Factors Influencing Clinical Outcomes on Patients on Highly Active Antiretroviral Treatment (HAART) at Vryburg District Hospital, Northwest Province in South Africa.

By

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DECLARATION

I, JB BOSOKO BOTOKEYANDE, hereby declare that the work on which this research is based is original and that neither the whole work nor part of it has been submitted for another degree at this or any other university.

Signature:

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iii. DEDICATION.

This degree in general—and the dissertation no less—stands as a monument of dedication to the Almighty God for the breath of life in me, his protection and blessings.

It is also dedicated to the following:
My dear ascendant families, The Botokeyande, Bonyafala, Selenga, Lingboso, Bokumi Wawana and The Ayomba Wayele;

My dear late Mother, Lombaya Suliya, whose maternal love, care and wisdom never cease to inspire my daily life;

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My dear sons, George, Wisdom Julius Tresor, Gerry and Archippe, for the endured sacrifice of having Daddy gone away time and time again when attending course sessions;

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My Colleagues and Friends with whom we shared our happy and difficult moments together during our training years,

And

All of you who inspired me in so many ways, so that this research project can be achieved, I also dedicate this work.

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v. Acronyms & Abbreviations

AIDS=Acquired Immune Deficiency Syndrome

ART= Antiretroviral Treatment

ARV=Antiretroviral

HIV=Human Immunodeficiency Virus

HAART= Highly Active Antiretroviral Therapy

3TC = Lamuvudine

d4T = Stavudine

EFV = Efanvirez

NVP = Nevirapine

AZT = Zidovudine

DDI=Didanosine

LPV/RTV= Lopinavir/Ritonavir combination

NNRTI=Nonnucleoside reverse transcriptase inhibitor

NRTI=Nucleoside reverse transcriptase inhibitor

PI=Protein inhibitor

LRTI= Lower Respiratory Tract Infection (s)

URTI= Upper Respiratory Tract Infection (s)

PVDS= Per Vaginal Discharge Syndrome

PID= Pelvic Inflammatory Disease

UTI= Urinary Tract Infection

PTB= Pulmonary Tuberculosis

TB= Tuberculosis

WL > 10%= Weight loss > 10%

WL < 10%= Weight loss < 10%

Hb= Haemoglobin

Kg (s) = Kilogram (s)

µl = microliter

ml=millilitre

BMI= Body Mass Index

VL= Viral load

CD4= Human lymphocyte T helper cells expressing CD4 antigen (T helper cells).

ALT= Alanine Aminotransferase

WHO= World Health Organisation

.

DOH= Department of health

RSA= Republic of South Africa

SD= Standard Deviation

Min= Minimum

Max= Maximum

P= page

Pp= pages

vi. Definition of terms

Patient Adherence: the extent to which a person's behaviour i.e. taking medication, following a diet, and/or executing lifestyle changes, corresponds with the agreed recommendation from a health-care provider.(WHO, 2003).

In the context of this study, the researcher defines adherence to HAART as patient's compliance to the negotiated and agreed management plan that includes medications dosages and frequencies, in respect of medications timing, dates of reviews for medications refills and blood tests, respect of nutritional, life style and safer sex practice advices, and the reporting of side effects/adverse events of drugs as soon as possible they occur.

Viral suppression: measured plasma HIV-1 RNA load < 400 copies/ml (US Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV, 2004)

Treatment failure: implies virologocal failure, immunological failure and clinical failure. For practical reasons, treatment failure is based on virological failure only (US Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV, 2004).

Virological failure: failure to achieve a viral load < 400 copies/ml at 24 weeks (6months), < 50 copies/ml at 48 weeks (12 months), or a confirmed rebound after virological suppression (US Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV, 2004).

The South Africa Department of health (2010) clinical guidelines for the management of HIV/AIDS adults and adolescents, defines virological failure as a measured plasma viral load > 1000 copies/ml on two occasions.

For the sake of analysis of data, viral load > 400 copies/ml is used by the researcher as virological failure and VL < 400 copies/ml is used as viral suppression.

Immunological failure: failure of the CD4 cell counts to increase by 25-50 cell/µl over baseline during the first year (US Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV, 2004).

The South Africa Department of health (2010) clinical guidelines defines immunological failure as dropping CD4 cell count.

The term immunological failure is used by the researcher to mean a decrease in CD4 cell count.

Clinical failure: clinical progression defined as a HIV-related event after at least 3 months of highly active antiretroviral therapy (US Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV, 2004).

The South Africa Department of health (2010) clinical guidelines defines clinical failure as the occurrence of new opportunistic infections for patients receiving HAART.

Immune reconstitution: consistent increase in CD4 cells count over time due to HAART.

Vii. List of tables & figures

Viii. Abstract

Background

The use of HAART in HIV/AIDS patients has been recognised worldwide to improve the quality of life and survival prospects. Neverthess, factors such as WHO clinical stage III-IV, CD4< 200, VL> 100,000, anaemia, blood transfusion, malnutrition, male gender, intravenous drug use, drug toxicity, HAART experienced by patients, hospitalization, older age and depression have been reported to be associated with negative outcomes whereas, in contrast, white ethnicity, adherence > 90%, antiretroviral naïve subjects, longer period of viral suppression, younger age, and female gender have been reported to be associated with positive clinical outcomes.

Methods

The researcher conducted a descriptive retrospective study of 78 systematically selected patients who initiated HAART during the period of 5 June 2007 to 5 December 2008. Data regarding demographics, nutritional status, patients' opportunistic infections, patients' use of ARV drugs and HAART regimens, side effects and adverse events, baseline and follow up measurements of CD4 cell count, VL, ALT and Hb were collected at initiation, 6 and 12 months of HAART and analysed, utilizing descriptive statistics.

Results

Of the 78 patients recruited for the study, 60 (77%) were females and 18 (23%) males, 77 (98.8%) black and 1 (1.2%) coloured. The majority of patients belonged to the two age-groups 26-35 years (35.9%), and 36-45 (37.2%). The majority of patients [73/78 (93.4%)] were unemployed and residents of Vryburg town. Nutritionally, 17/78 (21.8%) patients were underweight. Clinically, 79.4% were classified as WHO clinical stage III - IV. The mean weight improved in both sex at 6 and 12 months of HAART respectively, from 57.5kg (SD 8.0) to 63.0kg (SD 13.0) and 65.2kg (SD 4.5) for males.

Conclusion

The administration of HAART to patients attending ARV clinic at Vryburg District Hospital was followed by better clinical outcomes in terms of weight gain, correction of anaemia, increase in CD4 and achievement of virological suppression. Female gender, VL > 100,000 copies/ml, Younger age (< 46 years) and good adherence were found to have positive influence on clinical outcomes.

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Chapter 1
Introduction

1.1. Brief overview of the topic and its relevance

HIV/AIDS pandemic has become a chronically manageable disease since the era of HAART (Mahungu et al., 2009; Hogg et al., 1997). Nevertheless, there have been identified factors from previous research studies that influence clinical outcomes in patients on HAART, namely baseline CD4 (Sielenou et al., 2009; Fielden et al., 2008), VL (Fielden et al., 2009; ART-CC, 2010; Smith et. al., 2004; Shikuma et al., 2004), anaemia (Sielenou et. al., 2009; Buskin et al., 2004; Mocroft et al., 1999), blood transfusion (Buskin et al., 2004), gender (Sielenou et al., 2009; Fielden et al. , 2008; ART-CC, 2010), injection drug use (Fielden et al., 2008), opportunistic infections/conditions (WHO clinical staging) [Paton et al., 2006; Sielenou et al, 2009; Felden et al., 2008], nutritional status (Paton et al., 2006), adherence to treatment (George et. al., 2009), drug toxicity (Dai et al., 2006), previous exposure to ARV drugs (Shikuma et al., 2004), previous hospitalization (Fielden et al., 2008), age (ART-CC, 2010), depression (Hartzell et al., 2008) and not the least, patient's ethnicity (Smith et. al., 2004).

1.2. Problem statement

Patients attending ARV clinic at Vryburg District Hospital are in the majority coming from local impoverished black residential areas in Vryburg, the surrounding villages and farms. Though the administration of HAART to HIV/AIDS patients has been recognized world-wide to improve the quality of life and survival, there have been factors that have been identified by research studies to have an influence on the nature and extent of clinical outcomes. Given the peculiarity of South Africa in terms of its population ethnical groups and ways of livelihood, the health system structure and its population's access to health care services, in his context of practice (district hospital), and the South African National Antiretroviral Treatment Guidelines, the researcher wanted to know what could be the factors that influence clinical outcomes in

patients on HAART, specifically those attending Vryburg District Hospital ARV clinic.

1.3. Justification of the study

The treatment of HIV-infected patients with Highly Active Antiretroviral Therapy (HAART) leads to immune reconstitution as shown by the increase in CD4 cells count, decreased risk of opportunistic infections i.e. improved quality of life and improved survival (Mahungu et al., 2009; Hogg et al., 1997; New York State Department of Health, 2008; George et al, 2009; Paton et al, 2006; Dokekias et al, 2008).

The South African Government's response to the epidemic of HIV and AIDS has evolved significantly over the past few years. The year 2004 saw the production of the first National Antiretroviral Treatment Guidelines, as the standardized tool to be used by all clinicians involved in the care of the HIV/AIDS patients (South Africa Department of Health, 2004). The national strategic plan prescribed that teaching and provincial hospitals be the starting points for the initiation of HAART, followed by a progressive roll-out program in each province. In our district, renamed Dr. Ruth Segomotso Mompati from the former Bophirima District (where the researcher practices). Taung Hospital was used as initial site in 2004 at the same level as Klerksdorp-Tshepong Complex provincial hospital (initiated in April 2004). After proper assessment and recruitment of health care personnel, the programme was rolled-out at Vryburg District Hospital on the 3rd of June 2006, becoming the down-referral site for Klerksdorp/Tshepong Complex Hospital (level 2 hospital) and Taung District Hospital, the initial site in our district.

After being appointed as Medical Officer at Vryburg Hospital ARV clinic in June 2007, the researcher noted a diversity of HIV/AIDS patients being started on HAART and was concerned about the very sick, patients at WHO stage III-IV of HIV disease progression. The study intends to investigate factors that influence clinical outcomes in patients on HAART, in the context of

South African National Antiretroviral Treatment Guidelines and the researcher's practice (District Hospital)

Chapter 2

Literature review

2.1. Introduction

This chapter reviews studies done on the topic in a logical manner i.e. global, continental and local studies. The researcher used the following key words to perform his literature search: HIV/AIDS, HAART, ART, factors, outcomes, clinical outcomes, and laboratory outcomes. Google search engine and Cochrane library helped to find relevant articles.

2.2. Factors influencing Clinical Outcomes in patients on HAART

2.2.1. Global Studies

Evaluating the clinical outcomes and costs of three NNRTI-based HAART regimens in Kerala, India, George et. al. (2009) conducted a prospective observational study over a period of 6 months. One hundred and forty two (142) HIV/AIDS patients were enrolled, divided in 3 different treatment groups and given free NNRTI-based combination therapy. The mean age was 37.88 years, 64% of patients were male and 92% were married. Group I was given Zidovudine + Lamuvudine + Nevirapine [52 patients (37%)], group II was given Stavudine + Lamivudine + Nevirapine [51 patients (36%) and group III was given Stavudine + Lamivudine + Efavinrez [30 patients (27%). They observed that the increase in CD4 cell count was 107.46 (SD: 106.25). The mean medication adherence for the 104 patients who completed the study was 90.7%, respectively 92.06% for group I, 93.7% for group II and 85.71% for group III. Forty patients (38%) had at least one adverse event to HAART, with headache being the most common side effect (11.5%). The mortality rate was 3.5% during the course of the study. They concluded that the provision of free NNRTI-based combination therapy to HIV/AIDS patients in Kerala, India, resulted in greater than 90% adherence, leading to better clinical outcomes in

terms of increasing CD4 cell counts and low mortality, for patients consistently attending a treatment clinic.

Evaluating the impact of malnutrion on survival and the CD4 cell count response in HIV- infected patients starting antiretroviral therapy, Paton et al. (2006) conducted a retrospective cohort study of 394 HIV/AIDS patients attending the national HIV referral centre in Singapore. Patients had a CD4 cell count less than 250 cell/µl. Their body weight and height were measured and body mass index (BMI) calculated from the weight in kg divided by the square of the height in metres. Moderate to severe malnutrition was defined as BMI < 17 kg/m^2. They observed that 79 patients died during a median period of 2.4 years. At baseline, 16% of patients had severe to moderate malnutrition and were found to be an independent predictor of death [hazard ratio (HR) 2.17, 95% CI 1.29 -3. 73, P=0.004 for those with BMI < 17 compared to those with BMI > 18.5] as were stage of disease [HR: 2.47, 95% CI 1.20 – 5.07, P= 0.014 for those who were at stage C compared with those at stage A] and the type of antiretroviral therapy (HR: 0.50, 95% CI 0.27 – 0.93, P=0.03 for HAART compared to non-HAART treatment]. Malnutrition did not impair the magnitude of the increase in CD4 cell count at 6 or 12 months. They concluded that malnutrition at the time of starting antiretroviral therapy was significantly associated with decreased survival, but the effect appeared not to be mediated by impaired immune reconstitution. They suggested that more studies of malnutrition as an adjunct to the initiation of HAART were urgently needed in developing countries given the increasing access to antiretroviral therapy and the high frequency of HIV-associated wasting.

Evaluating the clinical outcomes and immune reconstitution in advanced AIDS patients, Dai et al. (2006) studied 103 advanced AIDS patients over a 12-month period of HAART. Their HAART regimens were constituted of 1 NNRTI (nonnucleoside reverse transcriptase inhibitor) + 2 NRTI (nucleoside reverse transcriptase inhibitor) or 1 PI (protein inhibitor) + 2 NRTI (nucleoside reverse transcriptase inhibitor). They found that one patient died and another was lost to follow up**.** For the remaining 101 patients, the plasma viral load (VL) was

reduced to 3.2 +/- 0.7 log copies/ml, the CD4 cells count increased to 165+/- 51cell/µl. The plasma viral load (VL) significantly declined within 1 month after HAART initiation, reached its lower level at 3 month and maintained until the end of the study. At 12 month of HAART, 62 patients had a VL < 50 copies/ml, 28 patients had a VL= 50- 500 copies/ml and only 13 patients had VL >500 copies/ml. The following side effects were reported: lipodystrophy related to Didanosine and Stavudine, bone marrow suppression to Zidovudine, skin rash and liver dysfunction to Nevirapine and Efavinrez, nephrolithiasis to Indinavir and gastrointestinal disorders could not be attributed to specific drugs.
In 13 cases, corresponding drugs were changed due to failure to control side effects by symptomatic treatment. Clinical outcomes consisted of complaints of fatigue, body malaise and weight loss. One patient died of hepatic failure due to Nevirapine toxicity and HCV-coinfection. Another was lost to follow up. Among the remaining 101 patients, no one developed opportunistic infections. At baseline, the opportunistic infections included tuberculosis (27 cases), Cytomegalovirus infections (8 cases), Candidiasis (24 cases), Herpes Simplex infections (6 cases), Pneumocystis jiroveci pneumonia (PCP, 6 cases), bacterial infections (5 cases) and sepsis (3 cases). Co-infections included HCV-infections (29 cases). The mean CD4 cells count was 106 +/- 85 cell/µl, and the mean plasma viral load was 5.2+/-0.8 log copies/ml.

Studying the prevalence of anaemia since HAART availability and the association between anaemia treatments and survival, Buskin and Sullivan (2004) followed a cohort of HIV- patients through 1996 to 2001**.** Describing anaemia as a haemoglobin (Hb) level of less that 10.5 g/Dl, they observed a decrease from 13 to 5 %. Patients with CD4 cells count less than 100 cell/ml had the highest anaemia prevalence. In total, 216 severely anaemic HIV-patients (mean Hb level, 8.1 g/dl) followed for a median of 13 months had a 37% mortality rate. Of these, 22 % were untreated (13% mortality rate), 42% received blood transfusion alone (52% mortality rate), 12% received erythropoietin alfa alone (19% mortality rate), and 24% received both (47% mortality rate). Blood transfusion was associated with a threefold excess mortality risk, but erythropoietin alfa prescription was not associated with

mortality. The Authors concluded that the prevalence of anaemia has decreased in the HAART era, and blood transfusion was positively associated with risk of death, suggesting limiting use of transfusions in nonemergency situations.

Similarly, Mocroft et al. (1999) analysed a cohort of 6,725 HIV-patients from across Europe (EuroSIDA Study group). They described normal haemoglobin (Hb) as Hb greater than 14 g/dl for men and 12 g/dl for women, mild anaemia as Hb of 8-14 g/dl for men and 8-12 g/dl for women and severe anaemia as Hb of less than 8 g/dl for both sex. They observed that at recruitment, 40.4% of patients had normal level of haemoglobin, 58.2% had mild anaemia and 1.4% had severe anaemia. At 12 months of the study, 3.1% of patients without anaemia were estimated to have died (95% CI: 2.3-3.9), 15.9% of patients with mild anaemia had died (95% CI: 14.5-17.2) and 40.8% of patients with severe anaemia had died (95% CI: 27.9-53.6; $P < 0.0001$). In a multivariate, time-updated Cox proportional hazards model, adjusted for demographic factors, AIDS status, and each antiretroviral treatment as time-dependent covariates, a 1g/dl decrease in the latest haemoglobin level increased the hazard of death by 57% [relative hazard (HR) 1.57; 95% CI: 1.41-1.75; $P < 0.0001$], a 50% drop in the most recent CD4 cells count increase the hazard by 51% (RH: 1.51; 95% CI: 1.35-1.70; $P < 0.0001$) and a log increase in the latest viral load increase the hazard by 37% (RH 1.37; 95% CI: 1.15-1.63; $P < 0.0005$). The Authors concluded that severe anaemia occurred infrequently among these patients but was associated with a much faster rate of disease progression. Among patients with similar CD4 cell count and viral load, the latest value of haemoglobin was a strong independent prognostic marker of death.

Determining factors that influence the increase in CD4 cell count of HIV-positive persons receiving long term HAART, Smith et al. (2004) studied a cohort of 596 patients over a median period of 2.5 years. They found that after 6, 12 and 24 months of HAART, the median increase in CD4 cell counts were 114, 181, and 248 cell/µl, respectively 84%, 84%, and 80% of subjects

had a viral load of < 400 copies/ml during the same periods. White ethnicity, higher pre-HAART viral load, and lower pre-HAART CD4 and CD8 cell counts were associated with greater increases in CD4 cell counts during the first 3 months of HAART. From 3 months onward, a greater cumulative proportion of time spent with viral load < 400 copies/ml was associated with a more favourable change in CD4 cell count (an average increase of 5.2 cell/µl/year [95% CI], 3.8 – 6.7 cell/µl/year for each extra 10% cumulative time spent with a viral load < 400 copies/ml (p < 0.0001). For every 100 cell/µl higher in baseline CD4 cell count, the increase was 6 cell/ul/year less (95% CI, 2 – 11 cell/µl/year) [P = 0.2]. Sex, risk group, age, and HAART regimen were not associated with increases in CD4 cell count. They concluded that maintaining virological suppression is an important factor in the increase of CD4 cell count and suggested that other factors may influence long-term CD4 cell response.

Determining changes in weight and lean body mass (LBM) during HAART, Shikuma et al. **(**2004) studied a cohort of 224 antiretroviral naïve patients during the period of 1997 – 2000. They observed that there was a modest increase of body weight (1.9 kg) and lean body mass (0.6 kg) after 16 weeks of therapy. Significantly greater median increases in body weight (2.1 vs. 0.5 kg; p=0.045) occurred in subjects who achieved virological suppression (HIV-1 RNA load, < 500 copies/ml) at 16 weeks than in subjects who did not. Subjects who were antiretroviral naïve at baseline gained more weight (median increase in body weight, 26 vs. 0.0 Kg; p < 0.001) and lean body mass (1.0 vs. 0.1 kg; p= 0.002) after 16 weeks of treatment than did subjects who were antiretroviral experienced. Subjects with lower CD4 cells count (< 200 cell/µl) and patients with higher baseline HIV-1 RNA loads (≥ 100,000 copies/ml) were more likely to show increases in lean body mass of > 1.5 kg (p=0.013 and p=0.005, respectively). They concluded that HAART had modestly favourable effects on body composition, particularly in patients with greater pre-treatment immunocompromise and virological compromise. They suggested that the difference between antiretroviral- naïve and antiretroviral experienced subjects with regard to the ability to increase body weight and lean body mass requires more study.

Determining the clinical predictors of hospitalization among HIV-infected persons initiating HAART and exploring the impact of gender and drug use on hospitalization, Fielden et al. (2008) studied a cohort of 1,605 HIV-positive individuals initiating HAART between 1996 and 2001, and found that 672 (42%) were hospitalized for one or more days. The risk of hospitalization increased among patients with high baseline viral load, HIV-RNA (HR for > 100,000 copies/ml: 1.26; 95% CI: 1.16 – 1.59] or low CD4 cell counts (HR [95% CI] compared to CD4 cell count ≥ 200 cell/µl: 1.6 [1.28 – 2.06] and 1.29 [1.07 – 1. 56] for < 50 and 50 – 99 cell/µl, respectively). Other factors included adherence, previous hospitalization, gender and injection drug use remained predictive of hospitalization. They stressed the importance of closely monitoring patients starting therapy with low CD4 cell count in order to mediate or prevent outcomes requiring hospitalization.

Studying the impact of depression on HIV outcomes in the HAART era, Hartzell et al. (2008) reviewed the literature to clarify the impact of MHI (Mental Health Illness) and specifically depression on clinical outcoumes. They found that the outcomes were worse due to poor adherence issues and recommended that the mental condition of HIV/AIDS patients be priory optimally managed to improve their outcomes on HAART.

The Antiretroviral Therapy Cohort Collaboration, ART-CC (2010) studied causes of death in HIV-1 patients treated with HAART, during the period of 1996-2006: collaborative analysis of 13 HIV cohort studies. A total of 39, 272 patients were enrolled and followed for 4 years. Amongst those enrolled, 27% were females and 73% were males. Main risk groups were constituted of gay and bisexual men (36%), heterosexuals (41%), and Intravenous Drug Users [IDUs (13%)]. Per age distribution, 82% were aged 30 years or older. Fifty three percent (53%) of patients had their CD4 cells count ≥ 200 cell/ul and 47% of patients had their VL ≥ 100,000 copies/ml.

Main observations were that for patients aged 37 years old, with CD4 cells count +/- 110 cell/µl, deaths unrelated to AIDS were due to cancers (12%),

infections (8%), cardiovascular diseases (8%), violence (8%) and liver disease (7%). The timing of death during the first year was due to AIDS in 63% of patients. Factors influencing death during the first year were constituted of being a male and an Intravenous Drug User (IDU). Death in the Intravenous Drug Users group was caused by liver dilated condition, lung related condition, violence and infections. Other factors influencing death were patients at WHO stage IV and VL > 100,000 copies/ml.

The influence of age on death was noted; as age increased, there was an increase in the risk of cancers unrelated to AIDS and cardiovascular diseases. The patients aged > 60 years old had an increase in kidney complications.

Concerning the influence of gender, females were less likely to die.

The benefit from using HAART was noted. Longer period of HAART reduced death from AIDS, non-AIDS infections or kidney failure.

Studying adherence to HAART, Mills et. al. (2005) conducted a systematic review of the literature to determine patient-reported barriers and facilitators to adherence to ART. They searched following databases: AMED, Campbell collaboration, CinAhl, Cochrane library, Embase, ERIC, Medline and NHS EED. They reviewed 37 separate meta-analyses.

They found that the important barriers reported in both economic settings included fear of disclosure, concomitant substance abuse, forgetfulness, suspicions of treatment, regimens that are too complicated, number of pills required, decreased quality of life, work and family responsibilities, falling asleep, and access to medication.

The important facilitators to adherence reported by patients in developed nation settings included having a sense of self-worth, seeing positive effects of antiretroviral drugs, accepting their seropositivity, understanding the need for strict adherence, making use of reminder tools, and having a simple regimen.

Authors found a large heterogeneicity in the generalization of findings amongst the 37 separate meta-analyses that they reviewed.

They concluded that important barriers to adherence are consistent across multiple settings and countries. Research is urgently needed to determine

patient's important factors for adherence in developing world settings. They suggested that clinicians should use this information to engage in open discussion with patients to promote adherence and identify barriers and facilitators within their own populations.

2.2.2. Continental Studies

Studying the outcome and predictive factors of mortality in hospitalized HIV-patients in Burkina Faso, Saleri et al. (2009) conducted a restrospective study on hospitalized patients in Ouagadougou, Burkina Faso. A total of 1,071 patients HIV positive patients were recorded between 1 January 2004 and 31 August 2006, the majority of whom were females (61.1%). The baseline CD4 cell count was higher in the female patients than in male ones (166.1 vs. 110.9 cell/ul). Gastroenteric symptoms were the first cause of hospitalization (61.7%). The crude mortality rate was higher in males than females (38% vs. 25.3%). Baseline WHO clinical stage IV (OR 9.22), neurological syndrome (OR 3.04) or wasting syndrome at admission (OR 2.9), positive malaria smear (OR 2.17), and an older age independently predicted death. Weight at admission > 40 kg and a higher platelet count at admission were independently associated with a better outcome. They observed that females were admitted to hospital earlier than males, probably as an indirect result of the prevention of Mother-to-child transmission (PMTCT) public health initiative. They suggested that an active search of HIV status in other members of the family (PMTCT-plus) may result in the detection of asymptomatic HIV infected patients as well. A plasmodium falciparum positive smear during admission significantly impacted on outcome as well as low platelet count.

Studying the determinants of survival in AIDS patients on antiretroviral therapy in rural centre of North of Cameroon, Sieleunou et al. (2009), conducted a retrospective cohort study of 1187 patients aged > 15 years who started HAART between July 2001 and December 2006. Their findings were that 90.4% of patients were in WHO stage III or IV and 56.1% had a BMI < 18.5. Median CD4 cells count was 105 cell/µl (IQR 40-173). At the end of the study

period, 338/1187 had died and 59/1187 were lost to follow-up. The survival probability was 77% at 1 year [95% CI: 75-80] and 47% at 5 years [95% CI: 40-55]. The median survival time was 58 months. CD4 cells count, haemoglobin (Hb), BMI, sex, and clinical stage at enrolment were independent predictors of mortality.

Evaluating HAART in HIV-infected adults in the department of haematology at the University of Brazaville in Congo, Dokekias et al. (2008) conducted a retrospective study during 32 months, from May 2003 to December 2005, over 157 HIV/AIDS patients receiving HAART for at least 12 months. At baseline, the average CD4 cell count was 133 cell/µl (range 1- 365) and plasma viral load measured in 96 patients was 214,000 copies/ml (extreme 30,000 and 999,000). The initial HAART regimens were constituted of Stavudine or Zidovudine + Lamivudine + Nevirapine (59%), Stavudine or Zidovudine + Lamivudine + Efavinrez (28.7%), Stavudine or Zidovudine + Lamivudine + Indinavir (8.9%) and Stavudine or Zidovudine + Didanosine + Nevirapine (3.2%). They found that the adherence during the first 12 months was of 84%, HAART was taken irregularly by 10.8% of patients, there was early submission of therapy in 5.2% of patients, there was an average weight gain of after 24 months of about 18 kgs and the global clinical response was positive. The immune response was characterized by an average increase in CD4 cell count of 353 cell/µl after 24 months. Among the 96 patients who had their plasma viral load measured, 71% had undetectable level after 12 months. Mild adverse drugs effects were observed and included cutaneous and nervous toxicity, anaemia, and digestive disorders, due to Indinavir. They concluded that their results confirmed the therapeutic significance of HAART in the improvement of the quality of life of HIV/AIDS patients but they had a concern on the possibility of drug resistance occurrence which could not be documented.

2.2.3. Local Studies

Studying Long Term Outcomes on ART in a large HIV/AIDS care clinic in Urban South Africa, Sanne et al. (2009) conducted a prospective cohort study

of 7,583 HIV infected patients who initiated care during the period of 1st April 2004 to 1st April 2008. They found that the overall mortality rate was low (2.9 deaths per 100 person years, 95% CI 2.6-3.2), but high in the first 3 months of HAART (8.4 per 100 person years, 95 % CI 7.2-9.9).Long-term on site-retention in care was relatively high (74.4% at 4 years, 95% CI 73.2-75.6). CD4 cells count was above 200 cell/µl after 6 months of treatment in almost all the patients. By the fourth year of HAART, the majority (59.6%, 95% CI 57.8-61.4) of patients had at least one first line drug (mainly Stavudine) substituted. Women were twice as likely to experience drug substitution (OR 1.97, 95% CI 1.80-2.16).

By 6 months of HAART, 90.8% of patients suppressed virus below 400 copies/ml. Among those with initial viral suppression, 9.4% (95% CI 8.5-10.3) had viral load rebound within one year of viral suppression, 16.8% (95% CI 15.5-18.1) within 2 years, and 20.6% (95% CI 18.9-22.4) within 3 years of initial suppression. Only 10% of women and 13% of men initiated second line HAART.

The Authors concluded that despite advanced disease presentation and a very large-scale program, high quality care was achieved as indicated by good long-term clinical, immunologic and virologic outcomes and a low rate of second line HAART initiation. High rates of single drug substitution suggest that the public health approach to HAART could be further improved by the use of a more durable first line regimen.

Similarly, Coetzee et al. (2004), studying Outcomes of providing ART in Khayelitsha, South Africa, found excellent results for patients who started HAART with very low CD4 cell count and high viral load. They concluded that HAART can be provided in resource-limited settings with good patient retention and clinical outcomes. They suggested that with responsible implementation, ART is a key component of a comprehensive response to the epidemic in those communities most affected by HIV. The Vryburg community is thus a case in point.

2.3. Summary of the literature

Summarizing the literature, following factors have been found to be associated with negative clinical outcomes on patients on HAART:

-the stage of disease progression (WHO stage III and IV) i.e. the severity of opportunistic infections/conditions (Paton et al., 2006; Sieleunou et al., 2009; Fielden et al., 2008);

-lower baseline CD4 cells counts < 200 /ul (Sielenou et al., 2009; Fielden et al., 2008);

-Higher baseline viral load > 100,000 copies/ml (Fielden et al., 2008; ART-CC, 2010);

-baseline anaemia (Sielenou et al., 2009; Buskin et al., 2004; Mocroft et al., 1999);

-blood transfusion (Buskin et al., 2004);

-baseline malnutrition (BMI < 18.5) (Paton et al., 2006);

- male gender (Sielenou et al., 2009; Fielden et al., 2008; ART-CC, 2010);

-Intravenous drug use (Fielden et al., 2008);

-poor adherence (George et al., 2009);

-drug toxicity (Dai et al., 2006);

- HAART experienced subjects (Shikuma et al., 2004);

-previous hospitalizations (Fielden e. al., 2008);

-depression (Hartzell et al., 2008);

- positive malaria smear (Saleri et al., 2004);

- low platelet count (Saleri et. al., 2004); and

- older age (ART-CC, 2010).

Nevertheless amongst other factors found to be associated with positive outcomes are:

- white ethnicity (Smith et al., 2004)),

- adherence > 90% (George et al., 2009),

- antiretroviral naïve subjects (Shikuma et al., 2004),

- longer period of viral suppression (Smith et al., 2004),

- higher baseline viral load (Smith et al., 2004; Shikuma et al., 2004),

- younger age (ART-CC, 2010),

- female gender (ART-CC, 2010; Saleri et. al., 2004), and

- baseline higher platelet count (Saleri et. al, 2004).

Chapter 3
Methodology

3.1. Aim of the Study

To determine factors thatinfluence the clinical outcomes in patients on HAART at Vryburg District Hospital, Northwest Province in South Africa.

3.2. Objectives of the Study

1. To determine the demographic characteristics of the patients on HAART at Vryburg District Hospital, North West Province;
2. To assess the patients' nutritional status ;
3. To document the opportunistic infections/conditions and hospitalization;
4. To assess patients' use of the ARV drugs and HAART regimens
5. To determine the side effects/adverse effects of the ARV drugs
6. To assess the patients' CD4 cell count, viral load (VL), liver function tests (ALT), and haemoglobin level at HAART initiation and follow up visits.

3.3. Research question

What are the factors that influence clinical outcomes in patients on HAART at Vryburg District Hospital, Northwest Province in South Africa?

3.4. Study Design

It was a descriptive retrospective study of HIV/AIDS patients on HAART.

3.5. Study setting

The study was conducted at Vryburg District Hospital, Northwest Province in South Africa.

Vryburg District Hospital is a +/- 80-bed hospital rendering preventive, curative, rehabilitative and health promotion care to the population of Naledi Sub-district and the neighbourhood.

3.6. Study population

The study population comprised of files of all HIV/AIDS patients aged ≥18 years who were on HAART at Vryburg District Hospital during the period of 5th June 2007 to 5th December 2008. During this period 420 HIV/AIDS patients were initiated on HAART.

3.7. Sampling frame and Sample size

With a sample population of 420 HIV/AIDS patients on HAART during the study period, using a 95% confidence level, 10% confidence interval, the sample size was calculated to be 78 patients.

Patient files that fulfilled the inclusion criteria over the stipulated period of time were 420. To arrive at the sample size, a systematic selection method was employed: 420 was divided by 78 which resulted in 5.4 (rounded to 5); a random number was selected from 420 and starting with that number, every 5th number was selected and the process repeated until 78 files were obtained.

Therefore, the sample comprised of 78 systematically selected files of HIV/AIDS patients aged ≥ 18 years old who initiated HAART during the period of the study, had been on HAART for at least 6 months and had complete information on demographic characteristics, clinical notes, ARV drug regimens, CD4 cell count, viral load (VL), liver function tests (ALT) and haemoglobin (Hb) results at HAART initiation and follow up visits.

3.8. Inclusion criteria

- HIV/AIDS patients aged ≥ 18 years old
- Patients on HAART for at least 6 months
- Patients with complete demographic data, clinical notes and laboratory findings on the hospital file.

3.9. Exclusion criteria

- Patients aged < 18 years old
- Patients on HAART for less than 6 months
- Patients with incomplete demographic characteristics, clinical notes and laboratory findings on the hospital file.

3.10. Variables of the Study

Clinical variables:

- Patients demographic characteristics (age, sex, race, employment, location of residence),
- Patients nutritional status (weight, BMI),
- Opportunistic infections at initiation and follow up visits,
- Hospital admissions

Laboratory variables:

- Baseline and follow up CD4 cell counts, viral load (VL), liver function tests (ALT) and haemoglobin (Hb) levels.

3.11. Data Collection

The researcher designed a data collection sheet related to the objectives of the study. Demographic, clinical and laboratory data were obtained from selected patient files and entered into the data collection sheet. The correctness of information entered was verified by an independent medical officer not directly involved with the study. Information entered in the structured data collection sheet formed the basis for analysis and interpretation.

3.12. Data Analysis

Simple descriptive analyses using Epi-info 6.04 software program was done with the assistance of my supervisors and a statistician. Data are presented as tables.

3.13. Materials

The following tools were used for the study:

- ARV clinic registers and files as sources of patients' data
- Data Collection Sheet to capture the necessary data
- Computers and the Epi info and Microsoft Excel software programmes to capture and analyse data.

3.14. Reliability and Validity

3.14.1. Reliability

Reliability is the extent to which a test measurement or device produces the same results with different investigators, observers, or administration of the test over time (Mosby's Medical Dictionary, 2009). To ensure that data were reliable (consistent or repeatable), the researcher designed a data collection sheet which was used to enter the information from patients' files and an independent medical officer counter-checked the correctness of data entry.

3.14.2. Validity

Validity is the extent to which a test measurement or other device measures what it is intended to measure (Mosby's Medical Dictionary, 2009). To ensure validity of the study, the content of the data collection sheet was subjected to peer and supervisors' review to ensure that it was able to gather the intended information for the study.

3.15. Study bias

Sampling bias or sample selection bias

Sampling bias is a systematic error due to a non-random sample of a population, causing some members of the population to be less likely to be included than others, resulting in a biased sample, defined as a statistical sample of a population in which all participants are not equally balanced or objectively represented. Selection bias is the tendency to favour the selection of individuals that have particular characteristics (Mosby's Medical Dictionary, 2009). To minimise sampling bias, serial file numbers of patients initiated on HAART during the period of the study guided the selection process, leading to

a systematically selected sample of 78 files of patients aged ≥ 18 years old with complete information on the variables of the study.

Bias in the presentation and interpretation of data or publication bias or reporting bias

Publication bias or reporting bias is the distortion produced in community perception or meta-analysis by not publishing uninteresting (usually negative) results, or results which go against the experimenter's prejudices, a sponsor's interests, or community expectations (Mosby's Medical Dictionary, 2009).

Presentation and interpretation bias may occur when the researcher analyses and draws conclusions of the study to suit his/her own preconceived ideas or opinion. Presenting the findings to the supervisors, colleagues and the statistician for peer review and independent opinion helped minimise these forms of bias.

3.16. Ethical considerations

Permission to conduct the research at Vryburg District Hospital was obtained from the Provincial/District Research and Ethics Committee and local hospital Managers. Patient confidentiality was ensured by keeping the information obtained from patient files anonymous. Since there were no interviews of patients, no consent form were required. Ethical clearance for the study was obtained from the Medunsa Research and Ethics Committee (MREC) of the University of Limpopo, Clearance Certificate, Project No. MREC/M/59/2010: PG, issued on 5th of May 2010.

Chapter 4
Results

4.1. Introduction

This chapter describes the results of the analysis of data. Data concerning demographic characteristics, patients' nutritional status, opportunistic infections/conditions and hospitalization, patients' use of ARV drugs and HAART regimens, ARV drugs side/adverse effects and selected laboratory parameters were analysed using descriptive statistics.

4.2. Demographic characteristics

Of the 78 selected patients 60 (77%) were females and 18 (23%) males; 77 (98.7%) were blacks and 1 (1.3%) coloured.

According to age groups: 13 were between 18-25 years (3.8%), 28 between 26-35 years (35.9%), 29 between 36-45 years (37.2%), 14 between 46-55 years (17.9%), 3 between 56-65 years (3.8%), and 1 over 65 years (1.3%).

By profession: one was a civil-servant (1.3%), one a driver (1.3%), one house worker (1.3%), two farm-workers (2.6%), and 73 unemployed (93.4%).

According to place of residence, 61 were from Huhudi location (78.2%), 5 from Colridge (6.4%), 2 from Monoto-Mosweu (2.6%), one from Vryburg-town (1.3%), one from Monoto-Mosetlha (1.3%), four from Stella (5.1%), three from Farms (3.8%) and one from Dithakwaneng (1.3%), i.e. 70/78 (90%) of patients were residents of different locations of Vryburg while 8/78 (10%) were residents of the surrounding villages around Vryburg.

Table I. Demographic characteristics

Characteristics		Frequency/Percentage
Gender	Male	18 (23%)
	Female	60 (77%)
	Total	78 (100%)
Race	Black	77 (98.7%)
	Coloured	1 (1.3%)
	Total	78 (100%)
Age group	18-25 years	13 (3.8%)
	26-35 years	28 (35.9%)
	36-45 years	29 (37.2%)
	46-55 years	14 (17.9%)
	56-65 years	3 (3.8%)
	> 65 years	1 (1.3%)
	Total	78 (100%)
Profession	Civil servant	1 (1.3%)
	Driver	1 (1.3%)
	Farm worker	2 (2.6%)
	Unemployed	73 (93.4%)
	House worker	1 (1.3%)
Place of residence	Huhudi location	61(78.2%)
	Colridge	5 (6.4%)
	Vryburg town	1 (1.3%)
	Monoto-Mosweu	2 (2.6%)
	Monoto-Mosetlha	1 (1.3%)
	Stella	4 (5.1%)
	Dithakwaneng	1 (1.3%)
	Farm	3 (3.8%)

The table above shows the predominance of females (60/78, 77%), blacks (77/78, 98.7%), 26-35 years (28/78, 35.9%) and 36-45 years (29/78, 37.2%) age groups and unemployment (73/78, 93.4%) in the study sample.

4.3. Nutritional status

At HAART initiation, over the 78 patients enrolled in the study, 71 had their BMI calculated as the weight in kilograms divided by the height square in meters. Seventeen (17) patients had their BMI < 18.5 kg/m^2 i.e. underweight (21.8%), 38 had their BMI between 18.5-24.9 kg/m^2 i.e. normal weight (48.7%), 13 between 25-29.9 kg/m^2 i.e. overweight (16.7%), 3 over 30 kg/m^2 i.e. obese and 7 did not have their BMI calculated due to missing data on the weight or height or both anthropometric parameters.

Mean weight and mean BMI were calculated separately in both sex groups at initiation, 6 and12 months of HAART.

At initiation of HAART, the mean weight was higher in males (57.5 kgs) than in females (53.8kgs).

The mean weight improved in both sex groups respectively in males, from 57.5 kg (SD 8.0, Min 45.0 kg, Max 69.5 kg) at initiation to 63.0 kg (SD 13.0, min 42.0 kg, max 93.5 kg) at 6 months and 65.2 kg (SD 4.5, min 59.0 kg, max 73.5 kg) at 12 months, and in females, from 53. 8 kg (SD 12.6, min 32.0 kg, max 92.0 kg) at initiation to 58.1 kg (SD 12.0, min 32.0 kg, max 94.0 kg) at 6 months and 59.5 kg (SD 12.0, min 38.5 kg, max 93.0 kg). Similarly, the mean BMI improved in both sex groups from initiation of HAART to 6 and 12 months of HAART.

Table II. Mean weight and mean BMI at initiation, 6 and 12 months of HAART by sex group

	Frequency	Mean	SD	Min	Max
Mean weight at initiation					
Male	17	57.5	8.0	45.0	69.5
Female	60	53.8	12.6	32.0	92.0

Mean weight at 6/12 Male	18	63.0	13.0	42.0	93.5
Female	60	58.1	12.0	32.0	94.0
Mean weight at 12 /12 Male	7	65.2	4.5	59.0	73.5
Female	36	59.5	12.0	38.5	93.0
Mean BMI at initiation Male	17	20.9	3.0	17.1	27.8
Female	55	22.5	9.0	14.2	75.4
Mean BMI at 6/12 Male	17	23.0	5.0	15.9	37.4
Female	54	23.4	4.5	15.2	34.1
Mean BMI at 12/12 Male	7	23.8	3.1	20.4	28.4
Female	33	24.3	4.0	18.3	35.4

Table II shows that at 6 and 12 months of HAART, the mean weight remained higher in males (respectively 63.0 kgs and 65.2kks) than in females (respectively 58.1 kgs and 59.5 kgs).

At initiation of HAART, the table shows that the mean BMI was higher in females (22.5 kg/m^2) than in males (20.9kg/m^2). Note the presence of extreme malnutrition (underweight, BMI=17.1kg/m^2) in a male patient and extreme obesity (BMI=75.4kg/m^2) in a female patient.

At 6 and 12 months of HAART, the table shows that there was similar increase in the mean BMI in both sex groups.

4.4. Opportunistic infections/conditions and hospitalization

At HAART initiation, 4/78 (5.1%) patients were asymptomatic i.e. classified WHO stage I, 12/78 (15.4%) were classified WHO stage II, 62/78 (79.4%) patients were classified as WHO stage III – IV [55/78 (70.5%) were WHO stage III, and 7/78 (8.9%) were WHO stage IV].

At initiation of HAART, 14/78 (17.9%) patients had tuberculosis (12 (15.4%) pulmonary tuberculosis and 2/78 (2.6%) pleural TB), 19/78 (24.4%) had gastroenteritis [16/78 (20.5%) chronic gastroenteritis and 3/78 (3.8%) acute gastroenteritis), 11/78 (14.1%) had skin conditions (2 bacterial skin infections, 2 non specific rash, 1 chronic eczema, 1 acute eczema, 1 herpes zoster, 1 chicken pox, 1 tinea vesicolor, 1 folliculitis and 1 genital warts), 11/78 (14.1%) had respiratory infections other than TB (9 LRTI and 2 URTI), 3 had PVDS, 2 had HIV encephalopathy, 2 had myelopathy, 1 otitis media, 1 external otitis, 1 oral candidiasis. At 2 weeks of HAART, 1 patient had PVDS and PID. At 1 month of HAART, 4/78 (5.1%) patients had skin conditions (1 Tinea capitis, 1 Genital Herpes simplex, 1 Herpes zoster, and 1 non specific rash). At 2 months of HAART, 2/78 had skin conditions (1 folliculitis, 1 Hespes Zoster), 1/78 patient had PID and UTI.

At 6 month of HAART, 2/78 (2.6%) patients had skin conditions (1 Herpes zoster, 1 Eczema), 4/78 had LRTI, 2 (33.3%) female patients had PVDS and 1(1.7%) had PID.

At 12 month of HAART, 3/78 patients had skin conditions (1 Bacterial skin infection, 1 Tinea rubrae and 1 Molloscum contageosum) and 1 female patient had PVDS.

Table III. Opportunistic infections/conditions at initiation of HAART and follow up visits

	Initiat.	2 weeks	1/12	2/12	6/12	12/12
Gastroenteritis	19	0	0	0	0	0
Tuberculosis	14	0	0	0	0	0

Skin condition	11	0	0	2	2	3
Resp. Infect.	11	0	4	0	4	0
PVDS	3	1	0	0	2	1
PID	0	0	0	1	1	0
HIV encephal.	2	0	0	0	0	0
Myelopathy	2	0	0	0	0	0
Otitis	2	0	0	0	0	0
UTI	0	0	0	1	0	0

Table III shows that gastroenteritis (19/78, 24.3%), tuberculosis (14/78, 18%), skin conditions (11/78, 14.1%) and non TB respiratory infections (11/78, 14.1%) were the most common opportunistic infections observed at HAART initiation and demonstrates the positive effect of HAART in reducing their occurrence at follow up visits.

During the pre-HAART period 6/78 (7.7%) patients were hospitalized; 3/6 (50 %) for acute gastroenteritis, 1/6 (16.7%) for HIV encephalopathy, 1/6 (16.7%) for PTB and 1/6 (16.7%) for PVDS.

During the post- HAART period 5/78 (6.4%) were hospitalized for few days; 1/5 for acute gastroenteritis (20%), 1/5 (20%) for anaemia, 1/5 (20%) for uterine fibroids, 1/5 (20%) for HIV encephalopathy and 1/5 (20%) for lactic acidosis.

Table IV. Causes of hospitalization before and during HAART

	Before HAART	During HAART
Gastroenteritis	3	1
HIV encephalopathy	1	1
Tuberculosis	1	0
PVDS	1	0
Uterine fibroids	0	1
Anaemia	0	1
Lactic acidosis	0	1

Table IV shows that before HAART, gastroenteritis was the most common cause for hospitalization (3/6, 50%) whereas, after HAART gastroenteritis remained an important cause for hospitalization (1/5, 20%) with other conditions (HIV encephalopathy, anaemia, lactic acidosis and uterine fibroids).

4.5. Patients' use of ARV drugs and HAART regimens

4.5.1. Patients' use of ARV drugs

Patients' use of ARV drugs was assessed at each visit. The respect for dates of appointments in terms of medication refills and blood tests repeat, medication timing and frequency, pills count, reporting of side effects and compliance to life style modification were defined as good adherence to HAART. Non respect to above parameters was defined as poor adherence.

At 4 weeks and 8 weeks of HAART, 4/78 (5.1%) patients experienced poor adherence to HAART compared to 74/78 (94.9%) who experienced good adherence. At 6 and 12 months of HAART respectively, 5/78 (6.4%) and 2/78 (2.6%) patients experienced poor adherence**.** At 6 and 12 months of HAART respectively, 3/5 (60%) patients and 1/2 patients (50%) who experienced poor adherence failed to achieve viral suppression.

4.5.2. HAART regimens

At HAART initiation, 72/78 (92.3 %) were initiated on lamuvudine + stavudine + efanvirez and 6/78 (7.7%) on lamuvudine+ stavudine + nevirapine.

At different periods of follow up visits, 7/78 (8.9%) patients had the above regimens adjusted (one of the components changed) or changed: 2/7 (28.6%) had stavudine changed to zidovudine due to peripheral neuropathy, 1/7 (14.3%) patient had stavudine changed zidovudine due to lactic acidosis, 1/7 (14.3%) patient had efanvirez changed to nevirapine due to breast hypertrophy (gynecomastia), 1/7 (14.3%) had efanvirez changed to nevirapine

due to pregnancy and 2/7 (28.6%) patients had their regimen changed to zidovudine+ didanosine + lopinavir/ritonavir due to virological failure.

4.6. ARV side effects / adverse events and long-term co-administered drugs

At 1 month of HAART, 3/78 (3.8%) presented with peripheral neuropathy, 2/78 (2.6%) with headache, 2/78 (2.6%) with rash not attributable to a specific drug, 1/78 (1.3%) with gastritis, 1/78 (1.3%) with vomiting, 1/78 (1.3%) with allergic reaction to cotrimoxazole, and 4/78 (5.1%) reported poor adherence.

At 2 months of HAART, 1/78 patient presented with peripheral neuropathy and 4/78 reported poor adherence.

At 6 months of HAART, 5/78 (6.4%) patients presented with peripheral neuropathy, 1/78 (1.3%) with breast hypertrophy (gynecomastia), 1/78 (1.3%) with bad dreams, 1/78 (1.3%) with lactic acidosis and 3/78 (3.8%) reported poor adherence.

At 12 months of HAART, 1/78 (1.3%) patients reported breast hypertrophy, 1/78 (1.3%) presented with peripheral neuropathy and 2/78 (2.6%) reported poor adherence.

Table V. ARV side/adverse effects at HAART follow up visits

	At 1month of HAART	At 2months of HAART	At 6months of HAART	At 12months of HAART
Peripheral neuropathy	3	1	1	1
Non specific rash	1	0	0	0
Gastritis	1	0	0	0

Vomiting	1	0	0	0
Cotrimoxazole allergy	0	0	0	0
Breast hypertrophy	0	0	1	1
Bad dreams	0	0	1	0
Lactic acidosis	0	0	1	0

Table V shows that peripheral neuropathy was the most common side effect reported by patients at follow up visits; 3/78 (3.8%) patients at 1 month of HAART and 1/78 (1.3%) patient respectively at 2, 6 and 12 months. At 6 and 12 months of HAART respectively, 1/78 (1.3%) patient reported breast hypertrophy. At 6 months, 1/78 (1.3%) patient reported bad dreams.

Long-term co-administered drugs at HAART initiation comprised of multivitamin which were prescribed to all the 78 patients (100%). Cotrimoxazole was prescribed to 45/78 (57.7%), rifampicin and INH to 5/78 (6.4%), ferrous sulphate and folic acid to 4/78 (5.1%), other drugs prescribed were pyridoxine, thiamine, griseofulvin and vitamin C.

Table VI .Long-term co-administered drugs at initiation of HAART

	Number of patients receiving the drug
Multivitamin	78 (100%)
Cotrimoxazole	45 (57.7%)
Rifampicin	5 (6.4%)
INH	5 (6.4%)
Ferous sulphate	4 (5.1%)
Folic acid	4 (5.1%)

Griseofuvin	2 (2.6%)
Pyridoxine	1 (1.3%)
Vitamin C	1 (1.3%)
Thiamine	1 (1.3%)

Table VI shows that the most commonly long–term co-administered drugs at initiation of HAART were constituted of Multivitamin (100%) and Cotrimoxazole (57.7%).

4.7. Laboratory parameters

4.7.1. CD4 cells count

At HAART initiation, of the 78 patients selected for the study, 71/78 (91%) had their CD4 cells count ≤ 200 [16/18 (88.9%) males and 55/60 (91.7%)] females and 7/78 (9%) had their CD4 count in the range of 200 – 350 [2/18 (11.1%) males and 5/60 (8.3%) females].

An increase of CD4 count from the base line value was considered as good response to HAART (immune reconstitution) and a non increase or decrease was considered as poor response to HAART (immunological failure).

At 6 months of HAART, 70/78 had their CD4 cells count measurements recorded; 65/70 (92.9%) showed good response to HAART (immune reconstitution) whereas 5/70 (7.1%) showed poor response (immunological failure).

At 12 months of HAART, 41/78 had their CD4 cell count measurements recorded, 29/78 had their CD4 results missing; 39/41(95%) showed good response (immune reconstitution) [5 (100%) males and 34(94.4%) females] to HAART whereas 2/41 (4.9%) showed poor response (all were females).

At HAART initiation, the mean CD4 was 131.4 (SD=11.8), with extreme values of 4 (minimum) and 312 (maximum).

At 6 month of HAART, there was an increase in the mean CD4 value (mean CD4=271, SD=124.4), with extreme values of 58 (minimum) and 600 (maximum).

At 12 months of HAART, there was further increase in the mean CD4 cell count value (mean CD4=322.1, SD=137.1), with extreme values of 106 (minimum) and 650 (maximum).

4.7.2. Viral Load (VL)

At HAART initiation, 66/78 (84.6%) had their VL measured; 23/66 (34.8%) had their VL < 100,000 copies/ml and 43/66 (65.2%) had their VL > 100,000 copies/ml.

Good response to HAART was evaluated by achieving viral load suppression. Viral suppression was defined as a measured plasma VL < 400 copies/ml. For the sake of data analysis, the researcher considered that all VL > 400 copies /ml be categorized as virological failure.

At 6 months of HAART, 73/78 (93.6%) had their plasma viral load measured; 66/73 (90%) had achieved viral suppression; amongst those 13/16 (81%) males and 53/57 (93%) females whereas 7/73 (10%) had virological failure; amongst those 3/16 (18.7%) males and 4/57 (7%) females.

Among patients who achieved viral suppression, 40/66 (60.6%) patients had their baseline VL > 100,000 copies/ml.

Compared by age groups, the majority of patients in all the groups experienced viral suppression (90.4%). The largest proportion of patients (38.5%) who had virological failure was found in the 46-55 years old age group.

At 12 months of HAART, 41/78 patients had their plasma VL measurements recorded, 37/78 patients had their VL results missing, 35/41(85.4%) achieved

viral suppression, amongst those 5/7 (71.4%) were males and 30/34 (88.2%) females whereas 6/41 (14.6%) had virological failure; amongst those 2/7 (28.6%) were males and 4/34 (11.8%) were females.
Overall, the proportion of patients who experienced virological failure increased from 9.6% at 6 months of HAART to 14.6% at 12 months of HAART.

The largest proportion of patients (33.3%) who experienced virological failure was found among the 46-55 years old age group. There was also a notable increase of virological failure from 3.7% to 14.3% amongst patients in the 26-35 years old age group.

4.7.3. Liver function tests (ALT)

ALT is a more specific index of hepatotoxicity compared to AST which also indicates muscle and liver cell destruction. ALT values were measured in the selected patients at initiation, 6 months and 12 months of HAART. Normal liver function was defined for ALT values between 40-80 U/l, mild liver toxicity for ALT values between > 80-200 U/l, moderate to severe toxicity for ALT values between 200 - 400 U/l and very severe toxicity for ALT values > 400 U/l.

At initiation of HAART, 75/78 had their ALT measured; 72/75 (96%) had normal liver function [16 (94.1%) were males and 56 (96.6%) females] and 3/75 (4%) had mild elevation of ALT [1(5.9%) male and 2 (3.4%) females]. The majority of patients in all the age groups had normal liver function.

At 6 months of HAART, 76/78 patients had their ALT measured; 75/76 (98.7%) had normal liver function (17 males and 58 females), 1 female had mild elevation of ALT (mild liver toxicity) and there was no difference in the different age groups.

At 12 months of HAART, 40/78 had their ALT measured; 39/40 (97.5%) had normal liver function [5 (100%) males and 34 (97.1%) females] and 1 female

had mild liver toxicity. Comparing all the age groups, there was a notable mild liver toxicity in the 36-45 years age group.

4.7.4. Haemoglobin level (Hb)

The haemoglobin level was measured at initiation, 6 and 12 months of HAART. The haemoglobin level (Hb) was defined as normal in both sex for Hb ≥ 12g/dl, mild anaemia for Hb = 10-11.9 g/dl, moderate anaemia for Hb = 8 - 9.9 g/dl and severe anaemia for Hb < 8 g/dl.

At initiation of HAART, 74/78 patients had their Hb measurements recorded; 30/74 (40.5%) had normal Hb level [11 (61.1%) males and 19 (33.9%) females]; 23/74 (31.1%) had mild anaemia [5 (27.8%) males and 18 (32.1%) females]; 18/74 (24.3%) had moderate anaemia [2 (11.1%) males and 16 (28.6%) females] and 3/74 (4.1%) had severe anaemia [all were females (5.4%)].

By age groups, there was mild anaemia in 50% of patients aged 36-45 years old; in 30.8% of patients aged 26-35 years old and in 33.3% of patients aged 56-65 years old. Moderate anaemia was significantly noted in the 18-25 years old age group (66.7%), the 46-55 years old age group (38.5%), the 36-45 years old age group (25%) and the 26-35 years old age group (15.4%).

At 6 months of HAART, Hb level was measured and recorded only in 4/78 patients; all of them (100%) had normal haemoglobin level [1 (100%) male and 3 (100%) female].

At 12 month of HAART, Hb level was measured and recorded only in 1/78 patient (female) who had normal haemoglobin.

Tables below summarise laboratory parameters results at initiation, 6 and 12 months of HAART.

Table VII. CD4, VL, ALT and Hb at initiation, 6 and 12 months of HAART by sex group

	At initiation	Male	Female	**At 6 months**	Male	Female	**At 12 months**	Male	Female
CD4	< 200	16 (88.9%)	55 (91.7%)	CD4 dec	0	5 (9.4%)	CD4 dec	0	2 (5.6%)
	> 200	2 (11.1%)	5 (8.3%)	CD4 incr	17 (100%)	48 (90.6%)	CD4 incr	5 (100%)	34 (94.4%)
VL	< 100000	4 (26.7%)	19 (37.3%)	VL<400	13 (81.3%)	53 (93%)	VL <400	5 (71.4%)	30 (88.2%)
	> 100000	11 (73.3%)	32 (62.7%)	VL>400	3 (18.7%)	4 (7%)	VL >400	2 (28.6%)	4 (11.8%)
ALT	0-80	16 (94.1%)	56 (96.6%)		17 (100%)	58 (98.3%)		5 (100%)	34 (97.1%)
	81-200	1 (5.9%)	2 (3.4%)		0	1 (1.7%)		0	1 (2.9%)
	201-400	0	0		0	0		0	0
Hb	≥ 12	11 (61.1%)	19 (33.9%)		1 (100%)	3 (100%)		-	1 (100%)
	10-11.9	5 (27.8%)	18 (32.1%)		-	-		-	-
	8-9.9	2 (11.1%)	16 (28.6%)		-	-		-	-
	< 8	0	3 (5.4%)		-	-		-	-

Table VII shows that the majority of males (88.9%) and females (91.7%) had their CD4 cells count below 200 cell/µl at initiation of HAART. Note that 100% of males and 90.6% of females, i.e. the majority of patients in both sex groups experienced an increase in CD4 cell count at 6 months of HAART.

At 12 months of HAART, note similar results of increase in CD4 count in all the males (100%) and the majority of females (94.4%).

The majority of patients in both sex groups [males (73.3%), females (62.7%)] had their baseline VL > 100.000 copies/ml at initiation of HAART. The majority of patients (90.4%) achieved viral suppression at 6 months of HAART. Note that more females (93%) than males (83.3%) achieved viral suppression.

Both sex groups had similar liver function profile at initiation, 6 and 12 months of HAART.

At initiation of HAART, the table shows the predominance of anaemia in female patients compared to male patients. Severe anaemia was noted in female patients only. Note the scarcity of Hb records at 6 and 12 months of HAART.

Table VIII. CD4, VL, ALT and Hb results at initiation of HAART by age group

Laboratory parameters		18-25	26-35	36-45	46-55	56-65	> 65
CD4 in cells/ul	CD4 < 200	2 (66.7%)	24 (85.7%)	27 (96.4%)	14 (93.3%)	2 (100%)	1 (100%)
	CD4 > 200	1 (33.3%)	4 (24.3%)	1 (3.6%)	1 (6.7%)	0	0
VL in copies/ml	< 100000	2 (100%)	9 (36%)	7(30.4%)	4 (26.7%)	1 (100%)	0
	> 100000	0	16 (64%)	16 (69.6%)	11 (73.3%)	0	0
ALT in Units/litre	0 - 80	3 (100%)	25 (92.6%)	28 (96.6%)	12 (100%)	3 (100%)	1 (100%)
	81-200	0	2 (7.4%)	1 (3.4%)	0	0	0
	201-400	0	0	0	0	0	0
Hb in g/dl	> 12	1 (33.3%)	12 (46.2%)	7 (25%)	7 (53.8%)	2 (66.7%)	1 (100%)
	10-11.9	0	8 (30.8%)	14 (50%)	0	1 (33.3%)	0
	8-9.9	2 (66.7%)	4 (15.4%)	7 (25%)	5 (38.5%)	0	0
	< 8	0	2 (7.7%)	0	1 (7.7%)	0	0

Table VIII shows that at initiation of HAART, the majority of patients in each age group had their CD4 < 200 cells/ul, VL > 100,000 copies/ml and normal liver function (ALT= 0 - 80 U/l).

Note the presence of mild anaemia in 50% of patients aged 36-45 years old, in 30.8% of patients aged 26-35 years old and 33.3% of patients aged 56-65 years old. Moderate anaemia was predominantly observed in 66.7% of patients aged 18-25 years old.

Table IX. CD4, VL, ALT and Hb results at 6 months of HAART by age group

Laboratory parameters		18-25	26-35	36-45	46-55	56-65	> 65
CD4 in cells/ul	CD4 decr.	0	2 (7.4%)	2 (8.3%)	1 (7.1%)	0	0
	CD4 incr.	2 (100%)	25 (92.6%)	22 (91.7%)	13 (92.9%)	2 (100%)	0
VL in copies/ml	< 400	3 (100%)	26 (96.3%)	26 (96.3%)	8 (61.5%)	3 (100%)	0
	> 400	0	1 (3.7%)	1 (3.7%)	5 (38.5%)	0	0
ALT in Units/litre	0 - 80	3 (100%)	27 (100%)	27 (96.4%)	14 (100%)	3 (100%)	1 (100%)
	81-200	0	0	1 (3.6%)	0	0	0
	201-400	0	0	0	0	0	0
Hb in g/dl	> 12	0	1 (100%)	-	1 (100%)	-	-
	10-11.9	0	0	0	-	-	-
	8-9.9	0	0	0	-	-	-
	< 8	0	0	0	-	-	-

Table IX shows that at 6 months of HAART, the majority of patients experienced an increase in CD4 cell count. A decrease in CD4 count was noted in the age groups 26-35, 36-45 and 46-55 years old patients. All age groups achieved similar viral suppression. Liver function profile remained as well similar in both age groups.

Table X. CD4, VL, ALT and Hb results at 12 months of HAART by age group

Laboratory parameters		18-25	26-35	36-45	46-55	56-65	> 65
CD4 in cells/ul	CD4 decr.	0	1 (6.7%)	0	1 (11.1%)	0	0
	CD4 incr.	2 (100%)	14 (93.3%)	13 (100%)	8 (88.9%)	1 (100%)	1 (100%)
VL in copies/ml	< 400	2 (100%)	12 (95.7%)	13 (92.9%)	6 (66.7%)	1 (100%)	1 (100%)
	> 400	0	2 (14.2%)	1 (7.1%)	3 (33.3%)	0	0
ALT in Units/litre	0 - 80	2 (100%)	14 (100%)	15 (93.8%)	7 (100%)	1 (100%)	0
	81-200	0	0	1 (6.3%)	0	0	0
	201-400	0	0	0	0	0	0
Hb in g/dl	> 12	-	-	-	1 (100%)	-	-
	10-11.9	-	-	-	0	-	-
	8-9.9	-	-	-	0	-	-
	< 8	-	-	-	0	-	-

Table X shows that at 12 months of HAART, the majority of patients in all age groups experienced an increase in CD4 cell count, achieved viral suppression

(VL< 400) and had normal liver function (ALT=0-80 U). Note the increase in virological failure in the 46-55 age group (33.3%) and further more scarcity of Hb results at 12 months of HAART.

Chapter 5
Discussions

5.1. Introduction

The administration of HAART to HIV/AIDS patients has been recognized worldwide to be accompanied with better clinical outcomes. Nevertheless there have been identified factors that influence outcomes in patients receiving HAART, notably age, gender, race (ethnicity), nutritional status, anaemia, baseline CD4 cells count, baseline viral load, WHO stage of disease progression, adherence, depression, malaria smear positive, platelet level and the list is not exhaustive.

In this chapter, the researcher is discussing the study findings on the factors that constituted the objectives of this study, notably patients' demographic characteristics, nutritional status, opportunistic infections/conditions and hospitalization, patients' use of ARV drugs and HAART regimens, ARV drugs side/adverse effects and laboratory parameters [CD4 cells count, viral load (VL), liver function (ALT), and haemoglobin (Hb) level] at initiation, 6 and 12 months of HAART, comparing those results with the reviewed literature.

5.2. Demographic characteristics

Demographically, 77% (60/78) of the study population were females and 23 % (18/78) males at initiation of HAART. Comparatively, at 6 and 12 months of HAART, female patients showed better response to HAART in achieving viral suppression, 53/57 (93%) VS 13/16 (81%) and 30/34 (88.2%) VS 5/7 (71.4%) respectively. This finding collaborates with what ART-CC (2010) and Saleri et

al. (2009) did observe that female gender was associated with better clinical outcomes. Saleri and his collaborators in Burkina Faso suggested that female patients were experienced better clinical outcomes than male patients due to their earlier and massive up take into prevention of mother to child transmission programs (PMTCT), thus earlier diagnosis and treatment of HIV infection.

Close to ninety-nine percent (98.7%) of the study population was constituted of subjects belonging to the black ethnic. Thus ethnicity was not found to be an influencing factor in this study. Whereas, Smith et al. (2004) found that white ethnicity was a favourable factor in clinical outcome in their study population. Ethnicity can only be studied in study populations where both ethnical groups are significantly representative.

Most of the patients enrolled in the study belonged to the age groups 26-35 years old (35.9%), 36-45 years old (37.2%) and 46-55 years old (17.9%). There was an increase in poor clinical outcomes in the age group 46-55 years old, respectively 38.5% and 33.3% of virological failure at 6 and 12 months of HAART. This finding collaborate with the Antiretroviral therapy Cohort Collaboration , ART-CC (2010) study which found that age > 37 years old was associated with poor clinical outcomes. The reason given by the Cohort Collaborative study, notably increased risk in this age group of cardiovascular diseases, malignancies and renal pathologies could not be identified in this study.

The rate of unemployment in the study population was very high (93.4%) and the influence of profession with high risk of HIV infection rate and poor adherence issues, such as Sex workers, Bus and Truck Drivers could not be established . Only 1 patient (1.3%) over the 78 patients selected for the study was a Truck-Driver. No patients in the study declared to be a sex worker due to the fact that the profession has not yet been legalised in South Africa, though it is commonly practised in big cities and residential areas of South Africa. Those factors related to unemployment (poverty) and high risk

professions for HIV-infection, Sex workers and Truck drivers (Hudson, 1996; Ramjee et al., 2002; Lankoande et al., 1998; Mbugua et al., 1995; Bwayo et al., 1994) were not found published in the reviewed literature. High risk professions for HIV-infection and unemployment (poverty) as potential factors that could influence clinical outcomes in patients on HAART needs more studies to be explored, especially in the South African context.

Similarly, overall 90% of the population of the study reside in different residential areas of Vryburg whilst 10% reside in the surrounding villages and farms. Although the percentage of patients residing outside Vryburg in the study sample is negligible, this raises the real problem of accessibility to health care services for patients residing outside Vryburg and how this factor could influence the clinical outcomes in patients on HAART in this group of the population attending ARV clinic at Vryburg District Hospital.

Although generally known that accessibility to health care impacts negatively on population health (U.S. Department of Health and Human Services, 2003), place of residence (accessibility to health care) as a potential factor that could influence clinical outcomes in patients on HAART was not found published in the reviewed literature and needs to be as well studied further in the South African context.

5.3. Nutritional status

At initiation of HAART, 17 (21.8%) patients over the 78 selected for the study were classified as underweight with their BMI < 18.5 kg/m^2, whereas Sieleunou et al (2009) found that 56.1% of their patients were underweight (BMI <18.5).

In both sexes, there was an increase in the mean weight at 6 and 12 months respectively. In male patients, the mean weight at initiation (57.5 kg, SD 8.0) increased respectively at 6 months (63.0 kg, SD 13.0) and 12 months of HAART (65.2 kg, SD 4.5). In female patients, it increased from 53.8 kg (SD 12.6) at initiation, to 58.1 kg (SD 12.0) at 6 months and 59.5 kg (SD 12.0) at

12 months of HAART. This finding collaborates with the trends that Dokekias et al (2008) observed in Brazaville/Congo Republic, during the 24 months of the administration of HAART to their patients and noted that there was an average weight gain of about 18 kgs.

The effect of malnutrition on clinical outcomes in patients on HAART at Vryburg District hospital was not collaborating with previous researchers. Among the 17 underweight patients enrolled for the study, 14 (82.4%) achieved viral suppression at 6 months whereas, Sieleunou et al. (2009) in Cameroon found that malnutrition was one of the independent predictors of death. Collaborating with the last study, Paton et al. (2006) observed that the presence of malnutrition at initiation of HAART was significantly associated with decreased survival, but it did not affect the increase in CD4 cells count (immune reconstitution).

Malnutrition as a factor influencing clinical outcomes in patients on HAART needs to be studied further in the South African context in general, and Vryburg in particular, since 21.8% of patients in the study were malnourished (underweight) and that higher unemployment rate (93.4%) observed in the study, may be an aggravating factor to poverty, thus malnutrition.

5.4. Opportunistic infections/conditions and hospitalization

The majority of patients (79.4%) were classified as WHO clinical stage III-IV. Similarly Sieleunou et al. (2004) in Cameroon observed that 90.4% of their patients were at WHO stage III-IV of HIV disease progression.

At initiation of HAART, 24.4% of patients had gastroenteritis, 17.9% of patients had tuberculosis, 11.1% of patients had skin conditions, 14.1% of patients had respiratory infections other than tuberculosis, 3 female patients had per vaginal discharge syndrome (PVDS), 2 patients had HIV encephalopathy, 2 patients had myelopathy and 3 patients had ENT infections (2 Bacterial otitis and 1 oral Candidiasis).

Similarly, at initiation of HAART, Dai et al (2006) observed that 27/103 (26.2%) of patients had tuberculosis, 24/104 (23.3%) had Candidiasis infections, 8/103 (7.8%) had Cytomegalovirus infections, 6/103 (5.8%) had Herpes simplex virus infections, 6/103 (5.8%) had Pneumocystis jiroveci pneumoniae, 5/105 (4.9%) bacterial infections and 3/103 (2.9%) had sepsis.

Before HAART initiation, 6/77 (7.7%) patients were hospitalized for few days: 3/6 (50%) for gastroenteritis, 1/6 (16.7%) for HIV encephalopathy, 1/6 (16.7%) for pulmonary tuberculosis (PTB) and 1/6 (16.7%) for per vaginal discharge syndrome (PVDS).

After HAART initiation, 5/78 (6.4%) patients were hospitalized: 1/5 (20%) for gastroenteritis, 1/5 (20%) for anaemia, 1/5 (20%) for uterine fibroids, 1/5 (20%) for HIV encephalopathy and 1/5 (20%) for lactic acidosis.

Comparatively, Saleri et al. (2009) in Burkina Faso found as well that gastroenteric symptoms constituted 61.7% of causes of hospitalisation in their study population. This finding collaborates with the observation that gastroenteritis was the major cause for hospitalization for patients on HAART at Vryburg District Hospital.

Hospitalization as a factor associated with poor clinical outcome (Fielden et al., 2008) was not established amongst the 6.4% (5/78) patients hospitalized during the period of the study. Further studies are needed to determine the influence of hospitalization on clinical outcomes in the South African context.

There was no death amongst patients selected in the study giving an erroneous impression of zero death rate. This impression could be justified by the small study population and the short duration of the study period.

5.5. Patients' use of ARV drugs and HAART regimens

Patients' use of ARV drugs in the study was good as demonstrated by the results of viral suppression at 6 and 12 months of HAART. Good adherence to

HAART was defined as patients' ability to respect dates of appointments for medication refills and blood tests repeats, medication timing and frequency, pills counts, reporting of side effects and compliance to life style modification. Non respect of above parameters was defined as poor adherence.

At 6 and 12 months of HAART respectively, 5/78 (6.4%) and 2/78 (2.6%) patients experienced poor adherence and of those, 3/5 (60%) and 1/2 (50%) patients failed to achieve viral suppression. This finding collaborate with the literature that poor adherence is a major factor for poor clinical outcomes (Mills et al., 2006; New York State Department of Health, 2008; South Africa Department of Health, 2004).

At initiation of HAART, the majority of patients were initiated on lamuvudine + stavudine + efanvirez (92.3%) and the minority on lamuvudine + stavudine + nevirapine (7.7%). At different periods of follow up visits, 7/78 (8.9%) patients had one component of the regimen substituted or the entire regimen was changed due to different reasons. Two over 7 (28.6%) patients had stavudine substituted with zidovudine due to peripheral neuropathy, 1/7(14.3%) patient had stavudine substituted with zidovudine due to lactic acidosis, 1/7 (14.3%) had efanvirez substituted with nevirapine due to gynaecomastia, 1/7(14.3%) had efanvirez substituted to nevirapine due pregnancy occurrence and 2/7 (28.6%) had the entire regimen changed to zidovudine + didanosine + LPV/RTV due to virological failure.

Similarly, Dokekias et al. (2008) in Brazaville / Congo Republic initiated their patients on stavudine or zidovudine + lamuvudine+ nevirapine (59%), stavudine or zidovudine + lamuvudine + efanvirez (28.7%), stavudine or zidovudine + lamuvudine + indinavir (8.9%) and stavudine or zidovudine + didanosine + nevirapine (3.2%).

Comparatively, Dokekias et al. (2008) preferred nevirapine based regimens (59%) than in the Vryburg District Hospital study (7.7%) where efanvirez based regimens were the most prescribed (92.3%).

Dai et al. (2006) used in their regimens 1 NNRTI + 2 NRTI or 1PI + 2 NRTI. They reported that 13 patients had their corresponding ARV drugs changed due to failure to control side effects. This finding confirms the importance of monitoring closely patients on HAART for timely identification of major side/adverse effects and HAART regimens adjustment or change.

Further more, complicated regimens have been mentioned to affect the adherence to HAART (Mills et al., 2006) and thus, clinical outcomes of patients on HAART. Complicate regimens was not a problem in this study since HAART regimens were simple, constituted of a maximum of 3 ARV drugs, with a daily frequency for each drug of 1 dose to 2 doses per day.

5.6. ARV side/adverse effects and long-term co-administered drugs

At 1 month of HAART, 3.8% of patients presented with peripheral neuropathy, 2.6% with headache, 2.6% with rash not attributable to a specific drug, 1.3% with gastritis, 1.3% with vomiting, 1.3% with allergic reaction to Cotrimoxazole, and 5.1% of patients reported poor adherence.

At 6 months of HAART, 6.4% of patients presented with peripheral neuropathy, 1.3% with gynaecomastia, 1.3% with bad dreams, 1.3% with lactic acidosis and 3.8% reported poor adherence.

At 12 months of HAART, 1.3% of patients presented with gynaecomastia, 1.3% with peripheral neuropathy and 2.6% reported poor adherence.

Long course co-administered drugs at initiation of HAART were constituted of Multivitamin which was prescribed in 100% of patients, Cotrimoxazole in 57.7% of patients, Rifampicin and INH to 6.4% of patients, and ferrous sulphate and Folic acid to 5.1% of patients. Other drugs were made of Pyridoxine, Thiamine, Griseofulvin and Vitamin C.

The co-administration of d4T and INH has been reported to have increased the occurrence of peripheral neuropathy in patients receiving both HAART and TB treatment (Breen et al., 2000). As mentioned above, peripheral neuropathy constituted the major reason (28.6%) for the substitution of d4T by another ARV drug in the study.

Comparatively, Dai et al. (2006) noted that fatigue, body malaise and weight loss were the most major complaints of their patients after being initiated on HAART during the 12 months of their study. They observed that one patient died from hepatic failure due to nevirapine and hepatitis C co-infection.

Severe side/adverse effects of ARV drugs (drug toxicity), as complex ARV drugs regimens, have been mentioned to affect the adherence of patients to HAART (Mills et al., 2006). This stresses the importance of closely monitoring patients on HAART, especially at HAART initiation periods and at substitution or regimens change periods for timely identification and management of side/adverse effects.

5.7. Laboratory parameters

5.7.1. CD4 cells count

At HAART initiation, the majority of patients (91%) had severe immunosuppression with their CD4 cells count < 200 cell/µl and only 9% of patients had their CD4 cells count within the range of 200-350 cell/µl. The South African ARV National Guidelines (2004, 2010) recommends that all the patients with CD4 cell counts < 200 cells/ul are started on HAART and those at WHO stage-IV of disease progression, no matter their baseline CD4 cell count values.

At 6 and 12 months of HAART, 92.9% and 95% of patients respectively showed an increase in their CD4 cells count. The mean CD4 cells count increased from 131.4 cell/µl (SD=11.8) at initiation of HAART to 271 cell/µl

(SD=124.4) and 322.1cell/µl (SD=137.1) at 6 and 12 months of HAART respectively.

Comparatively, Smith et al. (2004) measured CD4 cells count at 6, 12 and 24 months of HAART and noted the increase in CD4 cells count respectively of 114, 181 and 248 cell/µl. They observed that white ethnicity, higher pre-HAART viral load (VL > 100, 000 copies/ml) and lower pre-HAART CD4 and CD8 cells count were associated with greater increases in CD4 cells count (an average of 5.2 cell/µl/year , 95% CI). Maintaining viral suppression was an important factor for the increase in CD4 cells count. They could not establish the association between the increase in CD4 cells count and sex, age, risk group and HAART regimens.

Similarly Dai et al. (2006) in Singapore, noted that CD4 cells count increased to 165+/-51 cell/µl after 12 months of HAART and George et al. (2009) in India, observed that the increase in CD4 cells count was 107.46 (SD 106.25) after 6 months of HAART.

Dokekias et al. (2008) in Brazzaville/Congo Republic noted the increase in CD4 cells count of 353 cell/µl after 24 months of HAART.

Coetzee et al. (2004) in Kayelitsha/South Africa noted as well immune reconstitution in patients initiated on HAART with low CD4 cells count, confirming the beneficial effects of HAART in resource-limited settings.

All the studies mentioned above confirm the observation in the study that the administration of HAART to HIV/AIDS patients result generally in the increase of CD4 cell counts (immune reconstitution).

5.7.2. Viral load (VL)

The majority (65.2%) of patients had their baseline VL > 100,000 copies/ml and the minority (34.4%) had their VL < 100,000 copies/ml.

At 6 and 12 months of HAART respectively, 90% and 85.4% achieved viral suppression (VL < 400 copies/ml).

At 6 months of HAART, over the 66 patients who achieved viral suppression, 40 patients (40/66 i.e. 60.6%) had their baseline VL > 100,000 copies/ml. This observation collaborate with Smith et al. (2004) and Shikuma et al. (2004) who respectively observed that baseline VL > 100,000 copies/ml was associated with a greater increase in CD4 and gain in lean body mass.

Contrary to the study above, Fielden et al. (2008) found that higher viral load was associated with increased risk of hospitalization.

The majority of females than males achieved viral suppression respectively at 6 months (93% vs. 81%) and 12 months (82.2% vs. 71.4%).
This observation collaborate with ART-CC (2010) study which published that female gender was associated with better clinical outcomes.

Virological failure was significantly noted in the age group 46-55 years old at 6 months (38.5%) and 12 months respectively (33.3%). This observation collaborate with previous study that younger age (< 37 years) was associated with better clinical outcomes (ART-CC, 2010).

Comparatively, Smith et al. (2004) measured viral load at 6, 12 and 24 months of HAART in their patients and found that 84%, 84% and 80% of patients respectively had achieved viral suppression (VL< 400 copies/ml).

Similarly, Dai et al (2006) observed that after 12 months of HAART, viral load was reduced to 3.2 +/- 0.7 log copies/ml.

All the studies mentioned above confirm the observation in the study that the administration of HAART to HIV/AIDS patients is generally followed by the reduction in their viral load and viral suppression, which is the ultimate beneficial response.

Nevertheless the observation that the response to HAART reduced with time in previous studies suggest the occurrence of resistance to treatment which could not be established in this study, as this requires ARV drugs resistance testing and longer periods of exposure to ARV drugs.

5.7.3. Liver function (ALT)

The majority (96%) of patients had normal ALT range at HAART initiation. Similar proportion of males (94.1%) and females (96.6%) had normal liver function.

The trends remained similar in both sex groups at 6 months (98.7%) and 12 months (97.5%) of HAART. These observations collaborate with the fact that only 7.7% of the patients in the study were initiated on nevirapine based regimens, justifying that liver toxicity was not a major problem during the period of the study.

5.7.4. Haemoglobin level (Hb)

At initiation of HAART, mild anaemia described in both sex as Hb = 10-11.9 g/dl was noted in 31.1% of patients; moderate anaemia (Hb = 8 - 9.9 g/dl) in 24.3% of patients and severe anaemia (Hb < 8 g/dl) in 4.1% of patients.

At 6 and 12 months of HAART, anaemia was resolved in all the few patients who had their Hb measurements recorded. This observation suggests a corrective effect of HAART on anaemia.

Comparatively, Buskin and Sullivan (2004) describing anaemia as an Hb < 10.5 g/dl, noted that anaemia decreased from 13 to 5% with the provision of HAART during their prospective cohort study through 1996 to 2001. They also found that blood transfusion was associated with the risk of death. The latest observation could not be verified in the study since blood transfusion was not administered to enrolled anaemic patients.

Similarly, Mocroft et al. (1999) describing anaemia as an Hb < 14 g/dl in males and < 12 g/dl in females, observed that 58.2% of their patients had mild anaemia (Hb = 8-14 g/dl in males, 8-12 g/dl in females) and 1.4% had severe anaemia (Hb < 8 g/dl). They also observed that anaemia was associated with a much faster HIV disease progression and that anaemia was an independent prognostic marker of death.

In this study, anaemia was resolved in 100% of patients who had their haemoglobin level measurements recorded at 6 and 12 months of HAART, although only few patients had their Hb measurements captured. The fact that the haemoglobin results of the majority of patients were missing rendered the assessment of anaemia biased. Further more, due to hospital financial constraints; it is common practice that haemoglobin level testing is not routinely performed on all patients on HAART, but only on very ill looking patients and those experiencing symptoms and signs suggestive of anaemia, notably dizziness, asthenia, pallor and bleeding tendancies. Exception to the above practice is the recommendation in South African ART guidelines that patients receiving zidovudine based regimens have their haemoglobin levels monitored regularly so that any fall in the haemoglobin level be dealt with by prompt substitution of zidovudine by a safer haematofriendly ARV drug.

5.8. Limitations of the study

Amongst others, the researcher would like to recognise following limitations of this study:

- Short period (12 months) of the study for a life long treatment, not allowing to assess the long term effect of HAART on outcomes;

-Study sample made predominantly of female gender; making the comparison between genders biased;

- Small sample of the study for a treatment which is being administered to thousands of South Africans, as such, sample not suitable for inferential

statistics and affecting the generalization of the results of the study to the rest of the population and the power of the study;

- The sample selection process resulted in a study sample mainly made of residents of Vryburg whilst the population of patients on HAART at Vryburg district hospital is made of a good number of patients residing in villages and farms located several kilometres away from Vryburg, posing the real problem of accessibility to ARV clinic and adherence to HAART;

- The population of the study mainly belonging to the black ethnic group could not be representative for a multi-cultural society that South Africa is; making ethnicity as a factor that could influence outcomes on patients on HAART irrelevant for the study;

- The sampling process resulted in non selection of files of deceased patients during the period of the study giving the erroneous impression of zero death rate observed during the study period; and

- The missing data on laboratory parameters of the study (CD4 count, VL, ALT and Hb) affected the interpretation of study results on the real magnitude of the effect of HAART on immune reconstitution, viral suppression, liver toxicity and specifically the scarcity of haemoglobin results which made the interpretation of the corrective effect of HAART on anaemia non-substantiated (biased).

Chapter 6
Conclusions and Recommendations

The administration of HAART to HIV/AIDS patients residing in Vryburg, the surrounding villages and farms was followed by better clinical outcomes in terms of improvement of the overall weight (nutritional status), correction of anaemia, reduction of occurrence of opportunistic infections, increment of CD4 cells count and achieving viral suppression.

Younger age, female gender, VL > 100,000 copies/ml and good adherence were found to have a positive influence on clinical outcomes whereas older age, male gender and poor adherence had negative influence on clinical outcomes.

Other factors, such as, place of residence (accessibility to health care), unemployment (poverty), high risk professions for HIV infection (e.g. Sex workers, Bus and Truck drivers) and ethnicity (Race) could not be proven to have influenced the clinical outcomes in patients on HAART at Vryburg District Hospital due to their paucity in the study sample.

Further studies are needed to explore specifically those factors in Vryburg and other South African practices.

Nevertheless, given the proven universal positive effect of HAART in improving survival and quality of life, the beneficial effect of younger age on outcomes, the researcher recommends to local governments and relevant health institutions that:

- HAART be made accessible to all the patients affected by HIV disease and that mass education is provided to every young person emphasizing the importance of early diagnosis and early treatment on clinical outcomes;

-the recent initiative by the government of South Africa to have HAART initiated by nurses at primary health care level (NIMART= Nurse Initiated Management of Antiretroviral treatment), such important step towards achieving massive accessibility to HAART, be speeded up by all means and supported by all stakeholders for its immediate effective implementation.

References

Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1 patients treated with HAART.
Accessed on 7/6/2010 at: http://www.art-cohort-collaboration-org

Bekker, L.G., et al., 2006. Rapid scale-up of a community-based HIV treatment service: programme performance over 3 consecutive years in Guguletu, South Africa. S Afr Med J; 96(4):315-320

Boulle, A., et al., 2007. Substitutions due to ARV toxicity or contraindication in the first 3 years of ART in a large South African Cohort. Antivir Ther; 12(5): 753-760

Breen, A.M., Lipman, C.I., Johnson, M.A., 2000. Increased incidence of peripheral neuropathy with co-administration of Stavudine and Isoniazid in HIV –infected individuals. AIDS 14(5): 615

Buskin, S.E., Sullivan, P.S., 2004. Anaemia and its treatment and outcomes in persons infected with human immunodefiency virus. Transfusion; 44(6):pp.826-32.

Bwayo, J., et al., 1994. Human immunodeficiency virus infection in long-distance truck drivers in East Africa. Archives of Internal Medicine; 154 : 1391-96.

Coetzee, D., et al., 2004. Outcomes after two years of providing ART in Khayelitsha, South Africa. AIDS; 18(6): 887- 95.

Dai Y, et al., 2006. Clinical outcomes and immune reconstitution in 103 advanced AIDS patients undergoing 12-month highly active antiretroviral therapy. Chin Med J (Engl); 119(20): 1677- 82.

Dokekias, A.E., et al., 2008. Evaluation of antiretroviral therapy in HIV-infected adults in the Department of Haematology, University Hospital of Brazaville, Congo. Bull Soc Pathol Exot; 101(2):pp.109-12.

Ferradini, L., et al., 2006. Scaling up of HAART in rural district of MALAWI: an effectiveness assessment. Lancet; 367(9519): 1335-1342.

Fielden, S.J., et al., 2008. Predicting hospitalization among HIV-infected antiretroviral naïve patients starting HAART: determining clinical markers and exploring social pathways. AIDS Care; 20(3):297-303.

George, C., Yesoda, A., Jayakumar, B., Lal, L., 2009. A prospective study evaluating clinical outcomes and costs of three NNRTI-based HAART regimens in Kerela, India. J Clin Pharm Ther; 34(1): 33-40.

Hartzell, J.D., Janke, I.E., Weintrob, A.C., 2008. Impact of depression on HIV outcomes in the HAART era. J Antimic Chem.; 62(2): 246-255

Hawkins, C., et al., 2007. Antiretroviral Durability and Tolerability in HIV-infected adults living in Kenya. J Acquir Immune Defic Syndr; 45(3): 304-310

Hogg, R.S., et al., 1997. Decline in Deaths from AIDS due to new antiretrovirals. Lancet; 349: 1294

Hudson, C.P., 1996. AIDS in rural Africa: a paradigm for HIV-1 prevention. International Journal of Sexually Transmitted Diseases and AIDS; 7 (4): 236-43.

Lankoande, S., et al., 1998. HIV infection in truck drivers in Burkina Faso: a seroprevalence survey. Medecine Tropicale; 58 (1): 41-6.

Lawn, S.D., Myer, L.G., Wood, R., 2006. CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing ART in Sub-Saharan Africa. BMC Inf Dis; 6:59

Lawn, S.D., et al., 2006. Determinants of mortality and nondeath losses from an ART service in South Africa: Implications for program evaluation. Clin Infect Dis; 43(6): 770-776

Lawn, S.D., et al., 2005. Early mortality among adults accessing a community-based ARV service in South Africa: Implications for program design. AIDS; 19(18): 2141-1248

Mahungu et al., 2009. HIV as a chronic disease. Clin Med; 9 (2): 125- 8

Mbugua, G.G., et al., 1995. Epidemiology of HIV infection among long distance truck drivers in Kenya. East Africa Med J 72 (8): 515-18

Mills, E.J., et al., 2006. Adherence to HAART: A Systematic Review of Developed and Developing Nation Patient-Report Barriers and Facilitators. PLoS Med 3(11): e438.

Mocroft, A., et al., 1999. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA Study group. AIDS; 13(8):943-50

New York State Department of Health, 2008. Antiretroviral therapy. New York (NY): State Department of Health.

Paton, N.I., Sangeetha, S., Earnest, A., Bellamy, R., 2006. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. HIV Med.; 7(5):323-30.

Ramjee, G., Gouws, E., 2002. Prevalence of HIV among truck drivers visiting sex workers in Kwazulu-Natal, South Africa. Sexually Transmitted Diseases 29 (1): 44-9.

Saleri, N., et al. 2009. Outcomes and predictive factors of Mortality in hospitalized HIV-patients in Burkina Faso. Infection; 37(2):pp. not provided

Sanne, I.M., et al., 2009. Long Term Outcomes on ART in a large HIV/AIDS care clinic in Urban South Africa: a prospective cohort study. J Int. AIDS Soc; 12:38

Sieleunou, I., et al., 2009. Determinants of Survial in AIDS patients on antiretroviral therapy in a rural centre in the far-North Province, Cameroon. Trop Med Int Health; 14(1): 36-46.

South Africa Department of Health, 2004. National Antiretroviral Treatment Guidelines. South Africa, Department of Health.

South Africa Department of Health, 2010. Clinical Guidelines for the management of HIV and AIDS adults and adolescents. South Africa, Department of Health.

Shikuma, C.M., 2004. Changes in weight and lean body mass during highly active antiretroviral therapy. Clin Inf Dis.; 39(8):pp.1223-30

Smith, C.J, et al., 2004. Factors influencing increases in CD4 cells counts of HV-positive persons receiving long-term highly active antiretroviral therapy. J Inf Dis; 190(10):pp.1860-8.

WHO, 2008. BMI classification. Geneva

Appendices

Appendices contain copies of the approved protocol, authorization letters to conduct the research at Vryburg District Hospital and MREC clearance certificate.

APPENDIX I: RESEARCH PROTOCOL

APPENDIX II: AUTHORIZATION LETTERS

APPENDIX III: MREC CLEARANCE CERTIFICATE:MREC/M/59/2010:PG

APPENDIX- I --.

UNIVERSITY OF LIMPOPO

Medunsa Campus

Department of Family Medicine and Primary Health Care

Research Protocol:

Factors influencing clinical outcomes in patients on Highly Active Anti-Retroviral Therapy (HAART) at Vryburg District Hospital, Northwest Province in South Africa

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INTRODUCTION (MOTIVATION OF THE STUDY)

The treatment of HIV-infected patients with highly active antiretroviral therapy (HAART) leads to immune reconstitution as shown by the increase in CD4 counts decreased risk of opportunistic infections i.e. improved quality of life and improved survival.[1, 2, 3, 4]

The South African Government's response to the epidemic of HIV and AIDS has evolved significantly over the past few years. In 2004, appeared the first National Antiretroviral Treatment Guidelines, as a standardized tool to be used by all clinicians involved in the care of the HIV/AIDS patients.[5] The national strategic plan prescribes that teaching and provincial hospitals be the starting points for the initiation of HAART, followed by a progressive roll-out program in each province. In the district renamed Dr. Ruth Segomotsi Mompati (where the researcher practises), Taung Hospital was used as initial site at the same level as provincial hospitals. After proper assessment and recruitment of health care personnel, the programme was rolled-out at Vryburg District Hospital on the 3rd of June 2006, becoming the down-referral site for Klerksdorp/Tshepong Complex Hospital (level 2 hospital) and Taung District Hospital, the initial site in the district.

After being appointed as Medical Officer at Vryburg Hospital ARV clinic in June 2007, the researcher noted a diversity of HIV/AIDS patients being started on HAART and was concerned about the very sick patients at WHO stages 3- 4 of HIV disease progression. The study intends

to investigate factors that influence clinical outcomes in patients on HAART, in the context of South African National Antiretroviral Treatment Guidelines.

LITERATURE REVIEW

FACTORS INFLUENCING CLINICAL OUTCOMES IN PATIENTS ON HAART

Evaluating the clinical outcomes and costs of three NNRTI-based HAART regimens in Kerala, India, George et al. conducted a prospective observational study over a period of 6 months. One hundred and forty two (142) HIV/AIDS patients were enrolled, divided in 3 different treatment groups and given free NNRTI-based combination therapy. They observed that the increase in CD4 cell count was 107.46 (SD: 106.25). Their study concluded that the provision of free NNRTI-based combination therapy to HIV/AIDS patients in Kerala, India, resulted in greater than 90% adherence, leading to better clinical outcomes in terms of increasing CD4 cell counts and low mortality, for patients consistently attending a treatment clinic.[2]

Evaluating the impact of malnutrition on survival and the CD4 cell count response in HIV- infected patients starting antiretroviral therapy, Paton et al. conducted a retrospective cohort study of 394 HIV/AIDS patients attending the national HIV referral centre in Singapore. Patients had a CD4 cell count less than 250 cell/µl. At baseline, 16% of patients had severe to moderate malnutrition and was found to be an independent predictor of death [hazard ratio (HR)2.17, 95% CI 1.29 -3. 73, P=0.004 for those with BMI < 17 compared to those with BMI > 18.5] as were stage of disease [HR: 2.47, 95% CI 1.20 – 5.07, P= 0.014 for those who were at stage C compared with those at stage A] and the type of antiretroviral therapy (HR: 0.50, 95% CI 0.27 – 0.93, P=0.03 for HAART compared to non-HAART treatment]. Malnutrition did not impair the magnitude of the increase in CD4 cell count at 6 or 12 months.'' They concluded that malnutrition at the time of starting antiretroviral therapy was significantly associated with decreased survival, but the effect appeared not to be mediated by impaired immune reconstitution. They suggested that more studies of malnutrition as an adjunct to the initiation of HAART were urgently needed in developing countries given the increasing access to antiretroviral therapy and the high frequency of HIV-associated wasting.[3]

Evaluating HAART in HIV-infected adults in the department of haematology at the University of Brazaville in Congo, Dokekias et al. conducted a retrospective study during 32 months, from May 2003 to December 2005, over 157 HIV/AIDS patients receiving HAART for at least 12 months. At baseline, the average CD4 cell count was 133 cell/µl (range 1- 365) and

plasma viral load measured in 96 patients was 214,000 copies/ml (extreme 30,000 and 999,000). They concluded that their results confirmed the therapeutic significance of HAART in the improvement of the quality of life of HIV/AIDS patients but they had a concern on the possibility of drug resistance occurrence which could not be documented.[4]

Studying the determinants of survival in AIDS patients on antiretroviral therapy in rural centre of North of Cameroon, Sieleunou I et al, conducted a retrospective cohort study of 1187 patients aged > 15 years who started HAART between July 2001 and December 2006. Their findings were that 90.4% of patients were in WHO stage III or IV and 56.1% had a BMI < 18.5. Median CD4 cells count was 105 cell/µl (IQR 40-173). The median survival time was 58 months. CD4 cells count, haemoglobin (Hb), BMI, sex, and clinical stage at enrolment were independent predictors of mortality.[6]

Studying the prevalence of anaemia since HAART availability and the association between anemia treatments and survival, Buskin et al. followed a cohort of HIV- patients through 1996 to 2001**.** Describing anaemia as a haemoglobin (Hb) level of less that 10.5 g/Dl, they observed a decrease of anaemia from 13 to 5 %. Patients with CD4 cells count less than 100 cell/ml had the highest anaemia prevalence. The authors concluded that the prevalence of anaemia has decreased in the HAART era, and blood transfusion was positively associated with risk of death, suggesting limiting use of transfusions in nonemergency situations.[7]

Similarly, Mocroft et al. analysed a cohort of 6,725 HIV-patients from across Europe (EuroSIDA Study group). They described normal haemoglobin (Hb) as Hb greater than 14 g/Dl for men and 12 g/dl for women, mild anaemia as Hb of 8-14 g/dl for men and 8-12 g/dl for women and severe anaemia as Hb of less than 8 g/dl for both sex. They observed that at recruitment, 40.4% of patients had normal level of haemoglobin, 58.2% had mild anaemia and 1.4% had severe anaemia. At 12 months of the study, 3.1% of patients without anaemia were estimated to have died (95% CI:2.3-3.9), 15.9% of patients with mild anaemia had died (95% CI: 14.5-17.2) and 40.8% of patients with severe anaemia had died (95% CI:27.9-53.6; P < 0.0001). The Authors concluded that severe anaemia occurred infrequently among these patients but was associated with a much faster rate of disease progression. Among patients with similar CD4 cells count and viral load, the latest value of haemoglobin was a strong independent prognostic marker of death.[8]

Evaluating the clinical outcomes and immune reconstitution in advanced AIDS patients, Dai et al. studied 103 advanced AIDS patients over a 12-month period of HAART. Their HAART regimens were constituted of 1 NNRTI (nonnucleoside reverse transcriptase inhibitor)

+ 2 NRTI (nucleoside reverse transcriptase inhibitor); or 1 PI (protein inhibitor) + 2 NRTI (nucleoside reverse transcriptase inhibitor). They found that one patient died and another was lost to follow up**.** For the remaining 101 patients, the plasma viral load (VL) was reduced to 3.2 +/- 0.7 log copies/ml, the CD4 cells count increased to 165+/- 51 cell/µl. Clinical outcomes consisted of complaints of fatigue, general body malaise and weight loss. One patient died of hepatic failure due to Nevirapine toxicity and HCV-coinfection. Another was lost to follow up. Among the remaining 101 patients, no one developed opportunistic infections.

At baseline, the opportunistic infections included tuberculosis (27 cases), Cytomegalovirus infections (8 cases), Candidiasis (24 cases), Herpes Simplex infections (6 cases), Pneumocystis jiroveci pneumonia (PJP, 6 cases), bacterial infections (5 cases) and sepsis (3 cases). Co-infections included HCV-infections (29 cases). The mean CD4 cells count was 106 +/- 85 cell/µl, and the mean plasma viral load was 5.2+/-0.8 log copies/ml.[9]

Determining factors that influence the increase in CD4 cell count of HIV- positive persons receiving long term HAART, Smith et al. studied a cohort of 596 patients over a median period of 2.5 years. They found that after 6, 12 and 24 months of HAART, the median increase in CD4 cell counts were 114, 181, and 248 cell/µl, respectively, and 84%, 84%, and 80% of subjects had a viral load of < 400 copies/ml during the same periods. White ethnicity, higher pre-HAART viral load, and lower pre-HAART CD4 and CD8 cell counts were associated with greater increases in CD4 cell counts during the first 3 months of HAART. From 3 months onward, a greater cumulative proportion of time spent with viral load < 400 copies/ml was associated with a more favourable change in CD4 cell count (an average increase of 5.2 cell/µl/year [95% CI], 3.8 – 6.7 cell/µl/year for each extra 10% cumulative time spent with a viral load < 400 copies/ml ($p < 0.0001$). Sex, risk group, age, and HAART regimen were not associated with increases in CD4 cell count. They concluded that maintaining virological suppression is an important factor in the increase of CD4 cell count and suggested that other factors may influence long-term CD4 cell response.[10]

Determining changes in weight and lean body mass (LBM) during HAART, Shikuma et al. studied a cohort of 224 antiretroviral naïve patients during the period of 1997 – 2000. They observed that overall; there was a modest increase of body weight (1.9 Kg) and lean body mass (0.6 Kg) after 16 weeks of therapy. Significantly greater median increases in body weight (2.1 vs. 0.5 Kg; $p=0.045$) occurred in subjects who achieved virological suppression (HIV-1 RNA load, < 500 copies/ml) at 16 weeks than in subjects who did not. Subjects who were antiretroviral naïve at baseline gained more weight (median increase in body weight, 26 vs. 0.0

Kg; p < 0.001) and lean body mass (1.0 vs. 0.1 Kg; p= 0.002) after 16 weeks of treatment than did subjects who were antiretroviral experienced. Subjects with lower CD4 cells count (< 200 cell/µl) and subjects with higher baseline HIV-1 RNA loads (≥ 100,000 copies/ml) were more likely to show increases in lean body mass of > 1.5 Kg (p=0.013 and p=0.005, respectively). They concluded that HAART had modestly favourable effects on body composition, particularly in patients with greater pre-treatment immunocompromise and virological compromise. They suggested that the difference between antiretroviral-naïve and antiretroviral experienced subjects with regard to the ability to achieve increased body weight and lean body mass requires more studies.[11]

Determining the clinical predictors of hospitalization among HIV- infected persons initiating HAART and exploring the impact of gender and drug use on hospitalization, Fielden et al. studied a cohort of 1,605 HIV-positive individuals initiating HAART between 1996 and 2001, and found that 672 (42%) were hospitalized for one or more days. The risk of hospitalization increased among patients with high baseline viral load, HIV-RNA (HR for > 100,000 copies/ml: 1.26; 95% CI: 1.16 – 1.59] or low CD4 cell counts (HR [95% CI] compared to CD4 cell count ≥ 200 cell/µl: 1.6 [1.28 – 2.06] and 1.29 [1.07 – 1. 56] for < 50 and 50 – 99 cell/µl, respectively). Other factors included adherence, previous hospitalization, gender and injection drug use remained predictive of hospitalization. They stressed the importance of closely monitoring patients starting therapy with low CD4 cell count in order to mediate or prevent outcomes requiring hospitalization.[12]

AIM OF THE STUDY

To determine factors that influence the clinical outcomes in patients on HAART at Vryburg District Hospital, Northwest Province in South Africa,

OBJECTIVES

1. To determine the demographic data of the patients on HAART at Vryburg District Hospital, North West Province
2. To assess the patients' nutritional status
3. To document the opportunistic infections/conditions and hospitalization
4. To assess patients' use of the ARV drugs and HAART regimens
5. To determine the side/adverse effects of the ARV drugs

6.To assess the patients' CD4 cell count, viral load (VL), liver function tests (ALT), and haemoglobin level at HAART initiation and follow up visits.

RESEARCH QUESTION (S)

What are the factors that influence clinical outcomes in patients on HAART at Vryburg District Hospital, Northwest Province in South Africa?

Following questions related to the study objectives will be answered:

1. What are the patients' demographic data?
2. What are the patients' nutritional status?
3. What are the patients's opportunistic infections/conditions requiring hospitalisation?
4. What are the patients' uses of ARV drugs?
5. What are the side/ adverse effects of ARV drugs?
6. What are the patients' CD4 cell count, Viral load (VL), liver function test (ALT), and haemoglobin levels (Hb) at HAART initiation and follow up visits?

METHODS

STUDY DESIGN

It will be a descriptive retrospective study of HIV/AIDS patients on HAART.

SETTING

The study will be conducted at Vryburg District Hospital, Northwest Province in South Africa.

STUDY POPULATION

All HIV/AIDS patients aged ≥18 years started on HAART at Vryburg District Hospital during the period of 5th June 2007 to 5th December 2008. During this period 420 HIV/AIDS patients were initiated on HAART.

Study sample.

With a sample population of 420 HIV/AIDS patients on HAART during the study period, using a 95% confidence level, 10% confidence interval, the sample size will be 78 patients.

Sampling frame.

The sample will consist of 78 randomly selected HIV/AIDS patients aged ≥ 18 years old who initiated HAART during the period of the study, have been on HAART for at least 6 months and have complete information about demographic data, clinical notes, ARV drugs regimen, and CD4 cell count, viral load (VL), liver function test (ALT), haemoglobin (Hb) result at HAART initiation and follow up visits.

Inclusion criteria:

- HIV/AIDS patients aged ≥ 18 years old
- Patients on HAART for at least 6 months
- Patients with complete demographic data on the hospital file, clinical notes and laboratory records: CD4 cell count, viral load (VL), liver function test (ALT), haemoglobin level at baseline and follow up visits.

Exclusion criteria.

- Patients aged < 18 years old,
- Patients on HAART for less than 6 months,
- Patients with incomplete demographic data, clinical and laboratory records on CD4 cell count, viral load (VL), liver function test (ALT), and haemoglobin (Hb) at HAART initiation and follow up visits.

VARIABLES OF THE STUDY

Clinical variables:

- Patients demographic data (age, sex, race, employment, location of residence),
- Patients nutritional status (weight, BMI),
- Opportunistic infections at initiation and follow up visits,
- Number of hospital admissions

Laboratory variables:

- Baseline and follow up CD4 cell counts, viral load (VL), liver function test (ALT), haemoglobin (Hb) level.

DATA ANALYSIS

Simple descriptive analyses using Epi-info 6.04 software program will be done with the assistance of my supervisors and a Statistician. Data will be presented as tables, frequencies and graphs. The graphs will be generated using Microsoft Excel. For association of variables the chi-square test will be used. Findings with p-values ≤ 0.05 will be considered statistically significant.

MATERIALS.

The following tools will be used for the study:

- ARV clinic registers and files will be used as sources of patients' data
- Data Collection Sheet will be used to capture the necessary data
- Computers and the Epi info software program will be used to store and analyse data

DATA COLLECTION.

Demographic, clinical and laboratory data obtained from the selected patient files will be entered into a structured data collection sheet. The correctness of information entered will be verified by an independent medical officer not directly involved with the study. Information entered in the structured data collection sheet will form the basis for analysis and interpretation.

RELIABILITY

Reliability is the degree to which a measure gives the same results when used on more than one occasion with the same respondents under the same conditions. To ensure that data are reliable (consistent or repeatable), the researcher will design a data collection sheet which will be used to enter the information from patients' files and an independent medical officer will counter-check the correctness of data entry.

VALIDITY

Validity is the degree to which the measurement reflects the true value of the characteristic that the researcher actually intends to measure. To ensure validity of the study, the data collection sheet will be subjected to peer and supervisors review to ensure that it is able to gather the information required for the study.

BIAS

SELECTION BIAS.

Selection bias is the tendency to favour the sampling (selection) of individuals that have particular characteristics. A random sample of 78 files of patients aged ≥ 18 years old with complete information about variables of the study will be used. Serial file numbers of patients initiated on HAART during the period of the study will guide the selection process. Patients with incomplete information will be excluded.

BIAS IN THE PRESENTATION AND INTERPRETATION OF DATA

Presentation and interpretation bias may occur when the researcher analyses and draws conclusions of the study to suit his/her own preconceived ideas or opinion. Presenting the findings to the supervisors, colleagues and the statistician for peer review and independent opinion will help minimise these forms of bias.

ETHICAL CONSIDERATIONS

Permission to conduct the research at Vryburg District Hospital will be obtained from the Provincial/District Research and Ethics Committee and local hospital Managers. Patient confidentiality will be ensured by keeping the information obtained from patient files anonymous. Since there will be no interviews of patients, no consent form will be used. Ethical clearance for the study will be obtained from the Medunsa Research and Ethics Committee (MREC) of the University of Limpopo (Medunsa Campus).The information obtained from this study will serve for the purpose of this study only, as outlined in this protocol.

IMPLEMENTATION

Time frames

Activity	Time frame
- Approval of protocol by MREC	May2010
-Data Extract Sheet adoption (Peer review, pilot study)	May 2010
-Data collection	May 2010

-Data Entry	May 2010
-Data Analysis	May 2010
-Draft Report	June 2010
-Final Report	July 2010

Budget

Item	Amount
-Stationery	R 1,000
-Doctor, Nurse and Clerk allowance	R 3,000
-Analysis	R 2,000
-Write up	R 1,000
-Other related expenses	R 3,000
Total Expenses	R 10,000

All costs will be borne by the researcher.

VII.REFERENCES

1. New York State Department of Health. Antiretroviral therapy. New York (NY): New York State Department of Health 2008.

2. George C, Yesoda A, Jayakumar B, Lal L. A prospective study evaluating clinical outcomes and costs of three NNRTI-based HAART regimens in Kerela, India. J Clin Pharm Ther. 2009; 34(1): 33-40.

3. Paton NI, Sangeetha S**,** Earnest A, Bellamy R. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. HIV Med. 2006; 7(5): 323-30.

4. Dokekias AE, Galiba FO, Bokilo AD, Ntsimba P, Nsitou MB, Malanda F, Basseila GB. Evaluation of antiretroviral therapy in HIV-infected adults in the Department of Haematology, University Hospital of Brazaville, Congo**.** Bull Soc Pathol Exot 2008; 101(2): 109-12.

5. South Africa Department of Health. National Antiretroviral Treatment Guidelines. South Africa, Department of Health 2004.

6. Sieleunou I, Souleymanou M, Schonenberger AM, Menten J, Boelaert M. Determinants of Survival in AIDS patients on antiretroviral therapy in a rural centre in the far-North Province, Cameroon**.** Trop Med Int Health 2009; 14(1): 36-43.

7. Buskin SE, Sullivan PS. Anaemia and its treatment and outcomes in persons infected with human immunodeficiency virus. Transfusion. 2004; 44(6): 826-32

8. Mocroft A, Kirk O, Barton SE, Dietrich M, Proenca R, Colebunders R, Pradier C, dArminio Moncroft A, Ledergerber B, Lundgren JD. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA Study group. AIDS 1999; 13(8): 943-50

9. Dai Yi, Qiu ZF, Li TS, Li TS, Han Y, Zuo LY, Xie J, MA XJ, Liu ZY, Wang AX. Clinical outcomes and immune reconstitution in 103 advanced AIDS patients undergoing 12-month highly active antiretroviral therapy. Chin Med J (Engl) 2006; 119(20):1677-82

10. Smith CJ, Sabin CA, Youle MS, Kinloch-de Loes S, Lampe FC, Madge S, Cropley I, Jonhson MA and Phillips AN. Factors influencing increases in CD4 cell counts of HIV-positive persons receiving long-term highly active antiretroviral therapy. J Inf Dis. 2004; 190(10): 1860-8

11. Shikuma CM, Zackin R, Sattler F, Mildran D, Nyangweso P, Alston B, Evan S, Mullican K; AIDS Clinical Trial Group 892 Team. Changes in weight and lean body mass during highly active antiretroviral therapy. Clin Inf Dis. 2004; 39(8): 1223-1230.

12. Fielden SJ, Rush ML, Levy AR, Yip B, Wood E, Harrigan RP, Goldstone I, Guillemi S, Montaner JS, Hogg RS. Predicting hospitalization among HIV-infected antiretroviral naïve patients starting HAART: determining clinical markers and exploring social pathways. AIDS Care 2008; 20(3):297-303

VIII.APPENDICES

Following documents will constitute my appendices:

A. Data Collection Sheet

B. Authorization letter(s) by Vryburg District Hospital Authorities to conduct the research.

C. Ethical Clearance from the Medunsa Research and Ethics Committee (MREC) of the University of Limpopo.

APPENDIX-II-

Annexure A: Data Collection Sheet

Factors influencing clinical outcomes in patients on HAART at Vryburg District Hospital,

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1. ARV site:……
2. Patient's file number:…….
3. Sex……..Male [ ] Female [ ]
4. Weight……Height……cm BMI……kg/m^2
5. Patient's race: (*Tick appropriately)*

   Black……White……Coloured……Indian……Other (specify)……
6. Patient's age group: (*tick in the appropriate age group)*

   1/ 18-25 years: …..

   2/ 26-35 years: …..

   3/ 36-45 years: …..

   4/ 46-55 years: …..

   5/ 56-65 years: ……

   6/ 66 years and above: …..
7. Patient's profession: *(Tick appropriately)*

   1/Civil servant……2/Self-employed……..

   3/Farm-worker……4/House-worker/servant……

   5/Driver……..6/Other (*specify)*……....
8. Patient's physical address:……..

…….

9. HAART initiation Date:……..
10. HAART regimen at initiation:…….....

……..

(*Write down the ARV drugs combination)*

11. Co-administered long course drugs at HAART initiation:……...

……

…….....

12. Opportunistic infection(s)/condition(s) and WHO staging at HAART initiation:……..

…….

……

(Write down the condition or indicate none)

13. Opportunistic infection(s)/condition(s), drugs side/adverse effects and adherence at follow up visits:

    At 2nd week visit:…….

    ……..

    At 4th week visit:…….

    ……

    At 2nd month visit:……..

    ……

    At 3rd month visit:……..

    ……

    At 6th month visit:……

    ……..

    At 12th month visit:…….

    ……

    At 18th month visit:…….

    ……

    (Write down the condition(s)/side effect(s) or indicate none)

14. Baseline and follow up: Weight (BMI), CD4, VL, ALT, Hb

	At initiation	At 6 months	At 12 months	At 18 months
Weight(BMI)				
CD4				
VL				
ALT				
Hb				

15. Was HAART regimen changed? YES……NO……

(Only if YES, answer questions 14, 15, 16); if NO go to item 17.

16. If YES, HAART regimen change date:……

17. HAART regimen changed to:…….

……

(*Write down the new ARV drugs combination)*

18. Reason(s) for HAART regimen change:……..

    ……...

    ……..

19 Was the patient admitted in hospital during the pre-HAART period?

    YES…….NO…….. (*if NO, go to item no-20)*

20. If YES, what was (were) the reason(s) for admission to hospital?.....

……

(*Write down the medical condition(s))*

21.Date of admission: ……./……/……Date of discharge:……./ ……/…….

22. Was the patient admitted in hospital during post- HAART initiation period? YES……..NO……. (*Tick appropriately)*

23. If YES, what was (were) the reason(s) for admission to hospital?.....

……

(*Write down the medical condition(s))*

24 Date of admission: ……./……/……..Date of discharge: …../……../……

If deceased in Hospital, Date of death: ……./……../…….

If referred, Date of referral: ……/……/…….Reason for referral:…A……

……

……...

25. Where was patient referred to? ……

26. Date of death at Home (as reported by relatives when requesting death certificate to ARV clinic staff or as reported by the defaulter tracer Worker):……./……../…….

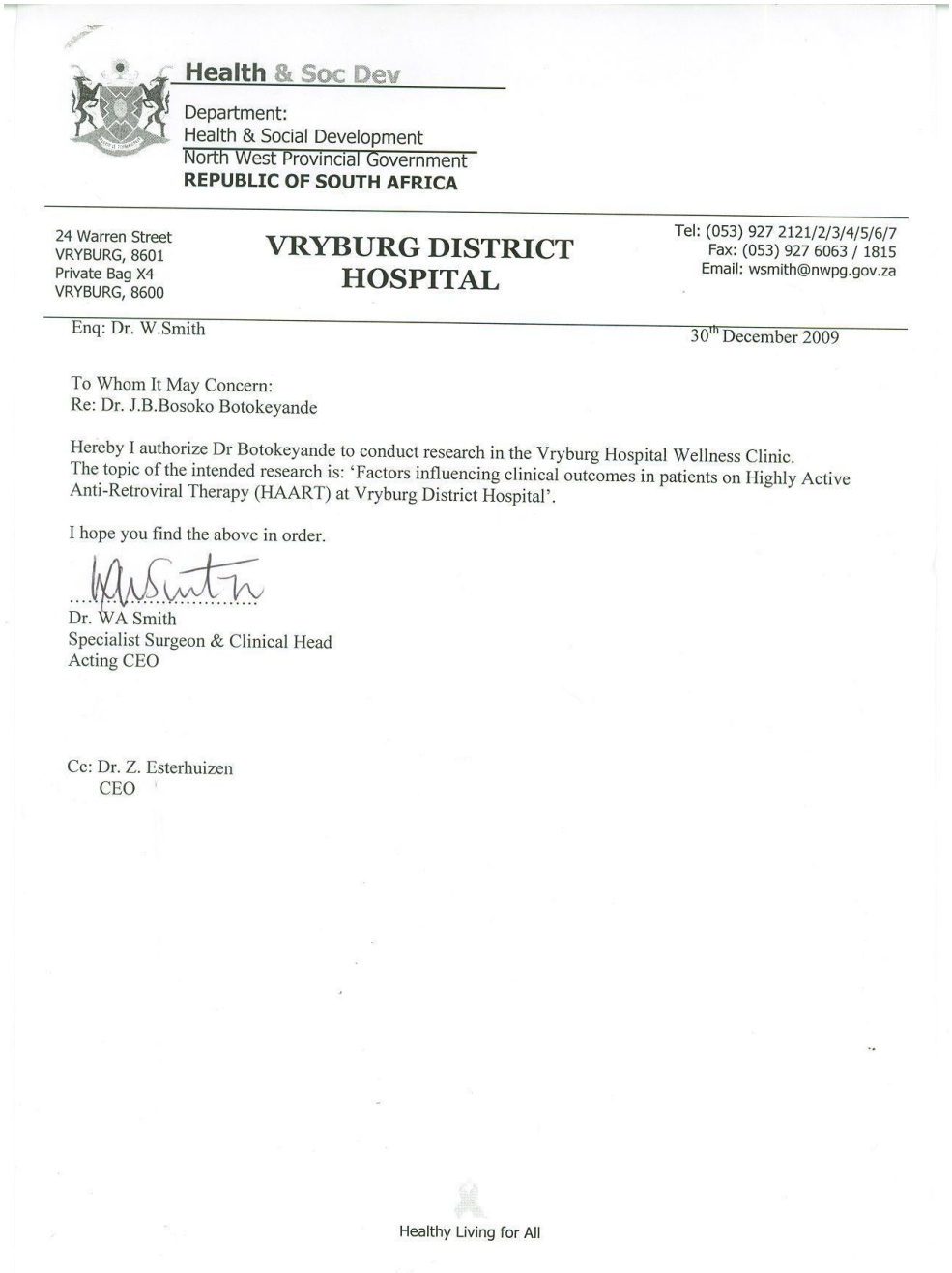
(*Applicable if patient died at home, if not write NA=Not Applicable)*

27. Patient was lost to follow up: YES…….NO……..

    (Tick appropriately).

APPENDIX-II-

Annexure B: Authorization letter(s) to carry on the research by Vryburg District Hospital Authorities.



Health & Soc Dev

Department:
Health & Social Development
North West Provincial Government
REPUBLIC OF SOUTH AFRICA

24 Warren Street
VRYBURG, 8601
Private Bag X4
VRYBURG, 8600

VRYBURG DISTRICT HOSPITAL

Tel: (053) 927 2121/2/3/4/5/6/7
Fax: (053) 927 6063 / 1815
Email: wsmith@nwpg.gov.za

Enq: Dr. W.Smith

30th December 2009

To Whom It May Concern:
Re: Dr. J.B.Bosoko Botokeyande

Hereby I authorize Dr Botokeyande to conduct research in the Vryburg Hospital Wellness Clinic.
The topic of the intended research is: 'Factors influencing clinical outcomes in patients on Highly Active Anti-Retroviral Therapy (HAART) at Vryburg District Hospital'.

I hope you find the above in order.

Dr. WA Smith
Specialist Surgeon & Clinical Head
Acting CEO

Cc: Dr. Z. Esterhuizen
CEO

Healthy Living for All

Health & Soc Dev
Department:
Health & Social Development
North West Provincial Government
REPUBLIC OF SOUTH AFRICA

32 Market Street
VRYBURG, 8600
Private Bag X32

Dr. RUTH SEGOMOTSI MOMPATI DISTRICT

Tel: (053) 927 0456/7/8
Fax: (053) 927 0009
Email:sduplessis@nwpg.gov.za

Enq ; Dr SE Abizu
RE ; Dr J B Bosoko Botokeyande

12 January 2010

To Whom It May Concern

On behalf of the District research committee, I hereby authorise Dr J B BOSOKO BOTOKEYANDE to conduct Research on factors influencing clinical out come in patient on highly active Antiretroviral therapy at Vryburg District Hospital

Thanks

Dr SE Abizu
District Senior Specialist Family Physician
and Chairman District Research Committee

12/Jan/2010

APPENDIX-III-

MREC CLEARENCE CERTIFICATE: MREC/M/59/2010: PG

Medunsa Campus

UNIVERSITY OF LIMPOPO

MEDUNSA RESEARCH & ETHICS COMMITTEE

CLEARANCE CERTIFICATE

P O Medunsa
Medunsa
0204
SOUTH AFRICA

Tel: 012 - 521 4000
Fax: 012 - 560 0086

MEETING: 04/2010

PROJECT NUMBER: MREC/M/59/2010: PG

PROJECT :

Title:	Factors influencing clinical outcomes in patients on HAART at Vryburg District hospital, North West province in South Africa
Researcher:	Dr JB Bosoko Botokeyande
Supervisor:	Dr LH Mabuza
Co-supervisor:	Prof GA Ogunbanjo
Hospital Superintendent:	Dr W Smith (Vryburg Hospital)
Department:	Family Medicine & PHC
School:	Medicine
Degree	MMED

DECISION OF THE COMMITTEE:

MREC approved the project.

DATE: 05 May 2010

RESEARCH & INTERNSHIP
2010 -05- 05
MEDUNSA CAMPUS

PROF N EBRAHIM
DEPUTY CHAIRPERSON MREC

Note:
i) Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.
ii) The budget for the research will be considered separately from the protocol.
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.