poor adherence, which could be due in part at least, to the high prevalence and distress of psychological symptoms and the relatively high global distress score amongst this group of patients. This is of particular concern as Lampe et al found that physical symptoms and symptoms of depression can point towards future virological failure on HAART, even possibly independently of poor adherence(37). If psychological symptoms that are unmanaged can cause such far reaching consequences as treatment failure from lack of HAART adherence, this is of great concern for the HIV clinician and again is a motivator for the urgent need for adequate psychological support and management of psychological symptoms for all patients with HIV, in a manner that recognises that holistic care is individualised care according to palliative care principles. Palliative care recognises that this care involves a journey with the patient along their path of life, assessing regularly and managing symptoms actively and holistically.

Another finding of this study is that a change in HAART was found to be predictive of an increase in total symptom distress (TMSAS). A change in HAART is associated with a large

degree of life stress, as the reason for the change may involve significant symptoms and may even involve hospitalisation if severe. The change itself may invoke psychological distress, such as fear and worry regarding the success of the new medication. All of these psychological symptoms require palliation so as to assist the patient in coping with this stressful life event while at the same time, palliative management of the physical symptoms relating to the failure of HAART is of great importance in relieving the physical suffering of the patient.

The majority of participants answered "yes" To the subjective question "Do you think any of your symptoms are because of your ARVs?" This indicates that ARVs could in themselves be burdensome to patients, either psychologically or in actually causing physical symptoms, as this is the subjective opinion of the participants who do take HAART. The finding that participants with an undetectable viral load do often blame their HAART for their symptoms, according to the subjective question asked, is of concern in and of itself, particularly with respect to future treatment adherence. Body fat distribution changes and numbness or tingling of hands and feet were the two most common symptoms that were attributed to HAART by patients. These do relate to the common side effects that are known to be due to HAART drugs(74). Regardless of what the cause of symptoms may be, it is important to address each of these symptoms with explanation and with appropriate pharmacological and non-pharmacological palliative management in a patient specific manner. Communication between the patient and the doctor is the basis for a sound assessment of the patient experience of their disease and gives the clues to what suffering the patient may be experiencing. In the often disempowered and vulnerable population group that this study sampled, patients may not voice concerns unless they are specifically asked about their concerns, their beliefs and their symptoms. Without this knowledge of their patients, clinicians will not assess problems accurately and therefore symptoms and suffering will go untreated. Palliative care principles enable the clinician and health care worker to come alongside their patients to make accurate assessments and so be able to manage symptoms effectively. If symptoms are very troublesome for patients and these symptoms are not addressed and managed by their doctor or relevant health care worker, there is a possibility that the patient may decide to stop taking the HAART. Severe and debilitating symptoms that are not addressed or managed by the patient's doctor may lead the patient to believe

that he is alone in his walk along the pathway of his life, with no real assistance from the medical personnel who are treating his disease. The patient may then start to make his own decisions regarding his HAART and these decisions will likely be based on his own beliefs about his disease and about the medication he is taking, rather than based on the education and guidance received from the foundation of a good doctor-patient relationship(75). Palliative care operates with the principle that excellent clinical care comes out of a relationship of trust between the health care worker and the patient. On this basis, the patient should not feel abandoned and will be able to address his concerns with his doctor, allowing adequate discussion and subsequent palliation of the distressing symptoms and therefore increased compliance on HAART.

The trend of the findings for the MSAS-SF subscales of this study are similar to other studies conducted on different population groups where many of the population have been diagnosed for some time and are on treatment for their disease, whether or not HAART has started as of yet or not – the trend seems to be that the physical symptom distress is less than the global distress and that the psychological distress is the most distressing of all(10,23-25). Fontaine et al found that physicians most correctly identified symptoms that were related to measurable physical signs but were definitely less reliable in identifying symptoms that were not readily measurable(18), showing the need for vigilance in enquiring about symptoms routinely for each patient and specifically for enquiring about psychological and less obvious physical symptoms. In a study amongst patients with cancer who were already receiving palliative care in South Africa and Uganda, the MSAS-SF subscale scores were higher for physical and global distress but similar for psychological distress(71). Vogl et al also found that AIDS outpatients and cancer patients had similar symptoms with AIDS patients actually experiencing more symptoms than the cancer patients used as a comparison(10). The findings that patients with HIV and patients with cancer have similar symptom prevalence and burden from symptoms, are further evidence for the need for symptom control and palliative care to be incorporated into the general HIV outpatient treatment clinic management of patients.

The MSAS-SF subscale scores in this study suggest that the symptom distress experienced by the cohort of this study is similar in all the categories (global, physical, psychological) to that experienced by patients who attend HIV outpatient clinics in London(23). The similarities of

the results of this study to the London based study are further evidence that patients with HIV who attend HIV treatment clinics and are on HAART do experience a large number of symptoms from which the symptom burden is marked. The similarities of the findings give further motivation for the need for symptom control and palliative care to be urgently incorporated into HIV treatment clinics in South Africa. Palliative care aims to "*improve the quality of life of patients and their families facing the problems associated with life-threatening illness*"(6). HIV disease remains a life-threatening disease even with HAART and as this study shows, symptoms occur frequently and with high degrees of distress and symptom burden. Symptoms are one of the components of the assessment of the quality of life of patients(28-30) and as such it is not possible to improve the quality of life of the patients at these HIV treatment clinics unless symptoms are "*impeccably*" assessed and managed(6). The symptom distress shown in this study motivates for palliative care to become routinely incorporated into the management of each patient attending the clinics, so that all patients benefit from improvements in their quality of life through adequate and ongoing symptom control. The aim of good quality of life for their patients, through the palliation of symptoms and suffering, is a very important aim for clinicians to pursue for all their patients who have a good life expectancy on HAART, not just for those patients whose life expectancy is imminently limited by their disease.

Limitations

This study was of a cross-sectional design and therefore no causality between the relationships can be established. The sampling method may be the biggest limitation of the study as convenience sampling may introduce selection bias. True random sampling was not possible in the clinic environment, and therefore to minimize bias, every 5th eligible patient was invited to participate. Selection bias was also involved due to the type of patient who attends the HIV clinics. Those patients unlikely to have attended the clinic (and thus excluded from the study) were those who did not know their HIV status, those who were too ill to go to the clinic, those who would not attend the clinic because of stigma, and those patients with a medical aid or who can afford to receive HIV management privately. Patients with HIV disease who were admitted to hospital due to complications or opportunistic infections were also not included in this study. It was the specific aim of this

study to sample patients attending the specific HIV treatment clinics described so the exclusion of hospitalised patients was anticipated and is accepted. No clinical data was collected on patients who did not choose to participate in this study and therefore it is not known if and how these patients differed from the participants of the study in any way.

Another potential limitation of the study was the participant understanding of the MSAS-SF but I believe this was satisfactorily improved by the translation of the MSAS-SF and by using an interviewer administered technique. The translated MSAS-SF was however not formally validated prior to use in this study. Another area for potential bias was participant acquiescence to the interviewer asking the questions. Therefore the research assistants were trained appropriately and they did in fact have significant previous experience in research work to be aware of this danger.

A number of participants who were staged as WHO stage 2 did have previous diagnoses that could have classified them as stage 3 (and for some, even as stage 4); however it is not known at which point in time these diagnoses were made. The WHO stages that were being assessed in this study were therefore the stages that the treating clinicians would find in the clinic file and would be assumed to be the WHO stage at diagnosis. However, it may have been that patients were initially incorrectly staged as WHO stage 2 while actually being of a higher stage. These discrepancies are not known to be the case but this would have caused an incorrect interpretation of the data analysis for symptoms relating to the WHO stages, but not to any other of the analyses.

This study did not make any social or family support assessment or a financial means assessment. Food security was not assessed and neither was there a nutritional assessment made. There was also no assessment of the level of education achieved by the participants. While it was not part of the aim and objectives of this study to research these variables, any of these variables may have confounded the relationships studied, as has been found by other authors in the Southern African and international literature(10,20,22). It is recommended that future research includes the study of these variables.

Conclusion of findings

This study has found that, among HIV positive patients who attend outpatient HIV treatment clinics in Johannesburg, South Africa, the symptom prevalence is high and similar to the findings of a study conducted amongst HIV outpatient clinics in the UK(23). The prevalence and burden of physical symptoms is high and the prevalence and burden of psychological symptoms is particularly high. The most prevalent symptom overall was "feeling sad", while the most prevalent physical symptom was "numbness/tingling in hands and feet" showing a high prevalence of neuropathic pain in comparison to other studies(12-14,17,20,22,24,25,33,48). Pain was the 6th most prevalent symptom. The vast majority of the participants were on HAART so it is clear that patients on HAART do experience symptoms and that these are highly burdensome and appear to be largely untreated, although symptomatic management was not specifically assessed.

The majority of the patients surveyed were relatively well functioning with the majority of KPS scores being 90% or 100%. Even these relatively well functioning participants had a large symptom prevalence and symptom burden. Symptom distress differences by CD4 count groups and viral load groups were not significant although the latest CD4 count was found to be predictive of physical symptom distress, as has been found by Lee et al(25) in their study in the USA. Although participants who were classified as WHO stage 2, 3 &4 did have significantly more symptoms than participants staged as WHO stage 1, participants in all four WHO stages had a large number of symptoms with associated high symptom burden.

The findings of this study suggest that symptoms and the distress generated by the symptoms can occur at any time in the course of HIV disease and that this phenomenon is multi-factorial. The findings point to a high level of unmet symptom control needs. Symptoms are under-appreciated and under-assessed for a number of reasons which may include the business of the clinic and the time pressure the health care workers work under. These unmet needs also point to a lack of appreciation by health care workers for the large potential for patients to experience symptoms at any CD4 count, at any WHO stage and even for patients on HAART. It is believed that this study does add to the evidence showing that symptom prevalence and symptom burden is high for patients attending outpatient HIV treatment clinics in Johannesburg. Each patient should be individually and thoroughly

assessed as often as they visit their clinic. Symptom management and palliative care should ideally be an integral part of the patient management provided by outpatient HIV treatment clinics.

Chapter 7

Conclusion and Recommendations

Conclusion

The aim of the study was to assess the prevalence and burden of pain and other symptoms amongst the population of patients attending three outpatient HIV treatment clinics in three academic hospitals in Johannesburg, namely the Charlotte Maxeke Johannesburg Academic Hospital, the Chris Hani Baragwanath Hospital and the Helen Joseph Hospital. This was achieved using the Memorial Symptom Assessment Scale – Short Form (MSAS-SF). The objectives of the study to assess the relationship between the symptoms and the burden related to the symptoms, with WHO stage, CD4 count results, viral load results, performance status as measured by KPS, gender and age were all achieved. A comparison of the symptom prevalence and symptom burden between those patients who were on HAART versus those who were not on HAART was not possible, as 98.44% of patients were on HAART already. Too few patients were naive to HAART to make any comparison. However, those patients who had had a change in HAART regimen were assessed for symptom prevalence and symptom burden instead, in relationship to those who had not had a change in HAART.

The findings show that pain and symptom prevalence is high in this population. The prevalence of pain and symptoms is comparable to other studies conducted in HIV infected populations(10,20,22-24), as well as to populations with advanced malignant disease(71). Physical and psychological symptoms are all common, with psychological symptoms being particularly common, which is also in agreement with the findings of previous studies(10,20,22-24).

The burden of the pain and symptoms experienced by the participants in this study population is also high, and again is also comparable to the burden found in other studies(10,23-25). There is high physical, global and psychological distress amongst this study population. The most consistent predictors, on multiple regression analysis, of

increased symptom distress for all the MSAS-SF distress subscales (MSAS-GDI, -PHYS, -PSYCH, and TMSAS) were a KPS score of <100%, WHO stage 2, 3 or 4, and the female gender. The findings also show that patients who report the presence of pain, regardless of distress rating, had statistically significant greater psychological distress than patients with no pain.

Viral load results, CD4 count results and age were found to have no significant relationship with the three MSAS-SF subscales, which is consistent with the findings from other studies(10,14,25). However on multiple regression analysis a lower latest CD4 count was predictive of increased physical distress, but not predictive of any of the other subscales, while a previous study found that the latest CD4 was predictive of global distress(24).

When comparing any previous change in the HAART regimen to symptom prevalence and MSAS-PHYS in this study, there was no significant difference found between those patients who had changed HAART, compared with those who had not changed HAART. The length of time on HAART was also not associated with symptom prevalence. However on multiple regression analysis, any previous change in HAART was predictive of an increased total symptom score (TMSAS), but was not predictive of any of the symptom distress subscales.

These results show a high symptom prevalence and burden for patients who are taking HAART, regardless of CD4 count, viral load, WHO stage, KPS, gender and age, indicating significant unmet needs in the patients attending the HIV treatment clinics involved in the study. There are unmet needs for physical symptom control, including nociceptive and neuropathic pain control, as well as significant unmet needs for psychological symptom control and support.

Recommendations

These results highlight the palliative care needs of patients with HIV to their health care workers at HIV treatment clinics in South Africa, and to HIV clinicians in South Africa in general. The large symptom prevalence and associated high burden of symptoms amongst the study population suggest that there is inadequate assessment and management of physical and psychological symptoms at the HIV treatment clinics. Of particular concern are

the high prevalence of pain (both nociceptive and neuropathic pain), the feelings of sadness and of worry, however all the symptoms experienced by patients deserve assessment and management. For symptoms to be treated effectively, the health care worker would first have to recognise that symptoms may be present, and that they should therefore be adequately screened for. A symptom screening tool would assist the clinician in the recognition of symptoms. Several symptom screening tools exist, but the most appropriate tool for the particular clinic should be selected, or as in the study by Green et al in Vietnam, an appropriate tool can be developed by the clinic themselves(36). The time required for use of the screening tool would need to be short enough for the tool to be realistically viable for use in a busy HIV outpatient treatment clinic. Ideally symptom screening tools should be used at each patient clinic visit. The tool could be used by a nurse when vital signs are checked prior to the patient seeing the doctor, with the results available for quick reference by the doctor. Once recognised, symptoms should be effectively and appropriately managed. The symptoms identified by the screening tool should guide the completion of a comprehensive and individualised care plan that will be a useful guide on each subsequent review of the patient, so as to be able to adequately assess the response to treatment. This requires that the health care worker should have the necessary training in symptom management and also in palliative care. Symptom management and palliative care should be seen as part of the regular service rendered to the patient, with the aim of improved quality of life for the patient, and so as to encourage, assist and improve HAART adherence among patients. It may be deemed practical to dedicate particular staff in each clinic to lead this initiative because training of all staff may be considered impractical, however, if all staff are trained in palliative care and conversant with the principles and tools used, more patients are likely to benefit from palliative care interventions.

To be able to effective and appropriately meet these aims, there will need to be increased health care worker education in the area of symptom control and palliative care – for doctors, nurses, counsellors, social workers, psychologists and allied health professionals. This education should occur for the staff at the HIV treatment clinics involved in this study, and in the longer term, also for staff at HIV treatment clinics throughout South Africa so that a meaningful difference to the lives of South Africans with HIV can be made, particularly for their quality of life. This education should be theoretically accurate but very practical in

nature, as it is the practice of palliative care which advances patient quality of life, not necessarily the theory of palliative care – theory must be translated into action. Palliative care principles and management principles should be incorporated into routine HIV patient clinic management, to the benefit of the patient. Green at al write that "*for integration to occur, palliative care needs to be "*routinized*" into HIV clinical settings*"(36). Green et al also talk of the mentoring process in their study which assisted the clinic staff in becoming familiar with the assessment and management of symptoms, both physical and psychological symptoms(36). Green et al found that physicians found increased job satisfaction at being able to treat their patients' symptoms effectively(36). This finding should assist in allaying concerns that the addition of the palliation of symptoms will increase the workload of physicians in HIV treatment clinics. Improved patient outcomes and patient satisfaction should improve health care worker job satisfaction and with this improved clinician competence could potentially streamline patient management.

The results of this study conducted in the three HIV treatment clinics described are also highly relevant for anyone involved in public health planning in South Africa. The results show a large prevalence of unmet physical and psychological needs. The literature shows that these needs, if unmet, can lead to future virological failure and poor HAART adherence(31,37). It is crucial to do all we can as health care workers to assist patients in their adherence to HAART, from humanitarian, medical, social and economic points of view. To be able to manage physical symptoms, drug availability will need to be ensured, at national, provincial, regional and local levels. Staff numbers would not need to be increased if all health care workers are well trained in palliative care and if protocols are in place for the routine implementation of palliative care for all patients. This requires ongoing work and collaboration between palliative care advocates, HIV clinicians and the public health planners.

This study raises questions that will require further research in the South African context. As social, financial, food and home circumstances were not enquired about in this study, there is a need to relate these factors to the influence they may have on the prevalence and burden of the MSAS-SF symptoms and on the biological data. This should include research into the nutritional status of patients and how this relates to symptoms and symptom burden and biological disease data(22). Vogl et al used the Social Support Questionnaire –

Short Form to assess the quality of social support(10), while Makoae et al included the access to a Disability Grant as an marker for financial security(20). Educational levels and employment have been found to impact symptom prevalence and burden elsewhere, including rural South Africa, and it would be useful to know the impact of these factors on the symptom prevalence and symptom burden of the population group studied(20,22,23).

Further study into the sites, types, intensity and treatment of specific pains in this population group is warranted. It would also be clinically useful to have more research amongst this population group into the relationships between nociceptive and neuropathic pain with psychological symptoms such as feeling sad, worrying and feeling irritable. This should therefore also include a more formalised assessment of depression amongst these patients. It would be beneficial to survey HIV physician knowledge and skills in pain and symptom management, so as to formally assess and quantify the training needs that have been shown to be present from the findings of this study. This knowledge and skill should also be surveyed among nurses so as to assess their specific training needs.

Other studies have raised the concern that HAART is related to symptom prevalence and burden(22,24). It would be most informative to do longitudinal studies of pain and symptoms from the time of diagnosis, throughout all stages of treatment, including treatment on HAART, for a significant length of time. The prevalence of HIV in South Africa is very high and thus the need for HAART is significant enough to warrant such studies so that these and other questions relating to adherence and the quality of life of HIV infected people can be better understood.

The most important recommendation from this study is that palliative care is required by all patients with HIV, so that patient outcomes can be improved. Therefore palliative care should be incorporated alongside the current routine HIV care that is presented in HIV treatment clinics. Without the routine palliation of symptoms at the clinic where patients receive their primary HIV care patients will continue to needlessly suffer from physical and psychological symptoms that do have evidence based and acceptable treatments.

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Appendices

Participant Information Form

Hello, my name is Dr Lindsay Farrant.
I am a doctor doing the following study, with the help of the nurse who is speaking to you. You are invited to take part in this study:

To survey the prevalence and burden of pain and symptoms amongst HIV positive patients attending HIV treatment clinics

This study wants to find out how common some problems are for people who are HIV positive in South Africa. This means that we ask each person who takes part in the study to answer some questions that will tell us what they feel or what problems they have. This way we can understand how common these problems are amongst people who are HIV positive in Johannesburg, South Africa. This should help doctors and nurses to better understand and treat people living with HIV in Johannesburg. This study is part of my studies for a degree and has been supported by the Research Ethics Committees of the University of Cape Town and the University of the Witwatersrand. It is being supported by the Gauteng Centre of Excellence for Palliative Care which is part of the Department of Medicine of the University of the Witwatersrand, as a non-profit research entity. The study is being supported by this Centre because it wants to improve our understanding of symptoms and pain among patients who are HIV positive.

You are free to choose if you want to take part in this study. The study is being conducted at this clinic where you usually get your treatment. Your treatment at this clinic will remain the same, whatever you decide. You may stop answering the questions at any time or choose not to answer some questions and you may withdraw from the study at any time. The doctors and nurses who are treating you in this clinic know about this study and accept it. They will receive the results of this study when it is completed. Once this study is finished, the results will be put on posters on the walls of this clinic, but will not include any of your details or your name. Your name and details will not be used or seen by anyone other than the person doing this study – the researcher's name is at the bottom of this page. All papers with your name and details will be stored carefully to ensure that everything is confidential and anonymous. Your name will not appear anywhere on any report that comes out of the results in this study.

If you agree to take part in this study, you are agreeing to a single interview in English, Sesotho or isiZulu, and to the interviewer copying down information from your file. This should all take around about 30 - 40 minutes. There are no direct benefits – you will not receive any money or gift – but this study will help us to understand important problems that you experience. There are no risks to taking part in this study. We will not be taking any blood or giving any

medication, but we will check your file for your results. Should we find any problems that have not been treated we will refer you to a doctor.

If you would like to, you can telephone the person doing this study for more detailed information, at any time, on 011 933 4916. The researcher's name is Dr Lindsay Farrant.

Thank you very much.

RESEARCHER **Dr Lindsay Farrant**
Wits Palliative Care, Chris Hani Baragwanath Hospital, Johannesburg
PO Box 212, Pimville, 1808
Tel: 27 11 933 4916 Fax: 27 11 933 1701

Contact details: University of Cape Town Research Ethics Committee
Mrs Lameez Emjedi
Faculty of Health Sciences
Research Ethics Committee
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Contact details: University of the Witwatersrand Human Research Ethics Committee
Ms Anisa Keshav
The Research Office
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10th floor
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Participant Consent Form:

Dear Patient,
You are invited to take part in this study:

To survey the prevalence and burden of pain and symptoms amongst HIV positive patients attending HIV treatment clinics

In this study I will answer questions about the problems I face in my daily life, especially the last week. I understand it will take about 15 minutes.

I am freely taking part in this study. I am here to see the doctor at the clinic where I normally get my treatment.

I understand that the person asking me the questions will use my clinic file but that all information will be kept strictly confidential and anonymous – no one else but the person asking the questions and the person doing the study will see the information. I understand that I may stop answering any questions at any time.

I have been given a telephone contact number for the person doing this study.

I understand that whatever I decide, my treatment at this clinic will remain the same.

I understand that once this study is finished, the results, without any names or patient details, will be put on posters on the walls of this clinic. I can also telephone the person doing this study for more detailed information on the results.

I understand this and the patient information sheet that I have received and agree that I have had sufficient time to think about this and ask any questions I have and to decide on my participation in this study. I agree to my file being used for the information needed and to answer the questionnaire. I now freely agree to take part in this study.

Signed / or Thumbprint (where unable to sign):_____

Name and Surname:_____

Date: _____Place:_____

Witness Signature_____

Hospital Number_____ Study number:_____

Participant Data Sheet:

Date:_____ Study Number:_____

Age at last birthday:_____ Gender: Male_____Female_____

Self-determined Ethnicity: Black_____Coloured___White_____Indian_____Other___

Latest CD 4 Count:_____ (date:_____) If not available: _____

Latest Viral Load:_____(date:_____) If not available: _____

Latest Albumin level: _____(date:_____) If not available: _____

Initial CD 4 count before starting HAART_____(date:_____) If not avail:____

Initial Viral Load before starting HAART_____(date:_____) If not avail:____

WHO staging: _____

HIV – Related diagnoses:

_____

Diagnoses unrelated to HIV: _____

Is patient on HAART? Yes_____No_____ If YES, the date of starting_____

If YES, the names of the drugs the patient is currently taking

_____

Has any change of HAART occurred? Yes_____No_____

If YES, Date of change _____& previous regimen_____

And reason for change_____

Additional information not in patient file:

Current Karnofsky Performance Status (KPS):_____(According to attached KPS Scale)

After the MSAS-SF, if the patient is on ARV's, ask the patient the following question:

Do you think that any of your symptoms are because of your ARV's: YES_____ or NO_____

IF YES: Which of the symptoms?_____

Karnofsky Performance Scale

(For use with persons ages ≥ 17 years)

100% = Normal; no complaints, 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

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 own needs

50% = Requires considerable assistance and frequent medical care

40% = Disabled, requires special care and assistance

30% = Severely disabled, hospitalization is indicated although death is not imminent

20% = Hospitalization necessary, very sick, active supportive treatment necessary

10% = Moribund, fatal processes progressing rapidly

0% = Dead

MEMORIAL SYMPTOM ASSESSMENT SCALE – Short Form [MSAS-SF]

1. **INSTRUCTIONS:** Below is a list of symptoms. If you had the symptom **DURING THE PAST WEEK**, please check Yes. If you did have the symptom, please check the box that tells us how much the symptom DISTRESSED or BOTHERED you.

		→→ IF YES: How much did it DISTRESS or BOTHER you?				
Check *all* the symptoms you have had during the PAST WEEK.	Yes [✓]	Not at All [0]	A little Bit [1]	Some-what [2]	Quite a Bit [3]	Very Much [4]
Difficulty concentrating						
Pain						
Lack of energy						
Cough						
Changes in skin						
Dry mouth						
Nausea						
Feeling drowsy						
Numbness/tingling in hands and feet						
Difficulty sleeping						
Feeling bloated						
Problems with urination						
Vomiting						
Shortness of breath						
Diarrhea						
Sweats						
Mouth sores						
Problems with sexual interest or activity						
Itching						
Lack of appetite						
Dizziness						
Difficulty swallowing						
Change in the way food tastes						
Weight loss						

MEMORIAL SYMPTOM ASSESSMENT SCALE Short Form [MSAS SF]

I. **INSTRUCTIONS: Below is a list of symptoms. If you had the symptom DURING THE PAST WEEK, please check Yes. If you did have the symptom, please check the box that tells us how much the symptom DISTRESSED or BOTHERED you.**

		➔➔ If YES: How much did it DISTRESS or BOTHER you?				
Check *all* the symptoms you have had during the PAST WEEK.	**Yes [✓]**	**Not at All [0]**	**A little Bit [1]**	**Some-what [2]**	**Quite a Bit [3]**	**Very Much [4]**
Hair loss						
Constipation						
Swelling of arms or legs						
"I don't look like myself"						
If you had *any other* symptoms during the PAST WEEK, please list them below, and indicate how much the symptom [ ] DISTRESSED or BOTHERED you.						
1.						
2. _____						

II. **Below are other commonly listed symptoms. Please indicate if you have had the symptom DURING THE PAST WEEK, and if so, how OFTEN it occurred.**

	➔➔ IF YES, How OFTEN did it occur?				
Check *all* the symptoms you have had during the PAST WEEK	**Yes [✓]**	**Rarely [1]**	**Occasionally [2]**	**Frequently [3]**	**Almost Constantly [4]**
Feeling sad					
Worrying					
Feeling irritable					
Feeling nervous					

2.

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22nd October, 2011

Re Dr Lindsay Farrant – corrections to dissertation

Dear Adri,

I have worked with Dr Farrant regarding the corrections to her dissertation following the recommendations from the external examiners and dissertations committee.
I am satisfied that she has addressed the external examiners' comments adequately. She has made the required corrections to her final dissertation submission.

Yours sincerely

Liz Gwyther

Valdora House
Flat 6
31 Grove Avenue
Claremont
7700
20 October 2011

Professor Blockmann
Dean of Postgraduate Studies
Faculty of Health Sciences
University of Cape Town
Anzio Road
Observatory

Dear Professor Blockmann

Re: Submission of corrections to the dissertation towards MPhil Pall Med
by Dr Lindsay Farrant, FRRLIN002

This letter serves to confirm and describe the corrections I have made to the Dissertation that I submitted to your office on 1 April 2011, according to the suggestions of the Examiners' reports.

The data of the Results chapter were re-arranged according to the Examiner's requirements. All tables, graphs and figures were named, numbered and indexed as requested. The demographic data was retained at the start of the Results chapter as this follows University practice, as discussed with my supervisor. The table of 'Demographic Information' was moved to the start of the demographics section of this chapter, as advised, and is now labeled Table 1. This table was also adjusted as advised, to include distinct lines for the ranges for Age, Initial CD4 count and Latest CD4 count. All the minor errors identified by the first examiner in the Results chapter were corrected. Graph 11 on p56 was changed so as not to be misleading. The grammatical error noted on p65 was also corrected.

The Examiner's "concern regarding equating high prevalence of symptoms with inadequate assessment and management by clinicians" was specifically addressed by rewording each such instance to indicate that this could only be suggested but could not be concluded. The Discussion chapter was further adapted to make it more focused, with clearer flow of thought and with less repetition. The concern of the Examiner regarding "body-fat distribution changes" and "I don't look like myself" is discussed in the Discussion chapter as being related and they were not analysed as one concept. The Introduction chapter was minimally adapted, to remove unnecessary repetition. The suggestion by the Examiner to shorten the Introductory and Discussion chapters was noted not to be essential and thus the chapters were not shortened greatly, apart from the changes noted already, as my supervisor and I considered these changes to be sufficient and also appropriate in retaining the integrity of the dissertation.

The typographical and grammatical errors noted by the External Examiner have all been corrected. The specific questions relating to the Literature Review chapter and Methodology chapter have now been clarified in the text. In the Discussion chapter, the Constitutional Symptom Subscale was reported on because it had been used for the first time and it was felt that the fact that it was found to be an unreliable scale was in itself important to report.

The corrected version of the dissertation has been discussed with my supervisor and I am now ready to submit this to the Postgraduate Office.

Yours sincerely,

Lindsay Farrant