Investigation of the factors that impact on outcomes of HAART in patients at Tshwane District Hospital

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DECLARATION

I, Sasje Venter, hereby declare that the work on which this dissertation 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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ABSTRACT

The study was conducted at Tshwane District Hospital (TDH) in Pretoria, Gauteng Province, South Africa. TDH is a district hospital that provides comprehensive primary level health care services to patients from a large part of the greater Tshwane Municipality (estimated population of 2,2 million people). TDH forms part of the University of Pretoria's training complex for pre- and post-graduate health professionals. The HIV clinic at TDH was started in June 2004 and, since opening their doors, has treated 5 870 patients. Currently 3 756 patients are still receiving HAART, 1 297 (22%) have been lost to follow-up and 296 have died.

The aim of this retrospective cohort study was to identify factors that may predict the outcome of individuals started on HAART and to formulate a guideline to assist health care workers to identify and better support patients more at risk of mortality or poor outcome.

Patients meeting the inclusion criteria were older than 18 years and started on HAART at TDH HIV clinic from June 2004 up to and including June 2009. A systematic random sampling method was employed for the selection of a representative sample, sampling every 10^{th} patient file. A univariate statistical analysis approach was followed.

This study aimed to identify factors/variables that could explain the variation in CD4 count among severe immune suppressed patients. Male gender, low body weight, high viral count, low hemoglobin level, high AST and ALT levels explained some of the variation in CD4 count and were more prominent in the CD4 < 50 group.

Secondly this study aimed to identify factors that could predict the outcome of patients started on HAART. Factors that showed some significance were unemployment, lower body weight, a low CD4 count, high viral count and low hemoglobin level. Owing to an overall low mortality rate of 5,4%, these factors did not show to have any predictive value. HIV is a life-threatening illness with an unpredictable course. This low mortality rate shows that HAART is a very effective palliative treatment modality which has the potential to improve morbidity and prolong survival in patients with HIV.

The third aim of this study was to determine the correct mortality rate among lost to follow-up patients. It showed a 39% mortality rate among lost to follow-up patients.

Better surveillance and follow-up care may further improve the outcome of patients initiated on HAART. Strategies that could be looked at may be a DOT (direct observed treatment programme) system for HIV (as in the case of tuberculosis) or home-based care may also assist to better monitor patients at risk of poor outcome or mortality.

CHAPTER 1 – INTRODUCTION

1.1 HIV Epidemic

An epidemic is defined as a rate of disease that reaches unexpectedly high levels, affecting a large number of people in a relatively short time[1].

HIV is a global epidemic with an estimated 40,3 million people infected with the virus worldwide, of which a large percentage (65%) live in Sub-Saharan Africa[2]. Aids-related illnesses is the leading cause of adult mortality and morbidity in this region[1]. It is estimated that 3 to 4 million people are infected each year and 2 to 3 million people in Sub-Saharan Africa die of Aids annually[2].

In Africa, more than in the rest of the world, there has been denial of the seriousness of the HIV epidemic which has lead to a delay in effective response to the epidemic. HIV highlights "global inequalities and its impact is felt more profoundly in poor countries"[1]. These inequalities include the quality, accessibility and availability of health care as well as necessary medications.

African countries also experience high levels of poverty. Poverty leads to malnutrition and other diseases associated with a poor quality of living, for example cholera and other gastro-intestinal diseases. These factors have an impact on the overall health of patients living with HIV infection as well as the speed at which HIV disease progress. Overcrowding, which is a common phenomena in poorer countries, leads to a higher risk of respiratory infections such as tuberculosis and other lower respiratory tract infections. The film '*Yesterday*' realistically portrays the HIV problem and some of the inequalities within the African setting that I have just mentioned and is therefore included to highlight the difficulties faced by people who are HIV-positive[3].

I would like to discuss some of the struggles the main character in this film faced. She started to have persistent respiratory tract symptoms, but battled to see a

doctor at the local clinic, a few kilometres from her home. She had to walk all the way to the clinic. Upon her arrival at the clinic she was told to go home because the doctor was going to see only a certain number of patients and she was too late. This went on for weeks and finally a friend paid for a taxi so that she could get to the clinic earlier. After appropriate investigations and counselling she was told that she was HIV-positive. She was also advised to disclose this to her husband (her only sexual partner) who was working in the city and to advise him to get tested. When she told him about her diagnosis he physically abused her.

Later in the film the husband came home with Aids and asked for her forgiveness. The women in the village started to suspect that he was HIV-positive and tried to force her to leave the village due to her husband's condition. This reaction was fuelled by their own ignorance about HIV transmission and their fear of contracting the disease. Desperate she tried to have her husband admitted to the local hospital, but was turned down because the hospital was full and had a waiting list. In the end this lady built a 'home' with scrap metal, away from the village, where she took care of her dying husband. I think this film portraits the realities many of our patients are facing in the African context, where resources are limited and health care system is failing our patients.

1.2 HIV Natural history and staging

"The human immunodeficiency virus (HIV) primarily infects and destroys cells in the immune system, particularly CD4 (helper) T-lymphocytes, causing profound immune suppression that gradually develops over a period of years and ultimately renders the patient vulnerable to opportunistic infections and malignancy. In addition to the effects on the immune system, HIV also infects nerve, renal and bone marrow cells with clinical important consequences"[4].

A person infected with HIV will usually go through various clinical stages over a period of time. The stages of HIV infection include "viral transmission, acute HIV syndrome, recovery and seroconversion, asymptomatic chronic HIV infection,

symptomatic HIV infection/Aids-defining complication, and death"[5]. This is not a linear progression and death can be delayed for years. The clinical condition of patients can be improved that restores health and active living by Highly Active Antiretroviral Treatment (HAART).

The disease may progress more rapidly in individuals who have a poor health status, such as "chronic disease, recurrent infections, anaemia, malnutrition or nutritional deficiency, repeated pregnancies without adequate recovery between pregnancies, malaria or TB". These are all more common in the sub-Saharan Africa population[2].

1.3 HIV and psycho-social concerns

HIV is a life-threatening illness with an unpredictable course. Over an above the complex clinical picture is the emotional, social and economic impact of this pandemic.[6]. Thulisili Ganyaza-Twalo and John Seager did a literature review on poverty and HIV/Aids and found that at social level, households have to deal with the issues of stigmatisation, social exclusion, disintegration of family structures and being overburdened with care and support roles[7]. They also found that at economic level, families have to deal with medical costs, funeral costs and loss of income if the breadwinner passes away. Sometimes Sub-Saharan Africa has households with more than one individual infected with HIV and families face multiple losses. Unfortunately rolereversal with children looking after sick parents and becoming the 'care takers' is also a reality.

An alarming increase in the number of orphans as a result of the HIV epidemic is also cause for concern. An 'orphan' is defined by the United Nations as a child who has 'lost one or both parents'. Worldwide, it is estimated that more than 15 million children under 18 have been orphaned by Aids. Around 11,6 million of these children live in sub-Saharan Africa[8].

Also of concern, as pointed out by Thulisili Ganyaza-Twalo and John Seager, is the infringement of children's rights with regard to education, food, nutrition, health and other issues[7]. The HIV epidemic not only affects households but also the country's economy in general. When large numbers of the workforce is infected, a decrease in daily productivity and an increase in sick leave taken is observed. The country's health care is also affected due to the increased burden of care faced in the health care setting.

There is no curative treatment modality known at this point, but HAART shows promising results in controlling the course of the illness. HAART transforms HIV from a chronic disease to a terminal illness. It reduces the burden of disease and can improve a patient's quality of life.

1.4 HAART

Highly active antiretroviral therapy (HAART) is a treatment modality aimed at stopping the progression of HIV disease by reducing the HIV viral load and thereby allowing for recovery of the immune system and subsequent reduction of HIV-related illness[4].

Current South African guidelines recommend initiation of HAART[9]:

A. Patients eligible to Start HAART

Patients with a CD4 count <200 cells/mm^3 irrespective of clinical stage or CD4 count <350 cells/mm^3 in patients with TB/HIV or pregnant women or World Health Organisation (WHO) Clinical Staging System[4] stage IV irrespective of CD4 count (Appendix 1) or MDR/XDR-TB irrespective of CD4

B. Patients requiring HAART initiation within 2 weeks of being eligible)

Pregnant women eligible for lifelong HAART or patients with very low CD4 (<100 cells/mm^3) or Stage 4, CD4 count not yet available or MDR/XDR-TB

"Ideally HAART should be commenced before very severe immune suppression has developed, as significant immune recovery may not occur once this point has been reached"[4].

The WHO, however, recommends that HAART should commence before the CD4 count drops below 350 cells/ul. Recommendations from the European guidelines for the initiation of therapy in naïve HIV-infected patients are as follows:

- CD4 <200 cells/mm^3: treatment recommended without delay
- CD4 201-350 cells/mm^3: treatment recommended
- CD4 350-500 cells/mm^3: treatment recommended when:
  - hepatitis C or B co-infection
  - HIV associated nephropathy
  - specific organ deficiency
  - viral load > 10^5 and/or CD4 decline > 50-100 mm^3/year
  - pregnancy
  - high cardiovascular risk
  - malignancy
- CD4> 500 cells/mm^3: treatment should generally be deferred[10]

1.5 Managing HIV as a chronic disease

With the introduction of HAART HIV is now a manageable chronic disease. Management of people with HIV/Aids now includes HIV viral suppression with HAART therefore delaying the onset of serious immune deficiency, opportunistic infections and Aids; and managing and supporting patients to adhere strictly to HAART drug regimen. It also includes avoiding and managing drug side-effects and toxicity as well as avoiding and managing emerging ARV drug resistance and the prevention of mother to child HIV transmission with the use of HAART. Counselling of affected people, supporting and caring for people who are ill and dying and implementing preventative strategies to control the spread of HIV are also included[4].

These above guidelines are based on palliative care principles. It is therefore important to look at the definition of palliative care. Prior to the introduction of HAART as a treatment modality palliative care had a natural place in Aids care. The presence of ongoing symptoms, the significant social problems and hospice's long association with Aids patients may however justify a palliative perspective.

1.6 WHO definition of palliative care

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.

Palliative care:

- Provides relief from pain and other distressing symptoms;
- Affirms life and regards dying as a normal process;
- Intends neither to hasten or postpone death;
- Integrates the psychosocial and spiritual aspects of patient care;
- Offers a support system to help patients live as actively as possible until death;
- Offers a support system to help the family cope during the patient's illness and in their bereavement;
- Uses a team approach to address the needs of the patient and their families, including bereavement counselling, if indicated;
- Will enhance quality of life, and will also positively influence the course of illness; and
- Is applicable early in the course of illness, in conjunction with other therapies that are implemented to prolong life, such as chemotherapy or radiation

therapy, and those investigations needed to better understand and manage distressing clinical complications'[11].

As HIV is a chronic disease marked by pain, distressing symptoms and possibly death, palliative care is important in HIV care. Palliative care also focuses on emotional, psychosocial and spiritual aspects of patients' care, as mentioned above, which plays a big part in the life of the patient living with HIV, as well as the lives of their families. Positively influencing the course of HIV is also important and here palliative care can also play an important role.

1.7 Motivation/Statement of the problem

Resource limitations has led to HAART being available only to South Africa's public sector once immune suppression has developed (as defined by a CD4 <200 cells/ul) although a study done by Jean B, Nachega MD, of the Harvard School of Public Health in Boston, and colleagues of 6 833 HIV-positive adults in South Africa who started HAART through a private sector programme, showed that high adherence to HAART in resource poor settings is associated with reduced overall direct health care cost[12].

Stephan Lawn also found that the mortality rate after starting treatment with a CD4 count below 100 and Aids-related illness the 48-month cumulative mortality, was 24,8%[13].

Due to late diagnosis or late presentation, many people are starting HIV treatment very late, with CD4 counts often below 50 cells/ul. These individuals are much more likely to develop serious illnesses or die soon after starting treatment.

The ideal would be the initiation of HAART earlier, but in a country with large numbers of infected patients, who present at a very late stage, it will be economically and practically unfeasible given severely limited resources. The

estimated antiretroviral therapy coverage in HIV-infected people aged 15-49 years in 2004 in South Africa was 7% (number of people needing ART 837 000 and number of people receiving ART 37 000-62 000) [14].

This leads to the question of whether there are factors that can be identified that will identify more vulnerable patients and will predict the outcome, as this will then enable us to look at strategies to support them better and, in doing, so better the outcome of treatment.

Factors that have been identified as predictors of outcome for patients starting on HAART include age, weight at HAART initiation, total CD4 count, viral load at HAART initiation, hemoglobin level, platelet count, liver function (with emphasis on AST and ALT levels), serum-albumin, the presence of opportunistic infections at initiation of HAART, the presence of co-morbid or HIV-related malignancies and emotional and social support[15, 16, 17, 18].

1.8 Study site background

The study was conducted at Tshwane District Hospital (TDH) in Pretoria, Gauteng Province, South Africa. TDH is a district hospital that provides comprehensive primary level health care services to patients from a large part of the greater Tshwane Municipality (estimated population of 2,2 million people). TDH forms part of the University of Pretoria's training complex for pre- and post-graduate health professionals. The HIV clinic at TDH was started in June 2004 and, since opening their doors has treated 5 870 patients. Currently 3 756 patients are still receiving HAART, 1 297 (22%) have been lost to follow-up and 296 have died.

In another study, Bisson et al. analysed a large public antiretroviral therapy programme in Sub-Saharan Africa and documented lost to follow-up 16,6% with a substantial death rate of 58,8% among these patients soon after initiating HAART[19]. With 41,2% of the lost to follow-up patients still alive and probably

defaulted treatment, this can serve as a marker for non-compliance, as non-compliance leads to poor patient outcomes.

This also illustrates how uncertainty about the death rate among patients lost to follow-up can result in both inaccurate estimates of survival and biased estimates of risk factors for death after HAART initiation. The question arises whether this problem will be less prominent if more vulnerable patients can be identified and strategies put in place to better support them?

1.9 Aim of the study

The aim of this retrospective study is to identify characteristics of patients with low CD4 count and to determine if there was any correlation between a low CD4 count and death.

1.10 Objectives of the study

The main objectives of the study are to:

- Identify the profile of patients with low CD4 count vs. the profile of patients with CD4 >50 cells/mm^3;
- Identify factors that predict outcomes of HAART in immune suppressed patients in a resource-limited setting;
- Determine the corrected mortality rate once lost to follow-up patients' data are reviewed and incorporated into the currently available data from TDH.

CHAPTER 2 – LITERATURE REVIEW

With HIV being a global epidemic and millions of people being infected worldwide and 65% living in sub-Saharan Africa it estimated that a further 3 to 4 million people are infected each year and 2 to 3 million people in sub-Saharan Africa die of Aids annually[2].

"Ideally HAART should be commenced before very severe immune suppression has developed as significant immune recovery may not occur once this point has been reached"[4]. Resource limitations have led to HAART being available to South Africa's public sector patients only once immune suppression has developed.

Important factors that have been identified as predictors of outcome for patients starting on HAART include age, weight, total CD4 count and viral load at HAART initiation, hemoglobin level, platelet count, liver function (with emphasis on AST and ALT levels), serum-albumin, the presence of opportunistic infections at initiation of HAART, the presence of co-morbid or HIV-related malignancies and emotional and social support.

According to the SOLVE methodology five psychosocial issues: stress, violence, alcohol and drug use, HIV/AIDS and tobacco consumption are interrelated. Evidence shows that psychosocial issues occur in cluster form. The stress of HIV positive status increased tobacco smoking, alcohol use or illicit drug use. There is a shown bidirectional interrelation. These psychosocial issues can have a negative impact on outcome of treatment by having an effect on adherence or patient's general health. [20]

A literature review on the topic of HAART initiation and outcomes focused on studies directly related to the outcome in immune-suppressed patients with

CD<200 cell/ul and certain specific predictive factors, including anaemia, weight at initiation, the presence of thrombocytopenia, co-morbid diseases, age and adherence. Optimal criteria for the initiation of HAART, as well as the mortality rate in general, were also reviewed.

The literature review will focus first on the effect of HAART on the general mortality rate and then focus on the different predictors of outcome.
The studies that were reviewed in this literature review were obtained through a Medline, advanced Google and an African health line search on the internet spanning a research period from 2000 up to now.

2.1 Mortality rate

It is well established that there is an improvement in the mortality rate of HIV/Aids patients receiving HAART.

Palella et al. report on the research study the Khayelitsha ARV treatment project[21] which was initiated to demonstrate that treating HIV/Aids with ARV drugs in a primary health care setting and in a resource-limited environment is feasible and replicable. Research was done in Khayelitsha with a study population of 288 between April 2001 to late 2002 and showed the following changes in clinical measures after one year of HAART:

- Mean weight gain of 10 kg;
- Decline in frequency of opportunistic infections;
- Viral load suppression;
- Mean overall CD4 count increase of 221 cell/mm^3; and
- 84% survival at 18 months of treatment (decreased mortality rate).

A prospective observational cohort study from 8 clinics in the USA with 1 022 participants, done by Palella et al., showed a decline in death rate from a quarterly mean of 29,5 deaths/100 person years of observation in 1995 (prior to widespread use of HAART) to a rate of 11,5 deaths/100 person years observed

by the fourth quarter of 1996 (when HAART utilisation had a prevalence of 65,7% of their patient cohort) [15].

A descriptive study done at St. Paul's Hospital, Vancouver, Canada by Wood et al., evaluated whether non-immune-based factors, such as physician experience and adherence, could affect survival among HIV-infected adults starting HAART[22]. A study population 1 416 was analysed and they concluded that survival rates following the initiation of HAART are "dramatically improved among patients starting with CD4 counts <200 x 106 cell/l once adjusted for conservative estimates of physician experience and adherence". The overall Aids mortality rate for patients after initiating HAART was found to be 7,8%.

Park et al. conducted an observational cohort study at a tertiary referral hospital in South Korea[23]. Their objective was to determine whether adherence to clinic visits early after initiation of HAART is predictive of long-term clinical outcome. Their study population was smaller (387) than the previously mentioned studies' populations, but still large enough to be significant. The patients were followed up for at least 1 year after initiation of HAART and the study was conducted over a 6 year period. The mean time to death was 35 months after initiating HAART and the mortality rate 2%.

Statistics South Africa also showed a 1,8% drop in deaths from 2006 to 2007. Whether this is due to the government's Aids treatment programme is still to be determined[24].

Although all of the studies discussed were done in different settings (from first-world to resource-limited settings) the conclusions were the same: initiation of HAART decreases overall mortality of HIV/Aids patients.

2.2 Predictors of outcome

2.2.1 General

Norval listed the following clinical signs and symptoms in the *Manual of Palliative Care in Aids*[25] to often be associated with decreased survival time:

- Poor performance status (>50% of day spend in bed)
- Chronic diarrhoea and rapid loss of weight or wasting

A prospective community-based cohort study on early mortality among adults accessing a community-based antiretroviral service in South Africa (Cape Town, South Africa), done by Lawn et al., found wasting syndrome, TB, acute bacterial infections, malignancies and immune reconstitution disease were the major causes of death. Most early in-programme deaths occurred among patients with advanced immuno deficiency who had not yet initiated ART[16].

The previously discussed article by Palella et al. also described the presence of co-morbid conditions, such as substance abuse and addiction as poor prognostic factors[15].

2.2.2 Anaemia

Mocroft et al. conducted an observational, prospective cohort analysis of 6 725 HIV patients from across Europe[26]. The objective was to describe changes in haemoglobin over time and to determine the joint prognostic value of the current haemoglobin, CD4 count and viral load. They found anaemia to be one of the clinical manifestations of auto-immunity and one of the most common hematological abnormalities affecting 70-95% of HIV-positive individuals. An association with increased risk of death was also found.

A study done by D Brittan[27], as well as various handbooks on HIV infection [4, 6, 28] reports that the anaemia associated with HIV infection is "characterised as normochromic, normocytic with a low reticulocyte count" [4]. This is similar to the anaemia found in other chronic disorders.

Johannessen et al. ask the question whether the "association between anaemia and mortality is casual or whether anaemia is rather a marker of progressive HIV disease"[17]. They conducted a cohort study of 320 treatment-naïve Tanzanian patients and found mortality to be at 19,2% within 3 months after initiating HAART and also that anaemia was a strong independent predictor of morality.

Anaemia was also found to be a feature of opportunistic infections. Some etiologies mentioned in their study included mycobacterium infections, parvovirus B19, micronutrient deficiencies, immunological myelosuppression, impaired erythropoietin production and blood loss from intestinal opportunistic disease.

Other causes of anaemia in HIV patients seen in the literature include myelosuppressive drugs as well as heamolysis[2, 6, 5].

2.2.3 Weight loss

The wasting syndrome has become increasingly recognised in adults infected with HIV in the United States and at present accounts for approximately 18% of initial Aids-defining conditions. Weight loss, with or without associated symptoms, has been described in many people with advanced HIV infection[29].

Primary HIV/Aids care by C Evian[2] list tuberculosis, diarrhoea, Pneumocystis carinii infection, lymphoma or HIV infection itself as common causes for weight loss. Weight loss is therefore often seen as a sign of an underlying opportunistic infection or a sign of advanced HIV infection.

Other HIV-related textbooks mention more factors which may also be involved in causing weight loss in HIV patients[4, 28]. These factors may include malabsorption associated with infective diarrhoea, increased metabolic rate, decreased intake due to anorexia, oropharyngeal or esophageal disease, economic reasons for unavailability of food and drug or alcohol abuse.

Wheeler et al.[29] conducted a community-based cohort study of 2 382 HIV-infected adults with all participants having a CD4 count of <500 cells/mm^3. The study concluded that mild (less than 5%) or moderate (5% to 10% of body weight over a 4-month period in study) weight loss in an HIV-infected patient was predictive of decreased survival and a risk of developing an opportunistic complication.

2.2.4 Co-morbidities

The incidence of opportunistic infections after the initiation of HAART in advanced Aids patients with very low CD4 cell counts is high. Immune reconstitution inflammatory syndrome (IRIS) could explain why this is observed. Two forms of IRIS are discussed in literature reviewed. The first one mentioned is where an immune-suppressed individual is unable to respond to an opportunistic infection, then after the initiation of HAART an inflammatory immune response occurs against the pathogen and resulting in worsening of the clinical condition of the patient also referred to as “unmasking”. The second form mentioned in the literature referred to as “paradoxical” is when deterioration in clinical condition is observed due to a raised inflammatory response to an antigen that was treated or controlled[30].

A prospective multicentre study was conducted by Sungkanuparph et al.[31] to investigate the incidence and spectrum of opportunistic infections after the initiation of HAART in advanced Aids patients with very low CD4 cell counts. Sixty patients with successful HAART treatment, which raised the median CD4 cell count from 9 to168 cell/µl at 48 weeks, were studied. The study found that tuberculosis was the most common opportunistic infection in the populations studied. Other opportunistic infections were Mycobacterium Avium complex infection, relapsed cryptococcal meningitis, herpes zoster, toxoplasmosis and herpes genitalis.

Koenig et al. analysed mortality among 201 patients with Aids and tuberculosis in Haiti[32]. They found that patients who received a diagnosis of tuberculosis during the first 3 months after the initiation of antiretroviral therapy were 3,25 times more likely to die than other patients with Aids and tuberculosis. It was concluded that failure to recognise active tuberculosis at initiation of antiretroviral therapy lead to increased mortality. Therefore, active TB that is not recognised when ART is started may, in part, explain the high mortality rate observed among patients with Aids in resource-poor settings.

2.2.6 Age

Most of the epidemiological features of older HIV-infected patients were determined before the introduction of HAART in 1996. Since then HAART has been reported to have a "less beneficial effect on the immunological outcome in older patients"[33]. A study conducted by Adler et al.[34] on HIV infection and aging describes mechanisms to explain the accelerated rate of progression in the older patient and Operalski et al.[35] on the influence of age, viral load and CD4+ count in the rate of progression of HIV-1 infection to Aids. Both showed older individuals to have a more severe HIV disease course and a shorter survival rate.

In contrast to the studies done by Adler et al. and Operalski et al. recent studies (during the HAART era) showed that despite a higher risk of adverse events in older patients, high therapy adherence and a successful immunological response in older patients lead to a disease outcome comparable to that of younger patients. Such recent studies include the retrospective observational cohort study conducted by Silverberg et al.[36], in which changes in HIV clinical markers after HAART initiation were compared among 2 259 patients aged 18 to 39 years (reference group), 1 834 patients aged 40 to 49 years, and 997 patients 50 years or older enrolled in an integrated health care system. Another recent study is the prospective case-control study done by Tumbarello et al.[33] on older HIV-positive patients in the era of HAART which showed that older patients under

HAART experienced a successful immunological response comparable to younger individuals.

Although the size of the study population and the follow-up time of these studies differed considerably, the outcomes were the same, and thus the conclusion is that age is not a predictor of poor outcome on HAART.

2.3 Optimal criteria for initiation of HAART

The decision of when to initiate HAART is very important. On the one hand it may be important to start treatment before clinical signs of immunodeficiency develop but on the other hand it is important not to expose individuals to costly treatment with possible severe adverse if not needed.

In 2000 Ormaasen et al.[37] conducted an observational study at the Ulleval University Hospital in Oslo Norway on 162 treatment naïve Norwegian patients. The objective was to identify optimal starting criteria regarding levels of CD4 cells and HIV(RNA) at initiation of HAART in chronically HIV-infected people. They concluded, with very low confidence that CD4 count alone should influence the decision of when to initiate HAART in asymptomatic patients. Their results indicated that to delay treatment until CD4 drops below 0.2 x 10^9 cells/l in asymptomatic patients, is advisable. These results were contradicted by an observational study done by Kaplan et al. [38].

Given the fact that "observational studies are low in the hierarchy of evidence, the ideal study to answer the question of 'when to start' would be a randomised control study, but the feasibility of such a trial may be limited by the willingness of patients and providers to participate and the sample size and length of time required to conduct a meaningful study". For this reason Kaplan et al.[38] conducted an observational in 2003 and 2 729 patients were included in this analysis. They concluded that patients with low CD4 counts (<200 cells/ul) when HAART was initiated were at higher risk of progression to Aids or death and did

not experience the same clinical benefit as patients receiving treatment earlier (CD4 count 200-349 cells/ul).

They suggest a discussion with patients whose CD4 count is between 200-349 cells/ul and initiation of HAART is considered. The decision maker should take into account uncertainties regarding disease progression, development of drug toxicities, emergence of antiretroviral drug resistance and impact on quality of life.

Wood et al.[22] commented in 2003 that therapeutic guidelines advise that 200-350 $x10^6$ cell/l may approximate an irreversible threshold beyond which response to therapy is compromised. They conducted an observational study of 1 416 treatment naïve Canadian patients who initiated triple therapy between 1996 and 2000 to evaluate whether non-immune-based factors, such as physician experience and adherence, could affect survival among HIV-infected adults starting HAART. Their results showed improved survival rates following HAART initiation among patients with starting CD4 counts < 200 x 10^6 cells/l, once adjusted for physician experience and patient adherence. Inappropriate care of patients with advanced disease and patient non-adherence may be the strongest determinants of patient survival according to this study. This supported the initiation of HAART for patients with CD4 counts < 200 x 10^6 cell/l. Current South African department of health guidelines use CD4 counts of < 350.

2.4 Adherence

As mentioned previously, the Khayelitsha ARV treatment project was initiated to demonstrate that HAART in the primary health care setting and in resource limited settings is feasible and replicable[21].

This programme used a patient selection process and patients were eligible for treatment if they were WHO stage III and IV and had a CD4 count of less than 200. Adherence to co-trimoxazole prophylaxis, TB treatment and regular clinic

attendance were used to assess ability to adhere to HAART. A home visit was also done before initiating HAART to assess the family environment and for disclosure. Progress was monitored weekly for the first two weeks, then two-weekly up to the end of the second month and thereafter monthly.

Factors included in this programme to further improve adherence were that patients had to have a treatment assistant who was someone living in the household, aware of the patient's status and willing to assist with medication if necessary. Individuals on HAART had to attend twice-monthly support groups and patients were also supplied with pill boxes, drug identifications charts, daily schedules, diaries and education material explaining the risks and benefits of HAART. They found that when simplified regimens with a low pill burden and a comprehensive individual support programme were combined, patients showed high levels of adherence to the medication.

Park et al.[23] conducted an observational cohort study in South Korea to evaluate whether one-year adherence to clinic visits after highly active antiretroviral therapy could be a predictor of clinical progress in HIV patients. The authors showed in their study that in the year after HAART was initiated, the number of missed clinic appointments and the next clinic visit were significant risk factors for occurrence of subsequent Aids defining illness or death. When the total number of days that elapsed between missed appointments were >30 days, the risk of Aids progression was increased. Furthermore adherence to clinic visits was associated with clinical improvement irrespective of clinical category pre-HAART.

Friedland et al.[39] suggest that an unexplored strategy is to integrate HIV/AIDS and tuberculosis care and treatment, including highly active antiretroviral therapy, through existing tuberculosis directly observed therapy programs. This strategy could potentially improve the outcome for both diseases by addressing the related issues of inadequate access and infrastructure and the need for enhanced adherence to medication. "HAART by direct observed treatment

(DOT)" becomes more practical due to the availability of potent once-daily regimens. Where HAART by DOT was implemented in special community based care programs it showed promising results.

Farmer et al.[40] implemented HAART by DOT in Haiti showing great promise. Each patient was assigned to a community- health worker who observes the ingestion of medication, responds to the patient's and family concerns being in a supportive role. Monthly meetings where patients discuss their illness were also implemented with great success.

2.5 Conclusions

Different studies of different study types, size and locations (resource limited as well as unlimited) were reviewed. Although the studies differed with regards to these aspects, the conclusions were similar making the results relevant to the South African setting as well as to my study.

The literature reviewed indicates that the following predictors negatively influence the outcome of patients started on HAART:

- Chronic diarrhoea, rapid weight loss or wasting;
- The presence of co-morbid conditions;
- TB, acute bacterial infections, malignancies and immune reconstitution disease;
- Poor performance status;
- Anaemia;
- Poor adherence; and
- Very low CD4 count

Age in itself is found not to be a predictor of poor outcome of HIV patients on HAART. Under ideal circumstances even patients with very low CD4 counts can do well on HAART.

However, further studies on this topic are recommended as the field of HIV medicine is a rapidly changing field and with HAART becoming more easily accessible the findings of the studies reviewed may well be supported or found not to be supported by newer or ongoing studies.

CHAPTER 3 – DATA AND METHODOLOGY

3.1 Study design

A retrospective cohort study to investigate the influence that certain identified factors has on mortality of HIV-positive patients on HAART.

3.2 Study site

All the data analysed come from the records of patients attending the HIV Clinic at Tshwane District Hospital (TDH) in Pretoria, Gauteng Province, South Africa.

3.3 Study population

Selection criteria

Inclusion criteria:

- Patients started on HAART at TDH HIV clinic from June 2004 up to and including June 2009
- Patients older than 18 years of age

Exclusion criteria:

- Patients younger than 18 years of age

3.4 Sampling design

3.4.1 Sampling frame and procedure

The target population for this study includes HIV-infected patients who started on HAART at the TDH HIV clinic during the period June 2004 to June 2009. According to medical records from TDH, a total of 5 870 valid charts/records were available from which data of 699 files were extracted for statistical analysis and predictive model building.

A systematic random sampling method was employed for the selection of a representative sample, sampling every 10th patient file. Each patient has a chart/record with a unique and distinctive identification number which was used for identifying patients.

3.4.2 Sample size

Ibrahim (2007), having conducted a study to evaluate the factors affecting the chance of survival/death status among HIV-positive people under a antiretroviral treatment programme at Adama Hospital located in Addis Ababa, Ethiopia, rightfully remarked that the selection of an appropriate sample size is an important decision to make, as a "too large sample implies a waste of resources while a too small sample reduces the usefulness of the results"[41]. Ibrahim (2007) furthermore noted that "in order to have an optimum sample size, there are a number of issues/points one has to take into account. Some of the issues are:

- Objective of the research
- Design of the research
- Cost constraint
- Plan for statistical analysis
- Degree of precision required for generalisation
- Degree of confidence required"[41]

Accordingly, Ibrahim[41] (2007) proposed the use of the following formula for sample size determination:

$$n_0 = \frac{Z_{\frac{\alpha}{2}}^{\ 2}\, p(1-p)}{d^2}$$

Where n_0 is the sample size, p the population proportion of death and d is the absolute precision defined as:

$$d = z_{\frac{\alpha}{2}} SE$$

SE is the standard error.

And if the sampling is from a finite population of size N, then:

$$n = \frac{n_0}{\left(1 + \frac{n_0}{N}\right)}$$

Using the following parameters for this study, the sample size is calculated as:

N = 5870
Proportion of death (*p*) = 7%
Absolute precision required (*d*) = 3%
Sample size (*n*) = 265

3.5 Data collection

3.5.1 Data collection tools

Data collection was done by using a data extraction sheet. The data extraction sheet was designed in Microsoft Access and automatically imported data into an Excel spreadsheet. The data extraction sheet had built-in validations, drop-down menus with the appropriate choices and automatic calculations from the identification number (date of birth and age). Refer to Appendix 2. This sheet was developed from discussions with colleagues (including the Head of the HIV Clinic at TDH), in consultation with the research supervisor and from a literature review on possible predictors of outcome.

The variables or factors were recorded in the tool (Appendix 6).

3.5.2 Data collection method

Before data were collected, approval from the following persons and departments was obtained:

- The Head of the HIV Clinic at TDH (appendix 3)
- The CEO at TDH (appendix 4)
- Human Research Ethics Committee approval from the University of Cape Town and the University of Pretoria (Research Ethics Committee of the Health Science Faculty). (Appendix 5)

Patient confidentiality was ensured by using locked cabinets to store information, not making the patients identity public and by using a secure numerical system only known to the researcher. Patients' names and file numbers have no correlation with the study number. The information required was recorded, by the patient, in a Microsoft access database. All data used for the statistical sampling was extracted without any fields that could potentially identify any patient, for example the identity number, name or surname. The master file was in the possession of the researcher and all cross referencing was done by the only researcher.

The researcher, with the help of one field worker, collected data from every tenth file of the patients (fitting our selection criteria) started on HAART since June 2004. All the patient records were available in the clinic itself. The field worker was trained to use the data extraction sheet correctly and to use the numerical system to ensure confidentiality. The electronic data extraction sheet had built-in validations to limit human error while collecting data.

ID numbers of patients lost to follow-up were used to trace public records on the website of the department of home affairs to determine whether the patient was still alive or not. Records of patients who had died were further investigated at the department of home affairs to see if they had died of natural causes and what the date of death was.

3.6 Data analysis

3.6.1 Model building

In order to build a statistical model to predict the outcome of HAART, based on the data available, logistic regression is proposed. Logistic regression is useful for situations in which you want to be able to predict the presence or absence of a characteristic or outcome based on values of a set of predictor variables. Although other multivariate techniques like multiple regression and discriminate analysis can also be used, it is best suited to models where the dependent variable is dichotomous (Norušis[42], 1994). Norušis also remarks that logistic regression requires far fewer assumptions than discriminant analysis, and even when the assumptions for discriminant analysis are satisfied, logistic regression still performs well[42].

The logistic model is written as follow:

$$\text{Prob(event)} = \frac{1}{1+e^{-z}}$$

Where $z = b_0 + b_1x_1 + b_2x_2 + \ldots b_px_p$

The logistic equation can be rearranged into a linear form by converting the probability into a log odds.

$$\log [\text{Prob(event)}/\text{Prob(no event)}] = b_0 + b_1x_1 + b_2x_2 + \ldots b_px_p$$

The dependent variable for the model will be survival status, where 1 = death and 0 = alive. The independent variables were defined from the other data extracted from patients' records.

The model building involved three steps. The first step involved the evaluation of single variables for inclusion in the model. This was done from the viewpoint of assessing the adequacy of each variable in terms of its statistical relationship with the dependent variable as well as its potential contribution to the overall fit of the model. Analyses involved in this phase involved constructing of univariate tables, cross tabulations and significant tests of independent variables with the dependent variable in order to study variation in the data.

The second step involved the construction of the statistical predictive model, in other words the logistic regression model.

The final step was evaluation of the model by looking at its predictive capabilities. This step also involved evaluation of diagnostic coefficients.

CHAPTER 4 – RESULTS

4.1 Introduction

This study set out to address three research objectives, namely (1) to identify factors/variables that statistically explain variation in CD4 count amongst immune suppressed patients; (2) to identify factors that predict the outcomes of HAART in immune suppressed patients; (3) to determine the correct mortality rate amongst lost to follow-up patients.

Chapter 4 presents the results obtained from the analysis pertaining to each of the objectives.

4.2 Results regarding the objectives

The outcomes of the statistical analysis are reflected under the relevant sub-headings below.

4.2.1 Identify variables that explain variation in CD4 count

The first objective aimed to identify those demographic, general health-risk behaviour (smoking and alcohol use) and health variables that statistically explain variation in CD4 count. For the purpose of the analysis and to align with clinical relevance, patients were categorised into two groups, namely those with a CD4 count up to 50 and those with a count of more than 50. The first group consisted of 87 patients and the second of 416. The results of the analysis are presented in tables 4.1 to 4.3. Both Chi-square Test of Independence and Mann-Whitney tests (for two independent samples) were performed.

4.2.1.1 Demographic variables

Inspection of the results show a significant difference in the proportional distribution of gender (p=0.004) by CD4 count, with a significant higher

proportion of females in the second group (CD4>50) than in the first (CD4<50). Conversely, the first group consisted of more males than the second group. The results also show significant differences in the mean weight recorded (p=0.000) between the two groups.

Table 4.1: Significant tests on demographic variables by CD4 count

DEMOGRAPHIC	CD4 <50 n = 87	CD4 50+ n = 416	p-value	Sig.
Gender				
Male	43.7%	28.1%		
Female	56.3%	71.9%	0.004	**
Age				
Mean	39.3	39.4	0.801	-
Race				
Black African	96.6%	96.2%		
Other	3.4%	3.8%	0.859	-
Education				
No education	26.4%	88.5%		
Grade 0-5	5.7%	9.9%		
Grade 6-7	11.5%	8.2%		
Grade 8-12	52.9%	55.5%		
Post Matric	3.4%	6.3%	0.328	-
Marital status				
Single	72.4%	68.8%		
Married	17.2%	20.7%		
Divorced/Widowed	10.3%	10.6%	0.754	-
Employed				
Yes	48.3%	49.5%		
No	51.7%	50.5%	0.833	-
Weight (kg)				
Mean	57.0	62.9	0.000	***

Signifcance levels

- \- Not signifcant
- * p<0.05
- ** p<0.01
- *** p<0.001

4.2.1.2 Risk behaviour variables

The results from the Chi-square tests presented in table 4.2 show that CD4 count does not have any statistical relationship with the two general health risk-behaviour variables (smoking and alcohol use).

Table 4.2: Significant tests on risk behaviour variables by CD4 count

RISK BEHAVIOUR	CD4 <50 n = 87	CD4 50+ n = 416	p-value	Sig.
Smoker				
Yes	10.3%	8.7%		
No	58.6%	56.3%		
Unknown	31.0%	35.1%	0.724	-
Alcohol use				
Yes	11.5%	8.2%		
No	58.6%	56.5%		
Unknown	29.9%	35.3%	0.452	-

Signifcance levels
- \- Not signifcant
- * p<0.05
- ** p<0.01
- *** p<0.001

4.2.1.3 Health variables

Four of the health variables showed significant differences between the two CD4 groups, namely viral count (p=0.000), hemoglobin (p=0.000), AST (p=0.001) and ALT (p=0.016). Significant only on a 90% level of confidence, TB (p=0.073) can also be regarded as explaining some variation on CD4 count.

Table 4.3: Significant tests on health variables by CD4 count

HEALTH VARIABLES	CD4 <50 n = 87	CD4 50+ n = 416	p-value	Sig.
Viral Load				
Mean	415,331	200,214	0.000	***
Serum albumin				
Mean	8.5	11.1	0.695	-
Hemoglobin				
Mean	11.1	13.5	0.000	***
Platelet count				
Mean	250.7	243.6	0.920	-
AST				
Mean	66.7	43.2	0.001	**
ALT				
Mean	46.2	31.6	0.016	*
HIV Status Disclosed				
Yes	39.1%	41.6%		
No	13.8%	11.1%		
Unknown	47.1%	47.3%	0.749	-
TB				
Yes	31.0%	20.0%		
No	44.8%	53.4%		
Unknown	24.1%	26.7%	0.073	-
WHO Stage Record				
Yes	36.8%	31.5%		
No	63.2%	68.5%	0.338	-

Significance levels

- Not significant
* p<0.05
** p<0.01
*** p<0.001

4.2.2 Identify factors that predict the outcomes of HAART

For the second objective, logistic regression was used to explore the association between the proposed independent variables and the response variable. The response variables or death status was coded as follows: 1 indicates that the patient died while on HAART and 0 indicates survival of the patient.

Inspection of the data reveal that the overall proportion of death while on HAART is low (Y = 5,4%). This may affect the predictive capabilities of the model. It is therefore with this understanding that the univariate and multivariate analyses are made in this study.

The first step in the analysis involves examining the relationship between the response variable and predictor variables. The results are presented in tables 4.4 to 4.6.

4.2.2.1 Demographic variables

Inspection of the results shows that across employment (p=0,036), a significantly higher proportion of death cases were recorded among unemployed patients (7,5%) than among employed patients (3,2%). The results also show significant differences in the mean weight recorded (p=0,013) between the response groups, with a lower average weight associated with death cases.

For all other variables, the proportion of deaths recorded did not differ significantly.

Table 4.4: Significant tests on demographic variables by status

DEMOGRAPHIC		Status Alive	Status Dead	p-value	Sig.
Gender					
Male	n = 155	94.2%	5.8%		
Female	n = 348	94.8%	5.2%	0.771	-
Age					
Mean	n = 503	39.3	40.6	0.535	-
Race					
Black African	n = 484	94.6%	5.4%		
Other	n = 19	94.7%	5.3%	0.984	-
Education					
No education	n = 107	94.4%	5.6%		
Grade 0-5	n = 46	95.7%	4.3%		
Grade 6-7	n = 44	90.9%	9.1%		
Grade 8-12	n = 277	94.6%	5.4%		
Post Matric	n = 29	100.0%	0.0%	0.566	-
Marital status					
Single	n = 349	94.8%	5.2%		
Married	n = 101	95.0%	5.0%		
Divorced/Widowed	n = 53	92.5%	7.5%	0.756	-
Employed					
Yes	n = 248	96.8%	3.2%		
No	n = 255	92.5%	7.5%	0.036	*
Weight (kg)		n = 476	n = 27		
Mean		62.3	55.6	0.013	*

Signifcance levels

- \- Not signifcant
- * p<0.05
- ** p<0.01
- *** p<0.001

4.2.2.2 Risk behaviour variables

For both risk behaviour variables, the proportion of deaths recorded did not differ significantly.

Table 4.5: Significant tests on risk behaviour variables by status

RISK BEHAVIOUR		Status Alive	Dead	p-value	Sig.
Smoker					
Yes	n = 45	91.1%	8.9%		
No	n = 285	94.0%	6.0%		
Unknown	n = 173	96.5%	3.5%	0.283	-
Alcohol use					
Yes	n = 44	93.2%	6.8%		
No	n = 286	93.7%	6.3%		
Unknown	n = 173	96.5%	3.5%	0.388	-

Signifcance levels
- \- Not signifcant
- * p<0.05
- ** p<0.01
- *** p<0.001

4.2.2.3 Health variables

Three of the health variables showed significant differences between the two response groups, namely CD4 count (p=0,001), viral count (p=0,025) and hemoglobin (p=0,000). AST (p=0,051) could be considered significant at a 90% level of confidence. For all other variables, either the proportion of deaths recorded did not differ significantly or no significant differences were evident in the average counts recorded.

Table 4.6: Significant tests on health variables by status

HEALTH VARIABLES		Status: Alive	Status: Dead	p-value	Sig.
CD4		n = 476	n = 27		
Mean		183.1	125.4	0.001	**
Viral Load		n = 476	n = 27		
Mean		220,355	538,285	0.025	*
Serumalbumin		n = 476	n = 27		
Mean		10.9	7.7	0.976	-
Hemoglobin		n = 476	n = 27		
Mean		13.2	9.6	0.000	***
Platelet count		n = 476	n = 27		
Mean		243.3	270.7	0.806	-
AST		n = 476	n = 27		
Mean		45.8	72.6	0.051	-
ALT		n = 476	n = 27		
Mean		33.4	46.6	0.647	-
HIV					
Yes	n = 207	93.2%	6.8%		
No	n = 58	93.1%	6.9%		
Unknown	n = 238	96.2%	3.8%	0.326	-
TB					
Yes	n = 110	92.7%	7.3%		
No	n = 261	93.9%	6.1%		
Unknown	n = 132	97.7%	2.3%	0.167	-
WHO Stage Record					
Yes	n = 163	92.6%	7.4%		
No	n =340	95.6%	4.4%	0.169	-

Signifcance levels

- Not signifcant
* p<0.05
** p<0.01
*** p<0.001

A problem with any univariate analysis approach is the fact that it ignores the multivariate predictive capabilities of a collection of weakly associated independent variables. In other words, a single variable might be weakly associated with the response variable, but when combined with other variables it can become an important predictor. For the logistic regression a forward stepwise likelihood ratio method was used to select variables.

The results from the logistic regression are presented in table 4.7. Only the weight variable was included as a predictor of death status. According to the equation a decrease in the weight of a patient by one unit (kg) increases the odds of death by 0,952.

Table 4.7: Variables in the logistic regression equation

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a] weight_kg	-.049	.004	193.987	1	.000	.952

a. Variable(s) entered on step 1: weight_kg.

Inspection of the classification table, however, reveals that overall the logistic equation can not be regarded as a sufficient model for predicting the outcomes of HAART as none of the death cases could be correctly predicted.

Table 4.8: Diagnostics – Classification table

Classification Table[a]

Observed			Predicted		
			Status		Percentage Correct
			Alive	Dead	
Step 1	Status	Alive	476	0	100.0
		Dead	27	0	.0
	Overall Percentage				94.6

a. The cut value is .500

4.2.3 Determine the correct mortality rate amongst lost to follow-up patients

The results show that amongst patients that were lost to follow-up, the mortality rate was 39%. This can be contrasted against the mortality rate for the patients attending the ARV clinic of 5,4%

Table 4.8: Mortality amongst lost to follow-up patients

		n	%
Death status:	Alive	43	61.4%
	Dead	27	38.6%
Total		70	100.0%

4.2.4 Risk of death

The risk of death for patients with a low CD4 is illustrated in table 4.9 and tested for differences.

Table 4.9: Risk of Death for Patients with low CD4 count

CD4 * Death status: Crosstabulation

			Death status:		
			Alive	Dead	Total
CD4	<50	Count	74	13	87
		Expected Count	82.3	4.7	87.0
		% within Death status:	15.5%	48.1%	17.3%
		% of Total	14.7%	2.6%	17.3%
	50+	Count	402	14	416
		Expected Count	393.7	22.3	416.0
		% within Death status:	84.5%	51.9%	82.7%
		% of Total	79.9%	2.8%	82.7%
Total		Count	476	27	503
		Expected Count	476.0	27.0	503.0
		% within Death status:	100.0%	100.0%	100.0%
		% of Total	94.6%	5.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	18.985[b]	1	.000		
Continuity Correction[a]	16.774	1	.000		
Likelihood Ratio	14.594	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	18.947	1	.000		
N of Valid Cases	503				

a. Computed only for a 2x2 table

b. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.67.

CHAPTER 5 – DISCUSSION

5.1 Introduction

The aim of this retrospective study was to identify factors that may predict mortality of individuals started on HAART and to formulate a guideline to assist health care workers to identify and better support patients at higher risk in a resource limited setting.

Since the introduction of HAART, HIV has become a chronic illness with an unpredictable course. The factors studied showed little value as predictors of outcome but may highlight patients at higher risk and assist health care workers to plan their treatment accordingly.

5.2 Identifying variables associated with low CD4 count

The following factors could explain variation in CD4 count as they were more prominent in the patient group with CD4<50.

5.2.1 Demographic variables

5.2.1.1 Male gender

More male patients were found in the CD4 <50 group which drew our attention to the possibility that more male patients presents late.

These findings are consistent with other studies[43, 44] which report that HIV-infected men present later for care than women and are therefore at greater risk of an adverse clinical course. Men delay seeking health care and have poorer clinical outcomes due to lower CD4 counts because of their late presentation. “The fact that women seek care earlier, or are identified earlier might be due to the fact that women are more likely to be tested earlier for HIV at an antenatal clinic or by a health-care provider they have visited to seek treatment for a dependent. Moreover, research suggests women seek care promptly because

they are the primary caregivers and feel a greater responsibility for remaining healthy"[43].

A cross-sectional survey of 129 patients in Venezuela found the main barriers to HIV testing, and therefore late presentation, to be "low knowledge of HIV/Aids, lack of awareness of the free HIV programme, lack of perceived risk of HIV-infection, fear for HIV-related stigma, fear of lack of confidentiality at testing site and logistic barriers". This study also found that heterosexual males to presented late compared to homosexual males and females[44].

These concerns should be addressed by treatment programmes and programmes adapted accordingly. Some health care providers have altered their clinic times so that patients do not need to take time off work to attend health care facilities. There is also merit in having clinics at the work place but the fear of stigmatisation should be addressed and confidentiality ensured. Home-based care programmes can also be of great value, because part of the service is to identify other ill patients in the household and educate the family, hoping to promote awareness and prevent late presentation.

5.2.1.2 Low body weight

The literature reviewed observes that weight loss has been described in many patients with advanced HIV infection. From the statistical analyses the conclusion was drawn that the patients in the CD4 <50 group had a lower mean body weight. The literature further indicates various reasons for decrease in body weight which include: malabsorption associated with infective diarrhoea, increased metabolic rate, decreased intake due to anorexia, oropharyngeal or esophageal disease, economic reasons for unavailability of food and drug or alcohol abuse.

This indicates the need to do routine weight monitoring and recording at each follow-up visit so that unexplained or ongoing weight loss can be identified and further evaluated and underlying causes treated appropriately.

Interventions to combat weight loss advise “frequent small meals with high energy-foods such as porridge, potato and rice. A high protein diet should be encouraged, including eggs, milk, lentils, meat and fish”. Nutritional support programmes to provide patients with commercial high-energy and calorie preparations as food supplements also have a positive effect on weight loss management[2].

Patients should be encouraged to eat a variety of food and include fresh fruits and vegetables in their daily diet. Community projects, such as food gardens, can have a valuable effect on nutrition. It should be emphasised that good nutrition and vitamin supplementation are advised alongside, not instead of HAART.

5.2.2 Risk behaviour variables

As this is a retrospective cohort study where the data reviewed came from patients attending the HIV clinic, only data that were available in the records could be analysed. The records indicated only two risk behaviour factors, smoking and alcohol use, which are general health risk factors. No sexual history was available and therefore could not be included in this study. The literature showed alcohol abuse to affect prognosis negatively in patients with HIV, one reason mentioned is nutrition associated with alcohol abuse. Alcohol abuse can also have a negative impact on adherence and therefore needs to be screened for before initiating HAART. The risk factors that were analysed showed no association with CD4 count statistically.

5.2.3 Health variables

5.2.3.1 Anaemia

From the literature the question is asked whether anaemia is a marker of progressive HIV disease or not. Most studies concluded that anaemia is associated with a significant increased risk of death.

Various etiologies could explain the anaemia, including: mycobacterium infections, parvovirus B19, micronutrient deficiencies, immunological myelosuppression, impaired erythropoietin production and blood loss from intestinal opportunistic disease. Most of the etiologies mentioned are seen in patients with advanced HIV. From the analysis done in this study the mean hemoglobin in the patients with CD4 count <50 (advanced HIV disease) were found to be 11,1 mmol/l. This means hemoglobin is not as low as expected in the context of poverty, malnutrition and chronic illness. The reason for this can be that this is an urban population study group with probably had adequate nutrition and general health before becoming HIV-positive.

The identification and treatment of anaemia can have a significant positive effect on patients' treatment outcome. Various opportunistic infections are mentioned as causes for anaemia and when treated correctly can decrease the burden of disease and positively influence the outcomes of HAART. Therefore health care workers should aim to identify the underlying etiology and treat patients accordingly.

5.2.3.2 High viral count

According to the literature, "a high viral count (RNA viral load quantification) indicates very active HIV disease and rapidly rising levels predict more rapid development of immune-deficiency"[45]. A higher viral count means a greater onslaught on the patient's immunity. Therefore this study's findings showing high

viral counts in patients with lower CD4 counts, correlates with literature on the subject and is seen as a risk factor for poor outcome.

The use of HAART is a treatment modality aimed at stopping the progression of HIV disease by reducing the HIV viral load and thereby allowing for recovery of the immune system and subsequent reduction of HIV-related illness[4]. Viral load is also one of the follow-up markers to determine whether patients are responding to HAART.

5.2.3.3 High AST and ALT levels

Minor abnormalities of liver function tests (enzymes up to 3 times normal levels) are a common finding in patients with lower CD4 counts. The etiologies mentioned in the literature are malnutrition, an acute phase response and alcohol. If, however, "the ALT and AST is raised more than 3 times normal levels, other etiologies should be investigated like drug toxicity, viral hepatitis, other viral infections or liver involvement by other opportunistic infections"[46]. The finding of raised liver enzymes in the patients with severe immune suppression is therefore not surprising and can aid health care workers in suspecting and identifying co-morbidities in patients with severe immune suppression. These patients should then undergo further special investigations and should then be treated according to the results.

A baseline liver function can assist the health care professional to monitor patients for possible liver toxicity as a result of most drugs used in the treatment of HIV-related illness or HAART.

5.3 Identifying factors that predict an increased risk of mortality

Factors that may play a role in predicting the outcome of patients started on HAART, include demographic variables, risk behaviour variables and health variables.

5.3.1 Demographic variables

5.3.1.1 Unemployment

Unemployment is used as a marker of economic status. Patients may be unemployed due to illness with inadequate unemployment benefits or it may be difficult to find employment once the patient's health status has improved due to the high unemployment rate in South Africa.

A lack of income has various influences on disease progression. Firstly this group of patients has a higher risk of poor nutrition, which is also seen as a possible predictor of poor outcome on HAART. Secondly these patients may experience difficulties with transport which can lead to poor adherence and follow-up. Thirdly, living conditions may be hazardous and predispose patients to certain infections, like gastro-intestinal infections and tuberculosis. Assessing a patient's risk profile can lead to prevention of poor outcome of treatment by adjusting their treatment care plan and enhanced treatment support according to their needs.

There is also the hypothesis that lower educational level may influence your understanding of the particular illness and therefore negatively influence treatment adherence. From this study no significant statistical correlation between educational level and poor outcome was shown.

5.3.1.2 Low body weight

The literature review showed evidence that weight loss in HIV-infected individuals to be predictive of decreased survival and increased their risk for developing opportunistic infections. The statistical analysis also showed a lower average weight associated with death cases. As previously mentioned this highlights patients at risk and can assist health care workers to plan interventions accordingly.

5.3.2 Risk behaviour variables

As mentioned in the literature review, an article by Palella et al.[15] described the presence of co-morbid conditions, such as substance abuse and addiction as poor prognostic factors. Although no data were available on sexual risk behaviour, the general health variables (smoking and alcohol use) were included in this study. No statistical correlation was found between the risk behaviour mentioned and the outcome on HAART in this study.

5.3.3 Health variables

5.3.3.1 Anaemia

From the literature anaemia was found to be one of the clinical manifestations of auto-immunity and one of the most common hematological abnormalities affecting 70-95% of HIV-positive individuals. An association with increased risk of death was also found.

The mean hemoglobin found from this analysis of data was 9,6 mmol/l in the patient group classified dead. The group classified alive had mean hemoglobin of 13,2 mmol/l. The difference is statistically significant and shows an association between anaemia and increased risk of death.

5.3.3.2 Low CD4 count

The CD4 count is known for being a “marker of the state of immunity in patients with HIV infection and a good indicator of the risk for acquiring HIV-related opportunistic infections and other immune-deficiency disorders”[45]. The low CD4 count correlates with an increase in immune suppression[46]. It is therefore also a possible predictor of outcome of HAART according to this study. Analysis of the cases reviewed in this study correlated with the literature.

5.3.3.3 High viral count

Viral load is a reliable predictor of disease progression and poor prognosis in HIV according to the relevant literature on the subject and predicts how rapidly the immune system will deteriorate. After the initiation of HAART it is a useful tool to evaluate the efficacy of treatment[45]. The possibility of predicting outcome of HAART pre-treatment is suggested from our statistical analysis but not concluded.

Due to the overall low mortality rate of 5,4%, these factors (unemployment, low body weight, low hemoglobin, low CD4 count and high viral load), as discussed above, did not show to have any statistically significant predicting value for mortality.

5.4 Determine correct mortality rate among lost to follow-up patients

Bisson et al. analysed a large public antiretroviral therapy programme in sub-Saharan Africa and documents that of the total enrolled patients 16.6% was lost to follow up soon after initiating HAART. The lost to follow up patients has a mortality rate of 58.8%[19].

The analysis showed a 39% mortality rate among lost to follow-up patients in this study. We are left with the question of whether these patients died after initiation of HAART, before the next follow-up appointments, or subsequent to them defaulting treatment. The other 61% of the lost to follow-up patients is of concern because the question is asked whether they defaulted treatment or whether they are receiving treatment at other facilities. Further studies could cast some light on this subject and help health care providers to improve follow-up care. Lost to follow-up data could assist health care workers in assessing adherence to treatment. The high mortality rate among these patients highlights the need to identify patients at risk early and adjust follow-up care accordingly. Strategies that can be looked at may be a DOT (direct observed treatment programme) system for HIV, as for TB. Home-based care may also assist to better monitor patients at risk.

5.5 Limitations of the study

This study only focuses on urban patients receiving care and HAART at Tshwane District Hospital's ARV clinic.

This is a retrospective cohort study which utilised patient records to obtain data and poor and incomplete data recording limited the analysis. This was most prominent with regard to risk behaviour where the patient records only had information on smoking and alcohol use, no sexual history was available. Further due to the design of this study the analysis is done at a specific point in time not allowing time for follow-up data to show statistical significance.

Given the low mortality rate of patients started on HAART among the study subjects, the study was under-powered to determine factors associated with death.

A univariate analysis approach was followed. The limitation of such an analysis approach is the fact that it ignores the multivariate predictive capabilities of a collection of weakly associated independent variables. In other words, a single variable may be weakly associated with the response variable, but when combined with other variables it can become an important predictor.

5.6 Suggestions for future research

To improve future research studies and the building of predictive statistical models, it is imperative to ensure that accurate and complete record keeping (historical clinical information) takes place. It is also important to keep such records over a long period of time as this will improve reliability of studies still to be done. The researcher believes that the success of HAART also relies on the keeping of complete patient records to assist in the correct evaluation and management of patients.

Future research can focus on building a model using multivariate predictive capabilities of collection of variables.

Future studies can also look into the reasons patients are lost to follow-up.

CHAPTER 6 – CONCLUSION AND RECOMMENDATION

6.1 Conclusion

This study aimed to identify factors/variables that could explain the variation in CD4 count among severe immune suppressed patients. Male gender, low body weight, high viral count, low hemoglobin level, high AST and ALT levels explained some of the variation in CD4 count and were more prominent in the CD4 < 50 group.

Secondly this study aimed to identify factors that could predict the outcome of patients started on HAART. Factors that showed some significance were unemployment, lower body weight, a low CD4 count, high viral count and low hemoglobin level. Due to an overall low mortality rate of 5,4%, these factors did not show to have predicting value. HIV is a life-threatening illness with an unpredictable course. This low mortality rate shows that HAART is a very effective palliative treatment modality which has the potential to improve morbidity and prolong survival in patients with HIV.

The third objective of this study was to determine the correct mortality rate among lost to follow-up patients. It showed a 39% mortality rate among lost to follow-up patients. It is believed that better surveillance and follow-up care may further improve the outcome of patients initiated on HAART.

6.2 Recommendation

The high prevalence of HIV in sub-Saharan Africa calls for an extensive ARV programme. Our programme needs to focus on the work–up and assessment of HIV patients prior to HAART initiation and to better follow-up care. Strategies need to be developed to further enhance adherence once HAART as been initiated.

Health care workers/stakeholders will need to revise social support and follow-up care for patients in resource-poor settings with respect to improving their nutrition (poor nutrition was shown to have an influence on outcome of HAART) and possible assistance in general.

Patients, who have lower CD4 counts and weight at baseline with low hemoglobin, should be closely monitored and additional support may be needed, clinical and non-clinical (e.g. home-based care). A focus on more regular contact with health care workers to identify opportunistic infections and detect side-effect of HAART early, for patients identified as at risk could improve outcomes of patients on HAART.

Strategies that could be looked at may be a DOT (direct-observed treatment programme) system for HIV (as for TB) or home-based care may also assist to better monitor patients at risk. DOTs (directly-observed treatment short course) have been used to successfully deliver tuberculosis treatment in some of the world's poorest countries. "The main elements of DOTs include political commitment, case detection, standardised treatment with supervision and patient support, an effective drug supply and management system and a monitoring and evaluation system"[47].

Home-based care treatment could really make a difference in the care of HIV patients if successfully implemented and is based on the principles of good palliative care. The home-care based team should be coordinated by a professional nurse, assisted by trained community caregivers and other trained volunteers, with the support of the patient's doctor and other members of the interdisciplinary team who will be referred to as needed. The objectives of home visits should include the following: to introduce the HCW to the patient and family, explain the purpose of providing home care, make a holistic assessment of the patient and family, plan care and support (involving family in all the stages of planning), evaluate the educational and training needs of the patient and

family and plan to meet those needs, evaluate the need for human, material and social resources, identify actual and potential problems and develop realistic plans to alleviate these problems, assess whether or when patients need to be referred to other agencies, manage pain and other symptoms, identify children in distress, provide counselling for patients and family, ensure a safe environment for patient and family (including infection control), assist with bereavement after the patient's death, empower patient and family to become as independent as possible in aspects of care and self-care[48].

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APPENDIX 1 – CLINICAL FEATURES OF HIV DISEASE

Table 5.3: WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection (2006 revision)

Clinical Stage	Associated conditions
1	Asymptomatic Persistent generalized lymphadenopathy
2	Unexplained moderate weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections
3	Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhea for longer than one month Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8.g/dl), neutropaenia (<0.5 × 10^9 per litre) and/or chronic thrombocytopaenia (<50 × 10^9 per litre)
4 (AIDS-defining conditions)	HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi's sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis) Recurrent septicaemia (including non-typhoidal *Salmonella*) Lymphoma (cerebral or B-cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

APPENDIX 2 – DATA EXTRACTION SHEET

File Number

Identity Number

Date of Birth

Educational Level

Racial Group

Employment

Marital Status

Gender

Age

Weight

Smoker

Alcohol / Abuse

Drug Abuse

CD4 Count %

CD4 Count Cell/ul

WHO Clinical Stage Recorded

Stage

Viral Load

Viral Load Log

Serum-albumin

Hemoglobin Level

Platelet Count

AST

ALT

TB Status

Date initiation HAART

Dead

Date of death

Cause of death

Status Disclosure

Loss to Follow-up

Comment:

APPENDIX 3 – APPROVAL HEAD OF HIV CLINIC AT TDH

ARV Clinic, Tshwane District Hospital
Dr Savage Road, Gezina
Tel: (012) 354-5979
Fax: (012) 354-5979

commitment for life...

18 February 2009

To Whom It May Concern

RE: RESEARCH PROJECT: INVESTIGATION OF THE FACTORS THAT IMPACT ON OUTCOMES OF HAART IN PATIENTS WITH CD4<50CELLS/UL AT TSHWANE DISTRICT HOSPITAL

The above research protocol has been discussed with me. I approve of the study design and plan of implementation. As clinical head of the ARV Unit, I hereby give my permission that the research may be conducted at our clinic based in Tshwane District Hospital.

The clinic staff will give the researcher full access to all medical records, as stipulated by her research plan.

Yours truly

Dr TM Rossouw
MBChB, MPH
Clinic Head
ARV Clinic
Tshwane District Hospital
+27(0)12-354-5979

APPENDIX 4 – APPROVAL CEO OF TDH

Updated 28-02-2007

Permission to access Records / Files / Data base at
Tshwane District Hospital Hospital / Clinic

TO: MRS O. I. UBOGU [Name]
Chief Executive Officer/Information Officer
Tshwane District Hospital
Hospital / Clinic

FROM : DR S VENTER [Name]
Investigator
University of Cape Town (UCT)
Hospital / Clinic OR University of Pretoria

Re: Permission to do research at Tshwane district hospital AHEU clinic **Hospital / Clinic**

TITLE OF STUDY: Investigation of the factors that impact on outcomes of HIV/AIDS patients with CD4 < 50 cells/µL at TDH

This request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

I am a researcher / student at the Department of Pulmonology at the University of Pretoria / UCT Hospital. I am working with [1] herewith request permission on behalf of all of us to conduct a study on the above topic on the hospital / clinic grounds. This study involves access to patient records.

The researchers request access to the following information: clinical files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely

Signature of the Principal Investigator

Permission to do the research study at this hospital / clinic and to access the information as requested, is hereby approved.

Title and name of Chief Executive Officer: MRS O. I. UBOGU

Name of hospital / clinic: TSHWANE DISTRICT HOSPITAL

Signature:-

Date: 30 March 2009

[1] Title(s) and surname(s) of co-investigator(s) / supervisor(s)

Official Stamp
Tshwane District Hospital
Dr Savage Road
PRETORIA
0001

APPENDIX 5 – ETHICS COMMITTEE APPROVAL UP AND UCT

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 13 Jan 2012.
- IRB 0000 2235 IORG0001762 Approved dd Jan 2006 and Expires 13 Aug 2011.

100 1908 - 2008

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee
Fakulteit Gesondheidswetenskappe Navorsingsetiekkomitee

DATE: 30/04/2009

PROTOCOL NO.	64/2009
PROTOCOL TITLE	Investigation of the factors that impact on outcomes of HAART in patients with CD4<50cell/ul at Tshwane District Hospital.
INVESTIGATOR	Principal Investigator: Dr S Venter
SUBINVESTIGATOR	None
SUPERVISOR	Dr Liz Gwyther liz.gwyther@uct.ac.za
DEPARTMENT	Dept: ARC Clinic, Tshwane District Hospital
	E-Mail: sasje@webmail.co.za Cell: 0827860549
STUDY DEGREE	M Phil (Palliative Medicine)
SPONSOR	None
MEETING DATE OF THIS STUDY	29/04/2009

This **Protocol** has been considered by the Faculty of Health Sciences Research Ethics Committee, University of Pretoria on 29/04/2009 and found to be acceptable.

* Members attended & Feedback at the meeting .

*Prof A Nienaber	(female) BA (Hons) (Wits); LLB; LLM (UP); PhD; Dipl.Datametrics (UNISA)
*Prof V.O.L. Karusseit	MBChB; MFGP (SA); MMed (Chir); FCS (SA)
*Prof M Kruger	(female) MB.ChB. (Pta); MMed. Paed. (Pret), M.Phil (Stellenbosch) cum laude; PhD. (Leuven)
Dr N K Likibi	MB.BCh; Med.Adviser (Gauteng Dept.of Health)
Dr T S Marcus	(female) BSc (LSE), PhD (University of Lodz, Poland)
Snr Sr J. Phatoli	(female) BCur (Eer.A) BTec (Oncology Nursing Science)
Dr L Schoeman	(female) B.Pharm, BA Hons (PSy), PhD
*Dr R Sommers	(female) MBChB; MMed (Int); MPharMed;
*Mr Y Sikweyiya	MPH; SARETI Fellowship in Research Ethics; SARETI ERCTP; BSC (Health Promotion) Postgraduate Dip in Health Promotion
Prof TJP Swart	BChD, MSc (Odont), MChD (Oral Path), PGCHE
*Dr A P van Der Walt	BChD, DGA (Pret) Director: Clinical Services of the Steve Biko Academic Hospital
*Prof C W van Staden	MBChB; MMed (Psych); MD; FCPsych, FTCL, UPLM; Dept of Psychiatry

DR R SOMMERS; MBChB, MMed (Int), MPharMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

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MS: dd 2009/07/15: C:\Documents and Settings\Sasje\Desktop\Haart\UP Ethics Approval.doc

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
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08 June 2009

REC REF: 257/2009

Dr S Venter
C/o Dr L Gwyther
Public Health & Family Medicine

Dear Dr Venter

PROJECT TITLE: INVESTIGATION OF THE FACTORS THAT IMPACT ON OUTCOMES OF HAART IN PATIENTS AT TSHWANE DISTRICT HOSPITAL

Thank you for submitting your study to the Research Ethics Committee for review.

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

Approval is granted for one year until 10 June 2010. Please submit an annual progress report if the research extends beyond the approval period, or a brief closing summary if the study finishes within the approved period.

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

Please quote the REC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

kmjodi

APPENDIX 6 – VARIABLES RECORDED

The variables or factors recorded in the tool were:

- age in completed years
- gender (male, female)
- race (black African, coloured, Indian, white)
- educational level (no education, primary, secondary, post matric)
- residence (urban, rural)
- weight in kilograms at HAART initiation
- total CD4 count (at HAART initiation)
- Viral load at HAART initiation
- Hemoglobin level
- Platelet count
- Liver function (with emphasis on AST and ALT levels)
- Serum-albumin (not routinely done at TDH)
- TB status (positive, negative, unknown)
- Smoke (yes, no)
- Alcohol abuse (yes, No)
- WHO stage of HIV disease (I-IV)
- Emotional and social support (noted as disclosure of HIV status)
- Lost to follow up, and
- Date HAART was initiated
- Survival status (died/ alive)
- Date of death (where indicated)
- Cause of death (natural/ unnatural)