DRUG ADVERSE EFFECTS IN HIV-INFECTED PATIENTS RECEIVING ANTIRETROVIRAL THERAPY – A PHARMACOVIGILENCE APPROACH

by

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DECLARATION

I, **Mr MD Gaula**, hereby declare that the work on which this study is based is original, except where acknowledgements indicate otherwise.

This dissertation is submitted for the degree Master of Science in Medicine (Pharmacy) at the University of Limpopo, Medunsa Campus. Neither the whole work nor any part of it has been submitted before for any degree or examination at this or any other university.

Signed  on the **29th** day of **November 2010.**

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ABSTRACT

Most pharmaceutical agents can result in side effects and toxicities that in some instances may be life threatening, especially if there is delay in their recognition. For various reasons it is therefore imperative to study adverse events associated with antiretroviral agents (ARVs). The aim of this study was to study the adverse events in adult HIV-infected patients receiving antiretroviral therapy at a public health treatment site, and to quantify the frequency of adverse events in different population subgroups. A retrospective cohort study was conducted in a sample of 99 patients (i.e. 70% females and 30% males) from a public health clinic providing antiretroviral drugs to more than 1500 patients. The reported adverse events were neurological disorders (33%), rash (17%), gastrointestinal toxicity (16%), lactic acidosis (14%), hepatitis (7%), lipodystrophy (7%), pancreatitis (5%), IRIS (3%), anaemia (1%), and gynaecomastia (1%). Based on the analysis of the presented data in this report, age, weight, gender, and pCD4 count are not the predictors for the development of lactic acidosis, pancreatitis, and peripheral neuropathy. The duration of treatment was found to be the predictor for the development of lactic acidosis, pancreatitis, and peripheral neuropathy in this study sample. More frequent and closer monitoring of the reported adverse events will be necessary for patients treated longer on ART. Information bias is possible as case data for all reported adverse effects were collected retrospectively from hand-written patient records which were not consistent and standardised.

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ACRONYMS

3TC- Lamivudine
ADR- Adverse Drug Reaction
AIDS- Acquired Immunodeficiency Syndrome
ALT- Alanine aminotransferase
ART- Antiretroviral Therapy
ARV- Antiretroviral
AST- Aspartate aminotransferase
AZT- Zidovudine
BMI- Body Mass Index
CCMT- Comprehensive Care, Management and Treatment
CD4- T-Lymphocyte cells
CNS- Central Nervous System
D4T- Stavudine
DDI- Didanosine
DNA- Deoxy-ribonucleic Acid
EFV- Efavirenz
FBC - Full Blood Count
FDA- Food and Drug Administration
FTC - Emtricitabine
GDG- Guidelines Development Group
GGT- Gamma-Glutaryl aminotransferase
HAART- Highly Active Antiretroviral Therapy
Hb- Haemoglobin
HCV- Hepatitis C Virus
HIV- Human Immunodeficiency Virus
HIV-1 RNA- Human Immunodeficiency Virus type-one Ribonucleic Acid
IRIS- Immune Reconstitution Inflammatory Syndrome
LPN/r-Lopinavir/ritonavir
NNRTI- Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI- Nucleoside Reverse Transcriptase Inhibitor
NVP- Nevirapine
PI- Protease Inhibitors

pVL- Plasma Viral Load

SD- Standard Deviation

SN- Sensory Neuropathy

TDF- Tenofovir-Disoproxil Fumarate

TB- Tuberculosis

WHO- World Health Organisation

CHAPTER 1

1. INTRODUCTION

This study was designed with the main aim being of studying the most common adverse events associated with the chronic use of ARVs in adult patients. Its main objects were to establish a database of adverse effects through retrospective capturing and recording of experienced or reported adverse effects associated with the chronic use ARV's.

The analysis involved identifying specific risk patient subgroups, establishing rates of occurrence of the events and characterising different adverse events. Lastly, the performed analysis assisted with the determination of specific proportions of patients who would likely experience specific effects on different antiretroviral regimens.

In an endeavour to quantify and study adverse effects, a survey was conducted through retrospective recording of experienced adverse events experienced by patients receiving ARVs from a public health facility. The subjects of the study resided in Region B of the Gauteng Province and they collected their chronic ART at the Emthonjeni Primary Health Care Clinic.

These are public health facilities providing primary health care services including comprehensive care and management of HIV/AIDS to society. A computerised programme customized to collect relevant data relating to the study objectives was developed. The components of the programme allowed for recording of adverse effects, creating a database of commonly experienced side effects and side effect patterns.

From the database, proportions of patients who experienced side effects were determined. Data were also drawn from an archived record data base of patients in the facility. Highly active antiretroviral therapy (HAART) was defined as regimen 1A (stavudine or zidovudine + lamivudine + efavirenz), regimen 1B (stavudine or zidovudine + lamivudine + nevirapine) and regimen 2 (lopinavir/ritonavir + lamivudine

+ didanosine or zidovudine) as described in the adults South African HIV/AIDS treatment guidelines (Department of Health, 2005.

A data collection tool (Appendix 2) was developed and, this tool was adapted from the Food and Drug Administration (FDA) safety information and adverse event reporting form and the SA Department of Health National Adverse Drug Reaction and Product Quality Problem. Data fields were built into the Microsoft Access template created to capture the data.

The co-administration of antiretroviral agents (ARVs), also known as highly HAART, has had a significant impact on the treatment of Human Immunodeficiency Virus (HIV) infection, with a reduction of HIV-1 replication, increase in CD4 T-lymphocyte counts and decrease in HIV-related morbidity and mortality (Re, 2000).

However, ARVs, like most pharmaceutical agents, can result in side effects and toxicities that in some instances may be life threatening, especially if there is delay in their recognition (South African HIV Clinical Society:2006).

A growing number of antiretroviral drugs have brought substantial advances into treatment for HIV-1 infection, reducing AIDS-related mortality and morbidity in HIV-infected patients. However, antiretroviral regimens are complex and can cause several side effects (Carosi *et al.,* 2002). These side effects could also be experienced over the long-term use of HAART (Kaduka, 2000).

In the current situation, many governments are under pressure to rollout the antiretroviral drug treatment programmes. This has also put pressure on the pharmaceutical research and development to develop and introduce new treatment regimes. Most of phase three clinical trials were conducted for short periods. In a South African study regarding the metabolic complications of HAART, it has been shown that the prevalence rate varied widely in cross-sectional studies, from 11% to 83% and the effects of ethnicity and genetic predisposition to insulin resistance and obesity need to be considered (George, 2006).

This study seeks to unravel the commonality of the existence of these toxicities in the study sample consistent with the previous findings in the literature. The research instrument used, reported the occurrence of these adverse effects in patients with different baseline characteristics.

In this study report, common adverse events associated with long-term antiretroviral drug use were identified. Like any other treatment modality, long-term treatment with HAART has shown to be associated with the development of adverse effects (Kaduka, 2000). According to Schooley (1999), the issue of long-term side effects has become relevant, since patients are now living longer because of HAART.

For various reasons it is therefore imperative to study adverse events associated with ARVs. Firstly, ARVs are a new group of drugs, therefore little is known about their potential problems associated with their use. Secondly, phase three antiretroviral clinical trials are often shorter than they should be and because of accelerated licensing and the emphasis placed on a twenty-four week virological data as a marker of clinical benefit (Carr, 2002).

In a publication by the World Health Organisation (WHO, 2004), it has been mentioned that, once put on the market, a medicine leaves the secure and protected scientific environment of clinical trials and is legally set free for consumption by the general population (WHO, 2004). At that point, most medicines would have only been tested for short-term safety and efficacy on a limited number of carefully selected individuals. In some cases as few as 500 subjects and rarely more than 5000, will have received the product prior to its release (WHO, 2004).

Another main reason to have conducted this study was to help better identify potential toxicities and any other risk factors that predispose patients to the development of HAART-related side effects within the context of the local clinics offering ARvs. A fact to acknowledge in this regard is that, little is known about the toxicity profile of ARVs in developing countries (WHO, 2007).

The data obtained from the study formed a basis from which to assess long- and short-term impact of toxicity of HAART within the present Primary Health Care setting

in South Africa. The study of HAART adverse events, analysis and reporting by academic, industry, regulators, conference reporters, report writers and journal editors has been poor and disappointing (Carr & Cooper, 2000).

In the next chapter, published literature on ARV side effects has been carefully studied in order to create more insight on the subject. The chapter includes an analysis of published studies on the principles of pharmacovigilance, the use of HAART in the era of HIV pandemic, and the reported adverse effects associated with the use of HAART. The chapter also takes a closer look at the use of HAART within the context of SA. In addition, the chapter also seeks to highlight the fundamental changes to the antiretroviral treatment guidelines in SA.

CHAPTER 2

2. LITERATURE REVIEW

2.1 PHARMACOVIGILANCE

The stringent requirements set to document the development of safety and the establishment of spontaneous reporting systems came about during the catastrophic experiences of the thalidomide adverse drug reactions around 1960 (Aagaard & Hansen, 2009). Several other adverse drug reaction (ADR) cases have been discovered after post-marketing. One of the recent examples of an ADR case that emerged unexpectedly is that of the worldwide withdrawal of Vioxx® (Rofecoxib) from the market in 2004.

The World Health Organisation (2002) has defined pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. Information about the ADR profile of a new medicine appears from the observations made during the clinical development process of the ARV's (Aagaard & Hansen, 2009). These adverse effects could be classified into dose-dependent ADRs related to the pharmacologic effect of the drug, sensitivity reactions, long-term use of antiretroviral therapy (ART) and drug-drug interactions (Aagaard & Hansen, 2009).

Since antiretroviral drugs are a new group of drugs for use by the society of today, it is quite imperative that we inculcate the safe practices and principles of pharmacovigilance in our daily practice when caring for patients consuming ART. Amongst many aims of the pharmacovigilance practices, are to detect problems related to the use of medicines, to communicate the findings in a timely manner, and to contribute to the assessment of harm and maximization of benefits (WHO, 2006).

Living in the highly resource strained circumstances; pharmacovigilance proves to be an essential and cost-efficient means of detecting and minimizing injury to patients and averting potential disaster (WHO, 2002). The cost of pharmacovigilance system is

small, compared with the cost of treating ADRs to a nation and to the total national expenditure on medicines (WHO, 2002).

2.2 HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

Highly active antiretroviral therapy usually consists of a combination of protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs). It has been proven in many studies including that of Sension (2007) that initial NNRTI-based HAART regimens are effective at reducing viral load and boosting CD4+ cell counts.

Because each HAART agent has its own unique adverse effect, it is important to select HAART agents with limited adverse effects when developing a multi-drug regimen (Sension, 2007). It is evident that HAART agents achieve impressive improvements in outcomes, but their use is limited because of side effects (Sension, 2007). Numerous safety concerns have emerged regarding the use of particular NRTIs (Sension, 2007).

Some of the agents in HAART, can cause adverse effects, for example in a high proportion of patients it can cause a metabolic syndrome, characterised by lipodystrophy/lipoatrophy, dyslipidemia, and insulin resistance that may be associated with an increase in peripheral artery and coronary artery diseases (Barbaro, 2003). In a study by Jain *et al.* (2001), it has been affirmed that there is currently no consensus on the best method for diagnosing and monitoring the metabolic effects of antiretroviral therapy.

In this study, lipid disorders and diabetes mellitus related parameters (such as lactate and morphological alterations observed) were used to assess the metabolic effects of HAART. The most visible alterations in HIV-subjects taking HAART, are a loss of subcutaneous fat from the face or limbs and increased abdominal girth or breast size (Jain *et al.,* 2001).

2.3 HIGHLY ACTIVE ANTIRETROVIRAL THERAPY: THE SOUTH AFRICAN PERSPECTIVE

The demand for antiretroviral therapy in developing countries like South Africa has increased dramatically in the advent of HIV/AIDS epidemic. As in any other country, the current health care system has been put under a tremendous strain with the high demand for the treatment options to curb the HIV/AIDS wave in all the spheres of life.

George (2006) reported that 25% of patients on HAART in South Africa discontinued their original regimen owing to treatment failure, non-compliance, or toxicity. Because of lost confidence in the safety of medicines and of the programme, patients are likely to stop these life-prolonging medicines leading to problems for themselves and society as a whole (WHO, 2007).

Antiretroviral agents as a relatively new group of drugs were not widely used on various population groups around the world especially developing countries like South Africa. Many governments in the developing countries face a challenge of fast tracking the rollout programmes of antiretroviral agents to salvage the debilitating effects of the HIV/AIDS epidemic. Newer public health programmes are developed and global resources invoked.

South Africa as a developing country, faced with a mammoth task of increasing the coverage of the population with mass treatment, using new medicines with greater benefits to more patients and using public-health-friendly regimens, is no exception. The large populations covered and the use of new medicines provides, at the same time, increases in both the potential for benefit and for harm.

A publication by the World Health Organization (2002), stated that the possibility of harm is great, especially if adverse reactions are not monitored by a strategy aimed at good reporting and early detection, review and management. In some countries, ADRs rank among the top 10 leading causes of mortality (WHO, 2004).

The availability of an increasing number of antiretroviral agents and the rapid evolution of new information has introduced substantial complexity into treatment

regimens for persons infected with HIV. This study was based on the South African HIV/AIDS Adults Treatment Guidelines published by the Department of Health (2005) preceding the recently revised Antiretroviral Treatment Guidelines also published by the Department of Health (2010). According to the South African Guidelines for the Management of HIV-infected adults, the first line adult ART consisted of regimen 1a and 1b (Department of Health, 2005).

Regimen 1a was recommended for all men and women on injectable contraception and condoms. This regimen was a combination of stavudine (D4T) 40mg or (30mg if patient weighed less than 60kg), lamivudine (3TC) 150 mg, and efavirenz (EFV) 600mg or (400mg if patient weighed less than 40kg).

Regimen 1b was recommended for women who are unable to guarantee reliable contraception while on therapy. This regimen consisted of the following combination; stavudine (D4T) 40mg or (30mg if patient weighed less than 60kg), lamivudine (3TC) 150mg and nevirapine (NVP) 200mg.

The second-line ART (i.e. regimen 2) for adults, sometimes referred to as the 'salvage' regimen was normally reserved for cases of confirmed virological failure of the first-line regimes due to the development of resistance. This regimen consisted of zidovudine (AZT) 300mg, didanosine (DDI) 400mg or (250mg if patient weighed less than 60kg) and lopinavir/ritonavir (LPN/r) 400/100mg.

There were modifications observed in practice to regimens 1a and 1b with the substitution of D4T with AZT due to D4T side effects experienced during chronic use.

The first line therapy for adults and adolescents in the recently revised South African Antiretroviral Treatment Guidelines, consists of; TDF + 3TC/FTC + EFV/NVP for all new patients needing therapy or D4T + 3TC + EFV/NVP for all patients currently on D4T based regimen with no side effects or AZT + 3TC + EFV/NVP for patients where TNF is contraindicated, especially in renal failure (Department of Health, 2010).

The second line therapy for adults and adolescents in the recently revised South African Antiretroviral Treatment Guidelines, consists of; TDF + 3TC/Emtricitabine

(FTC) + LPV/r for patients failing on a D4T- or AZT-based first line regimen or AZT + 3TC + LPV/r for patients failing on a TDF-based first line regimen (Department of Health, 2010). All patients that fail on any of the second line regimes should be referred to a specialist (Department of Health, 2010).

The fundamental change from the previous guidelines to the recently revised ones was the introduction of TDF and FTC in the regimens for patients who cannot tolerate D4T due to side effects. In addition, the guidelines recommend that all ART naïve patients eligible to start on ART should be initiated on TDF-based first line regimen.

Judging from the change in the regimes, it suggests that D4T was the major contributor to ART intolerability. It was therefore imperative that this study engages in a fact-finding mission with the intent to making rational judgement on the change of the guidelines.

From one of the publications of the World Health Organisation (2006), evidence from various sources of research has shown that D4T is now recommended at the dose of 30 mg twice daily for all adult and adolescent patients regardless of body weight (WHO, 2006).

Based on available evidence, the WHO guidelines development group (GDG) has concluded that the 30 mg formulation of D4T, dosed twice daily, should be used for all adult and adolescent patients, irrespective of body weight (WHO, 2006). However, in South Africa, there are some of the patients still treated on the 40mg doses of D4T. This is due to poor drug procurement and tendering systems that are not consistent with the ever-changing drug information around the globe. The prescribing patterns could also play a role where most of the ART physicians do not keep abreast with the changes in treatment options.

2.4 MONITORING THE OUTCOMES OF HAART USING VIRAL LOAD AND CD4 CELL COUNT MEASUREMENTS

The clinical status, CD4 cell count, and plasma Human Immunodeficiency Virus type-one Ribonucleic Acid (HIV-1 RNA) levels (if available) can be used in an integrated

fashion to determine whether HIV disease is progressing on therapy and whether a change from first-line to second-line therapy should be made (WHO, 2006). The CD4 cell count remains the strongest predictor of HIV-related complications, even after the initiation of therapy.

In a report by Phillips *et al.,* (2008), it has been mentioned that the decision of when to switch a patient from a first to a second-line regimen in lower-income settings will have to be based on incidence of new HIV-related clinical disease and if available, CD4 cell count changes, rather than on the basis of viral load. It was found in a study of Phillips *et al.,* (2008) that, there is little suggestion that monitoring of CD4 cell counts, results in improved survival compared with clinical monitoring.

In this report, the recorded pre-treatment CD4 counts and the HIV-1 RNA levels were analysed in order to monitor treatment success at various stages of treatment in comparison to routine CD4 and HIV-1 RNA level measurements. However, precise thresholds that define treatment failure in patients starting at various CD4 levels are not yet established (WHO, 2006).

The World Health Organisation (2006) has defined the reasonable working definitions by immunological failure as: (1) CD4 count below 100cells/mm^3 after six months of therapy; (2) a return to, or a fall below, the pre-therapy CD4 baseline after six months of therapy; or (3) a 50% decline from the on-treatment peak CD4 value (WHO, 2006).

When treatment failure is defined on the bases of clinical and/or CD4 criteria the diagnosis may be made later than when viral load is being monitored (WHO, 2006). According to the World Health Organisation (2006), this provides another strong argument for moving towards the wider availability of plasma viral load testing in resource-constrained settings. In particular, simple point-of-care assays are needed which identify, qualitatively or semi-quantitatively, viral load thresholds that inform clinical management decisions (WHO, 2006).

Virological failure is defined by World Health Organisation (2006) as a plasma HIV-1 RNA level above 10 000 copies/ml in a person who has been on a regimen for more

than six months and in whom drug adherence is determined to be sufficient. Due to certain study limitations, adherence levels were not assessed, but HIV-1 RNA levels were recorded with the aim of performing an analysis of treatment success in subjects receiving chronic ART.

The World Health Organisation (2006) defined virological success as a plasma HIV-1 RNA level below the limit of detection of the assay being used (e.g. HIV-1 RNA < 50 copies/ml or < 400 copies/ml after six months of treatment). However, the viral load threshold triggering a switch in ART is not yet defined in literature (WHO, 2006).

From an analysis in a research report by Jevtovic *et al.* (2005), it has been found that within a mean follow-up period of 33 months, discrepant immunological and virological responses occurred in 50% patients (Jevtovic *et al.,* 2005). Of those patients, 174 (39%) did not have a rise in CD4+ T cells to above 400 per µl despite a good virological response, while 49 (11%) had a rise in the CD4+ T cell count to at least 200 per µl but their VL was not undetectable (Jevtovic *et al.,* 2005).

The risk factors for immunological failure despite an undetectable plasma viral load (pVL) were baseline CD4+ T cells below 100 µ (Jevtovic *et al.*, 2005). The introduction of HAART has resulted in maximal control of viral replication and reconstitution of immune system functions among patients with HIV-induced immunodeficiency, allowing overall reduction in late stage complications of HIV infection including death. However, a proportion of patients cannot achieve a significant increase in circulating CD4+ T cells, even though their pVL becomes undetectable (Jevtovic *et al.*, 2005).

In South Africa, the prevention and management of side effects of drugs used to manage HIV and AIDS are a challenge to clinicians, patients, health care workers, family members and all those affected (Department of Health, 2006). For one to better manage these challenges there is a need to study, record and understand the manner in which ART adverse reactions present during their chronic use.

In its endeavour to respond proactively to these challenges, the government has established some pharmacovigilance centres on the country, the so-called ‘centres of

excellence'. The following sections of the literature study include an in-depth study of the reported side effects associated with the use of ARV's.

The threshold of 200 CD4+ T cell per 100 µl was taken arbitrarily, since it protects from developing major opportunistic infections, while a count above 400 per µl was considered most desirable as one approaching normal values (Jevtovic *et al.,* 2005). In addition to low baseline CD4+ T cell counts, factors associated with poor immune reconstitution during HAART in previous studies quoted from the reports of Teixeira *et al*. (2001), Greub *et al*. (2000), and Grabar *et al*. (2000), by Jevtovic *et al.* (2005), included high baseline pVL, older age, Hepatitis C Virus (HCV) co-infection and pre-treatment with mono or dual treatment regimens.

2.5 SPECIFIC ADVERSE EFFECTS REPORTED WITH THE USE OF HAART

2.5.1 Hepatotoxicity

Most antiretroviral agents have been associated with hepatic toxicity. NRTIs have been found to cause hepatic staetosis, generally after more than six months of therapy (Carr and Cooper, 2000). One of the risk factors for the development of severe hepatotoxicity in a nevirapine treated cohort was the baseline CD4 cell count of less than 50cells/mm^3 and an increase in CD4 cells greater than 50cells/mm^3 during therapy (Sulkowski *et al.,* 2002).

Shepard (2004), the managing director of Boehringer Ingelheim, in his letter dated February 2004 on safety information on nevirapine use, warned that women with $CD4^+$ cell counts of more than 250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk (12 fold) of hepatotoxicity.

The aforementioned subset of patients were identified by analyses of $CD4^+$ count at the time of initiation of nevirapine therapy and the greatest risk of severe and potentially fatal hepatic events occurred in the first six weeks of nevirapine therapy (Shepard, 2004).

2.5.2 Neurological

In a study conducted by Carr (2000), the most common adverse effects that were identified with the use of efavirenz affected the central nervous system, and included dizziness, insomnia, somnolence, impaired concentration, vivid dreams, nightmares, and insomnia. These reactions occurred in about 40% of patients in the first few days to weeks, but were severe enough to warrant discontinuation in only 3%, since most symptoms resolved spontaneously (Carr and Cooper, 2000).

In a study by Max and Sherer (2000), 3TC had relatively few adverse effects and tolerated across all ART regimes. The most common adverse effects that were reported with the use of lamivudine were diarrhoea, malaise, fatigue, and headache and sometimes sleep disturbances (Max & Sherer, 2000).

2.5.3 Pancreatitis

In a study of 8451 subjects conducted by Reisler *et al.* (2005), the overall pancreatitis rates that were observed were 0.61 per 100 person-years clinical and 2.23 per 100 clinical/laboratory. Pancreatitis is a potentially life threatening condition that is characterised by abdominal pain, nausea, and vomiting and biochemically by the elevations of lipase and/or amylase. In the very same study, Reisler *et al.* (2005) observed that the combination of NRTIs had an impact on the incidence of pancreatitis.

2.5.4 Hepatitis and Rash

The NNRTIs have gained a definitive place in the treatment of HIV infection since the approval of nevirapine in 1996 and delavirdine in 1998 by the Food and Drug Administration (FDA) and the impressive results from the clinical trials of efavirenz (Max and Sherer, 2000). However, for every benefit that they offered there were common adverse effects observed with their use.

The adverse effects observed with the use of nevirapine included, rash, fever, elevated [Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and/or

gamma–glutaryl aminotransferase (GGT)], nausea, headache and Stevens-Johnson syndrome. The use of EFV was associated with rash, central nervous system (CNS) effects and elevated ALT and AST levels (Max and Sherer, 2000).

2.5.5 Mitochondrial toxicity

NRTIs suppress HIV replication by inhibiting the viral enzyme reverse transcriptase (Kaduka, 2000). However, this class of drugs also has the potential to directly inhibit the human enzyme mitochondrial DNA polymerase gamma (γ), which is responsible for mitochondrial DNA synthesis Brinkman *et al.,* (1998). The consequence is the formation of mitochondria that are structurally and functionally impaired, resulting in impaired oxidative capacity of each mitochondrium (Ogedegbe *et al.,* 2003).

The nucleoside analogs potency order with regard to their inhibitory effect on the mitochondrial DNA production and cell viability is as follows: zalcitabine> stavudine> zidovudine> didanosine (Mokrzycki *et al.*, 2000). D4T, a potent NRTI entered clinical trials in 1989 and was found in a study by Cherry *et al.* (2003) to be a potent inhibitor of mitochondrial DNA-polymerase-γ leading to mitochondrial toxicity.

Most common clinical symptoms associated with mitochondrial toxicity include peripheral neuropathy, myopathies, pancreatic dysfunction, and metabolic abnormalities including diabetes mellitus and lactic acidosis (Cherry *et al.,* 2003). From the findings of a study by Brinkman *et al.* (1998), his experience with NRTI therapy has revealed important adverse effects ranging from mild (myopathy) to fatal in some cases (pancreatitis, liver failure and lactic acidosis).

Behind most of these side effects there appeared to be a common mechanism: a decreased mitochondrial energy-generating capacity that will accumulate during long-term treatment with antiretroviral nucleoside analogues (Brinkman *et al.,* 1998).

According to Brinkman *et al.* (1998), this failure can affect virtually all organ systems, but tissues with the highest energy demand (i.e. the liver, pancreas, heart, skeletal muscle, nervous system, haematopoietic system, kidney, and eye) are most

susceptible. A major problem with this toxicity is its time dependency and therefore delayed onset (Brinkman *et al.,* 1998).

Brinkman *et al.* (1998), further asserts that multi-organ side effects are seen in long-term therapy (several months) with nucleoside analogues. Possible risk factors that contribute to the development of these side effects have been poorly defined.

The concluding statement made by Brinkman *et al*. (1998), that additional studies be performed to determine which factors play a role in the predisposition to develop this toxicity supports the objective of identifying specific risk patient categories.

2.5.6 Lactic acidosis

The underlying risk factors for developing hyperlactataemia include high body mass index or rapid weight gain, women, pregnancy, underlying liver disease and appear to be unusual in young children (Southern African HIV Clinicians' Society, 2006). In one study conducted by John *et al.* (2001), out of 516 patients observed, two patients experienced severe fulminant lactic acidosis (lactate > 5mmol/l) and a further five patients with lesser elevations of lactate (2.8-4.1mmol/l) but with symptoms of nausea or abdominal discomfort and evidence of hepatic staetosis had NRTI therapy revised.

In the very same study by John *et al.* (2001), most remaining patients on HAART had mild, chronic, asymptomatic hyperlactataemia, with mean lactate level between 1.5mmol/l and 3.5mmol/l most commonly. Severe lactic acidosis is typically symptomatic with nausea, vomiting severe malaise and prostration and may occur precipitously after months or even years of NRTI treatment (John *et al.,* 2001).

Treatment with D4T appeared to be the predominant risk factor for the development of chronic hyperlactataemia (John *et al.,* 2001). In a report on five cases of lactic acidosis associated with D4T administration by Mokrzycki *et al.* (2000), the mean duration of D4T therapy was 9.4 months, and the mean observed peak lactate level ± Standard Deviation was 10.3±5mmol/L.

In these case studies, it has been shown that after discontinuation of D4T treatment, lactic acidosis improved in four patients after 4-60 weeks, and one patient died (Mokrzycki, 2000). According to Mokrzycki *et al.* (2000), acquired deficiencies in riboflavin and thiamine, the co-factors required for oxidative phosphorylation, may predispose to the development of lactic acidosis. With the debilitating effects of the ARVs, quality of life assessment will be necessary for the evaluation of the patient's wellbeing.

Boxwell and Styrt (1999) as quoted by Caffrey (2000) identified 60 cases of lactic acidosis associated with combination NRTI therapy where 3TC and D4T were the 3TC and D4T. From the same study, 36 cases of patients taking 3TC and D4T, 20 had died, 85% who died were women, and the sample had a mean age of 40.3 years.

2.5.7 Hyperlipidemia and lipodystrophy

Burgoyne *et al.* (2005) assert that the use of HAART has more recently been associated with fat redistribution and metabolic abnormalities, a phenomenon known as the lipodystrophy syndrome. Lipodystrophy has raised concerns about the potential negative psychological consequences and deterioration in quality of life (Burgoyne *et al.,* 2005).

Dyslipidemia (lipid abnormalities) has been reported with the use of protease inhibitors (e.g. LPV/r). The clinical features include an increase in total cholesterol, an accumulation of visceral fat in the abdomen and loss of subcutaneous fat in the face (lipodystrophy), and diarrhoea (Department of Health, 2005).

The major risk factors that predispose patients to the development of lipodystrophy as outlined by Burgoyne *et al.* (2005), include but are not limited to D4T therapy, older age, lower body weight before commencement of therapy, lower CD4 count before commencement of therapy, diagnosis of AIDS before commencement of therapy and long duration of therapy. In one study reported in the work of Schooley (1999), a report of 116 HIV-positive patients taking at least one protease inhibitor, 64% of the participants developed lipodystrophy after a mean of ten months.

2.5.8 Anaemia

In a study conducted by Carr and Cooper (2000), anaemia and granulocytopenia affected about 5-10% of patients who received zidovudine. Hassan *et al.* (2009) reported a case of zidovudine induced anaemia and bone marrow aplasia in a patient infected with HIV who has been on HAART (zidovudine, lamivudine and nevirapine) for one year. In this report by Hassan *et al.* (2009), it has been concluded that Zidovudine was a well-known cause of anaemia and thus should be used with caution in the initiation of antiretroviral therapy.

This chapter focused on the published literature pertaining to the problems associated with the chronic use of HAART. The following chapter will address the findings of the literature through the stated aim, objectives, and methodology of the study. The purpose of the study was to study the adverse events associated with chronic use of ART and to quantify their frequency of occurrence. The stated objectives were designed to find the existence of commonality and differences in studied population subgroups in as far as ART side effects are concerned.

CHAPTER 3

3. METHODOLOGY

This chapter outlines the research methodology followed through in this report in order to achieve the stated objectives. In addition, this chapter captures the main aim and objectives of the study.

3.1 AIM

The main aim of this study was to study the adverse events in adult HIV-infected patients receiving antiretroviral therapy at a public health treatment site, and to quantify the frequency of adverse events in different patient subgroups.

3.2 OBJECTIVES

3.2.1 To establish a data base of adverse effects experienced during ART

3.2.2 To record adverse effects in patients on ART

3.2.3 To study adverse events in patients on ART through:

(i) Identifying specific risk patient categories

(ii) Establishing the rates of adverse events (i.e. establish the frequency of occurrence of specific adverse effects)

(iii) Characterizing and describing the different adverse reactions

3.2.4 To determine proportions of patients who experience adverse events on different antiretroviral regimens

3.3 DESIGN

This study captures the analysis of both retrospective and prospective data related to reported adverse effects by patients taking ART. This study is a blend of both qualitative and quantitative methods. It is a descriptive cohort study with the intention to describe the frequency of possible determinants of the development of side effects in HIV patients taking HAART. Further than that, this cohort study has

been designed to see if there is a correlation between exposure to ART and reported side effects.

3.4 SITE

The study was undertaken at the Comprehensive Care Management and Treatment of HIV (CCMT) site in the Sedibeng Health District. The study site is the Primary Health Care Clinic (Emthonjeni Primary Health Care Clinic) accredited to issue ART in the Gauteng Province. Patients presenting at the site undergo Voluntary Testing and Counselling.

Either the nurse or the doctor performs eligibility assessment for ART initiation. Baseline assessment and screening is performed at the site prior to initiation of therapy. The baseline assessment includes screening for measurements of CD4 count, pVL, screening for Tuberculosis (TB) and WHO HIV clinical staging. At routine follow up visits, patients are screened for CD4 count, pVL, ALT, full blood counts (FBC), creatinine, and fasting cholesterol based on the regimen they are taking.

3.5 POPULATION

The full study cohort comprised of 99 active patients (i.e. adult HIV positive patients receiving chronic ART) from Emthonjeni Primary health Care clinic. Patient files were randomly identified and those who were found to be on ART were enrolled for the study.

3.5.1 INCLUSION: All adult patients (both male and female) treated on ART, were monitored for the development of adverse effects.

3.5.2 EXCLUSION: All children and adolescents less than 18 years were excluded from the study.

3.6 DATA COLLECTION

A sample of 100 patients in a clinic providing antiretroviral drugs to more than 1500 patients was randomly selected. However, during the filtering of the data for the

purpose of statistical analysis, it was discovered that one patient was duplicated. Therefore the analysis presented in the next chapter represents a sample size of 99 patients. Patients files were selected randomly and those who were found to be more than six months on ART were considered for the study. These patients were assigned identification numbers created by the Microsoft Office Access (2003) programme. Patients who were more than six months on ART were enrolled to participate in the study. Prior to commencement of the study, a Microsoft Office Access data collection tool was designed. Data fields were assigned based on the type of data to be collected.

The data types that were collected included a retrospective and prospective collection of the adverse drug events experienced by the patients on antiretroviral drugs. Included on the template, was a once-off baseline characteristics pertaining to age, weight, viral load, CD4+ cell counts, haemoglobin, alanine-aminotransferase, original prescription drugs including drug name, dose and frequency and the ART start date.

To capture the follow-up entries, a sub-form was created to capture data on routine laboratory results which included CD4+ counts, viral loads, alanine-aminotransferase, serum lactic acid levels, serum amylase, and haemoglobin. Drug events were recorded according to ART start date, event description, date when event was reported, problem medicine, duration on ART when event was reported, and the action taken.

Medicine problems that were self-reported and doctor investigated retrospectively were also recorded. All these medicine problems were abstracted from the patient's medication history on the doctor's notes recorded in the file. These patients were monitored on a monthly basis as they came to collect their refill prescriptions. Records reviewing and unstructured interviewing formed the means of data collection.

An unstructured interview was conducted which included questions directed to the prescriber, on the causality assessment and verification of the reported events. Patients were interviewed during their follow-up visits to verify the correctness of the

recorded information regarding the experienced side effects on a regular basis (i.e. every time they came to collect their repeat prescriptions.

It has been reported by the WHO that, the concept of pharmacovigilance is not well understood, either by health professionals, patients or the general population. To attain a coherent pharmacovigilance system, it is most important that guidelines and standards be developed which describe the practical details of the intended information flow (WHO, 2004). In this study, basic principles of pharmacovigilance approach that included spontaneous reporting of adverse effects were applied.

In addition to that, medical records were reviewed retrospectively to analyse any unusual events reported by patients on ART over a period of more than six months. The researcher conducted unstructured interviews prospectively, in order to develop an understanding of the reported adverse events during the regular treatment visits by the patients. Due to the limited scope of this study, the reported adverse effects were not submitted to any pharmacovigilance centre, however the data were used to study the adverse effects experienced by patients taking ARV agents over a period of six months for the purpose of fulfilling the requirements of obtaining a masters degree.

3.7 DATA ANALYSIS

The computerized events data collated, was organised into clinical strata and laboratory strata using structured events tables and charts created on Microsoft Access, Excel Workbooks, and Microsoft Word (2003). Frequency distributions of different data were calculated for individual events, groups of related events, and for the treatment regimens. Suspected causes of adverse events were compared for different treatments.

Specific risk factors were identified taking into account age, sex, weight, plasma $CD4^+$ count, plasma viral load, and duration of therapy. Mean laboratory values were computed for different investigations. In this manuscript, mixtures of ordinal and interval data were analyzed using descriptive statistics. Tables and bar graphs were utilized to present some aspects of the data.

The statistical analysis of this data also included some measures of central tendency (e.g. mean) and some measures of variation (e.g. standard deviation). Since most of the analysis dealt with the interval level of measurement, the mean was used to describe the average value of the study data. To measure the relationships amongst different patient subgroups, a t-Test statistic and Fisher's exact test were used as a statistical instrument to measure that relationship.

To measure the existence of a statistical relationship between the two samples means (i.e. mean for age, weight, pCD4 count and duration of treatment), the two means were compared using the two-sample test, called t-Test procedure. A t-Test statistic for the differences in two means of the data sample for different baseline characteristics was computed. In testing for the statistical differences between the two sample means, the level of significance, $\alpha = 0.05$, was used.

3.8 ETHICAL CONSIDERATIONS

A clearance certificate to conduct this study has been obtained from the Medunsa Campus Research and Ethics Committee. Further approval was obtained from the Sedibeng District Health Services. A consent form was administered to the subjects prior to enrolment into the study.

CHAPTER 4

4. RESULTS

Chapter 4 is the presentation of the results and their analysis based on the collected data. This data were analysed using both descriptive and comparative statistics. From the methodology in the previous chapter, the sample size consisted of 99 subjects. A brief description of the demographic data is presented followed by the detailed analysis of the side effects reported by the patients.

4.1 DEMOGRAPHIC DATA

Figure 4.1 shows the frequency distribution of the demographic data with respect to gender and age group at initiation of ART.

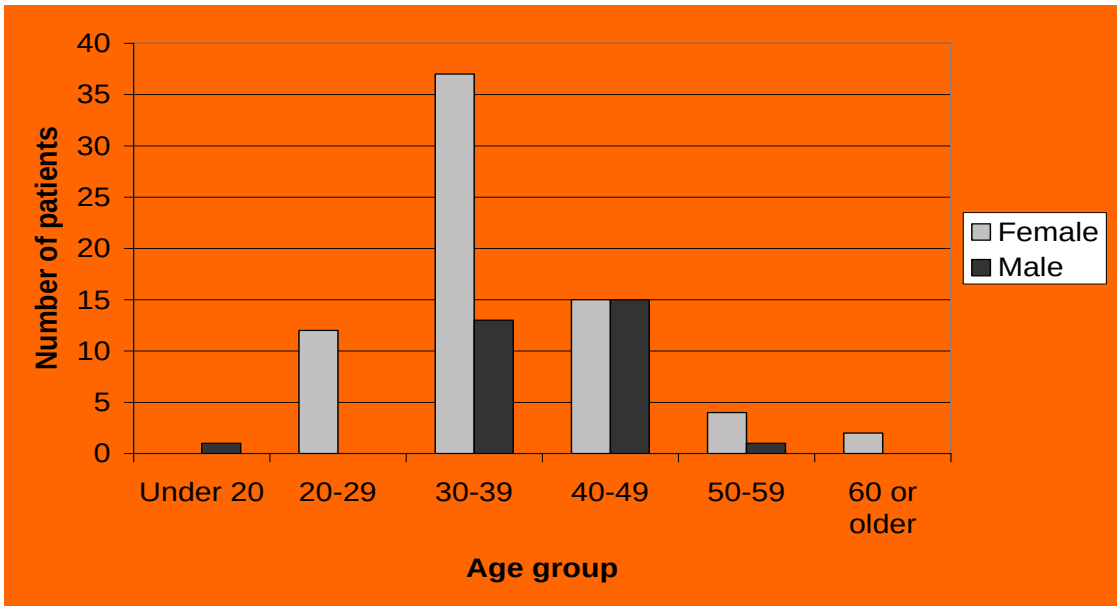

Figure 4.1: Frequency distribution of subjects by age and gender

There were more female 70% (n=70) participants in this study compared to the male group 30% (n=29). More participants were from the age group 30-39 years (i.e. 37 females and 12 males) and the least from the age group below 20 years (i.e. only one male patient). The occurrence of ART adverse effects were compared between both male and female categories.

Of this proportion, the female and male representation were 37% and 12% respectively as shown in Figure 4.1.

Only two females in the age category of 60 and older were enrolled for the study. In the age group 40-49, an equal number of both males and females i.e. 15 subjects each, participated in the study.

4.2 PRESCRIBED DRUG REGIMENS

Treatment allocation to the patients was based on baseline clinical assessment results. Drug treatment was prescribed and dispensed according to the adult ART standard treatment guidelines (Table 4.1). Individual drug dosage was dependent on the patient baseline weight and the pre-existing clinical conditions.

Table 4.1: Antiretroviral drug regimens prescribed at initiation of ART

Regimen	Drug combinations	Female	Male	Total
1a	D4T 30, 3TC 150, EFV 400	1	0	1
	D4T 30, 3TC 150, EFV 600	19	19	38
	D4T 30, 3TC 150, EFV 200	1	0	1
	D4T 40, 3TC 150, EFV 600	13	7	20
1b	D4T 30, 3TC 150, NVP 200	21	0	21
	D4T 40, 3TC 150, NVP 200	11	2	13
1a modified	AZT 300, 3TC 150, EFV 600	3	1	4
1b modified	AZT 300, 3TC 150, NVP 200	1	0	1
	Total	**70**	**29**	**99**

D4T-stavudine; 3TC-lamivudine; EFV-efavirenz; NVP-nevirapine; AZT-zidovudine

Most of the patients (38) as shown in Table 4.1 were prescribed regimen 1a (i.e. D4T 30, 3TC 150, EFV 600). Of these 38 patients, 19 were females and 19 were males.

All patients who were on regimen 1b (D4T 30, 3TC 150, and NVP 200) were female patients (21). Of the patients that were treated on regimen 1a, 20 of them were on a regimen containing D4T 40mg. From these 20 subjects, 13 were females and seven were males. From the analysis as depicted in Table 4.1, it is observed that two NRTIs (i.e. NVP and EFV) were used in the regimen combinations.

The majority of patients were treated on an EFV containing regimen accounting for 64 patients compared to 34 who were treated on NVP. Following the standard

treatment guidelines, more females (33) were on NVP and 27 males on EFV. A few variations from the standard treatment guidelines were observed. These patients were put on modified regimens. These patients were initially treated on AZT containing regimens also known as modified treatment regimens. Only five patients were receiving AZT at initiation of therapy.

4.3 DURATION OF ART

Table 4.2: Duration on ART

Months	Female	Male	Total
0-6	2	0	2
>6-12	1	0	1
>12-18	8	0	8
>18-24	10	3	13
>24-30	16	3	19
>30-36	13	10	23
>36-42	16	9	25
>42	4	4	8
Total	**70**	**29**	**99**

The duration of ART was measured in months. The different periods that patients were on ART were spaced in periods of six months. Table 4.2 is the presentation of a frequency distribution of patients taking ART for a specified duration. The longest duration of ART observed in patients that were studied is greater than 36 months to 42 months. Out of 25 patients observed in this duration band, 16 were female subjects and nine were male subjects.

The other band with most patients was observed for the duration band of more than 30 months to 36 months. By the end of October 2008, the longest duration of treatment of more than 42 months was observed in four males and four females taking chronic antiretroviral therapy.

4.4 PLASMA CD4 CELL COUNT MEASUREMENTS

The numbers of CD4 count results were also recorded for different stages of treatment. These measurements included CD4 counts taken at baseline prior to initiation of ART and during routing monitoring as depicted by Table 4.3 below.

Table 4.3: Number of CD4 count results recorded at different stages of ART

Stage of treatment	**Number of results recorded**
>6-12 months before initiation	19
3-6 months before initiation	85
0-3 months after initiation	38
>3 to 6 months after initiation	45
>180 days - 1 year after initiation	114
up to 2 yrs after initiation	164
More than 2 years after initiation	105
No start date of ART recorded	27
Total	**597**

Table 4.3 shows that more than 85 results were recorded prior to initiation of therapy. Follow-up monitoring results were recorded after initiation of therapy and the most recordings (164) of the results were observed in the periods of up to 2 years after initiation of therapy. A total number of CD4 cell count results that were recorded were 597.

Apart from number of CD4 cell count results recorded at different stages of ART as depicted by Table 4.3 above, further analysis of the average CD4 counts and the degree of variance from average value were computed at different stages of treatment (Table 4.4). The table is giving a more detailed analysis of the CD4 cell counts. The aim was to see the degree at which the CD4 cell count changed at various stages of ART.

Table 4.4: Average CD 4 counts at different stages of ART

Duration of ART	N*	Average CD4	Std deviation	% CD4 incremental rate
Baseline	100	100	62	0
0-3 months	38	158	168	58
>3 to 6 months	45	231	135	46
>6 months – 12 months	114	243	165	5
up to 2 yrs	164	336	187	39
More than 2 years	105	374	200	11

*** N-** number of times the results were recorded at different stages of treatment.

The recorded CD4 cell counts at baseline were from a sample of 99 patients. The mean CD4 cell count at baseline was 100 cell/mm^3 (SD = ± 62) as shown by Table 4.4. There were no incremental rates observed at baseline. After initiation of HAART at 0-3 months, the fraction of the CD4 cell count from baseline increased by 58%. Subsequent to the sharp incremental rate, there was a sudden drop of 12%, as the CD4 counts moved from 58% to 46%.

The standard deviation was used as a measure of variation that takes into account how all the values in the data were distributed around the mean (Figure 4.2). There was a tendency for high variability (standard deviation = 200) of the CD4 count during the period, more than two years of therapy.

At the duration of up to two years, 164 results of the CD4 counts were recorded, and the average CD4 count was 336.2. An average of 58% incremental rate in the average CD4 cell count was observed from zero to two months duration of treatment. The highest rate of increase in CD4 counts was recorded within this period.

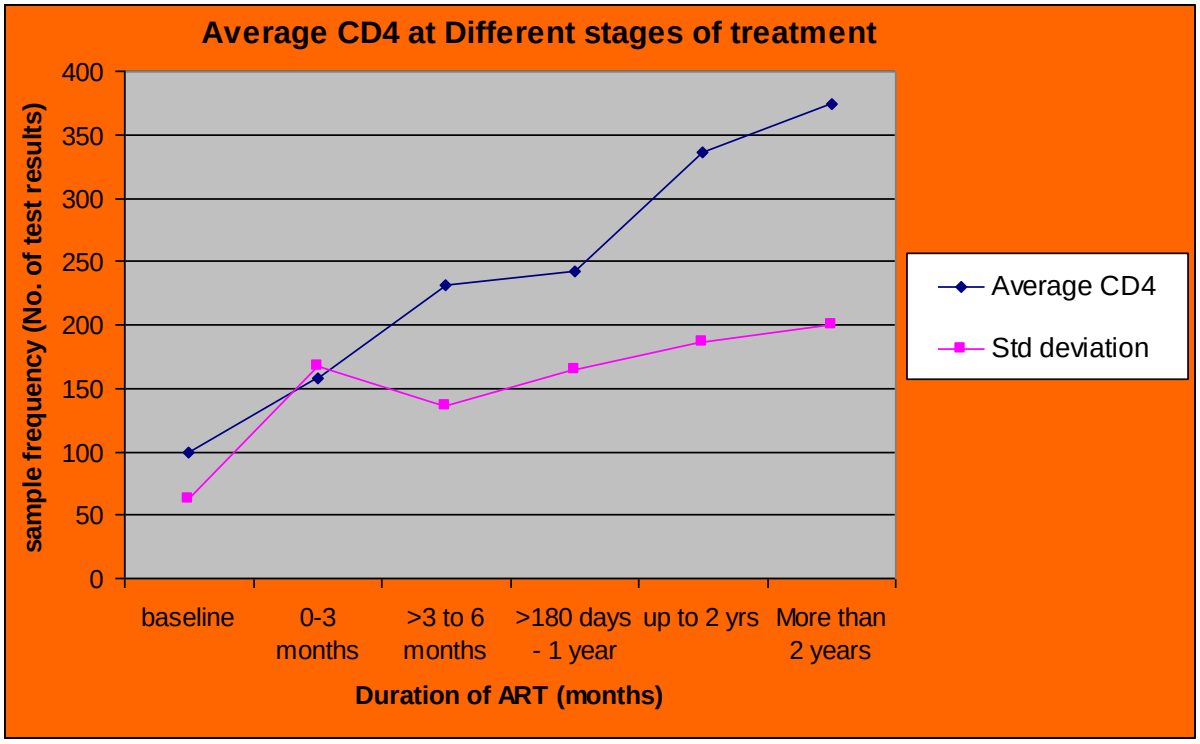

Figure 4.2: Average CD4 count at different stages of treatment

Looking at the graphical presentation of the mean CD4 cell count in Figure 4.2, at different stages of ART, a steady increase in the plasma CD4 count was observed from the time period 0-3 months (i.e. from 100 to 158 cells/mm^3) to more than 2 years of ART duration (i.e. to 374 cells/mm^3). The mean CD4 counts ranged from a minimum of 158 at 0-3 months to 373 at more than 2 years duration of treatment.

The level of variation from the mean CD4 count remained constant throughout the duration of treatment. Most recordings of the plasma CD4 count results were observed at the periods up to 2 years. The least recordings were observed during the periods prior to initiation of therapy to three months.

The highest incremental rates (peak increase in the proportion of CD4 cell count was only observed at the period 0-3 months of ART. The smallest increases in concentrations (i.e. 5% incremental rate) were observed at the period more than 6 months to one year. From three months of treatment, the incremental rate in plasma CD4 cell count has stayed below 50% as observed in Figure 4.2.

4.5 PLASMA VIRAL LOAD MEASUREMENTS

The levels of viral load were computed at various stages of HAART as shown in Table 4.5. A number of viral loads were recorded at baseline and during treatment. The total number of viral load results recorded was 488 (Table 4.5).

Table 4.5: Viral load measurements recorded at different stages of treatment

Phase of treatment	Number of results recorded
>6-12 months before initiation	15
3-6 months before initiation	67
0-3 months after initiation	41
>3 to 6 months after initiation	29
>180 days - 1 year after initiation	103
up to 2 yrs after initiation	117
More than 2 years after initiation	90
Total	**488**

Most of the viral load results (117) were observed at the period of up to 2 years after initiation of therapy. The most number of plasma viral load results (117 out of 488) were recorded during the period of up to two years after initiation of therapy. The least number of recordings was at more than six months to 12 months before initiation of treatments.

Further than just the number of viral load results recorded in Table 4.5 above, the rate at which viral load was suppressed during HAART was also analysed as shown in Table 4.6.

The definition of the fraction in the column with a heading, number of results < 400 copies/ml as shown in Table 4.6, denotes that, the numerator is the number of measurements where the levels of viral load were below 400 copies/ml and the denominator is the total number of viral load measurements at the corresponding duration of ART. Out of 100 samples, the mean plasma HIV-1 RNA copies recorded

at baseline was 306 187 copies/ml. At baseline the plasma VL ranged from a minimum of 29 copies to a maximum of 2, 000, 000 copies per ml.

Table 4.6: Proportions of viral load results indicating viral load suppression at different stages of ART

Duration of ART	**Number of results < 400 copies/ml plasma**	**% VL Suppression**
Baseline	100/100	0
0-3 months	2/41	5
>3 to 6 months	21/29	72
>6 months - 1 year	62/103	60
> 1 year up to 2 years	95/117	81
More than 2 years	66/90	73

According to the World Health Organisation (2006), the significant viral load suppressions on HAART are observed at HIV-1 RNA copies less than 400 copies/ml on assay. At the period 0-3 months, two out of 41 viral load recordings, the assayed HIV-1 RNA copies were found to be less than 400copies/ml. This is the first recording that indicated some degree of plasma viral load suppression. The percent viral load suppression at this stage was 5%.

As more levels of viral loads were recorded at later stages of therapy, more viral load suppressions were observed (Table 4.6). The highest degree of viral load suppression (81% viral load suppression) during therapy was observed at the duration of therapy of up to two years. After two years and over, levels of viral load suppression declined from 81 copies to 73% VL suppression (Table 4.6). No further recordings were recorded beyond this point, due to limitations of the time frames of this study (Table 4.6).

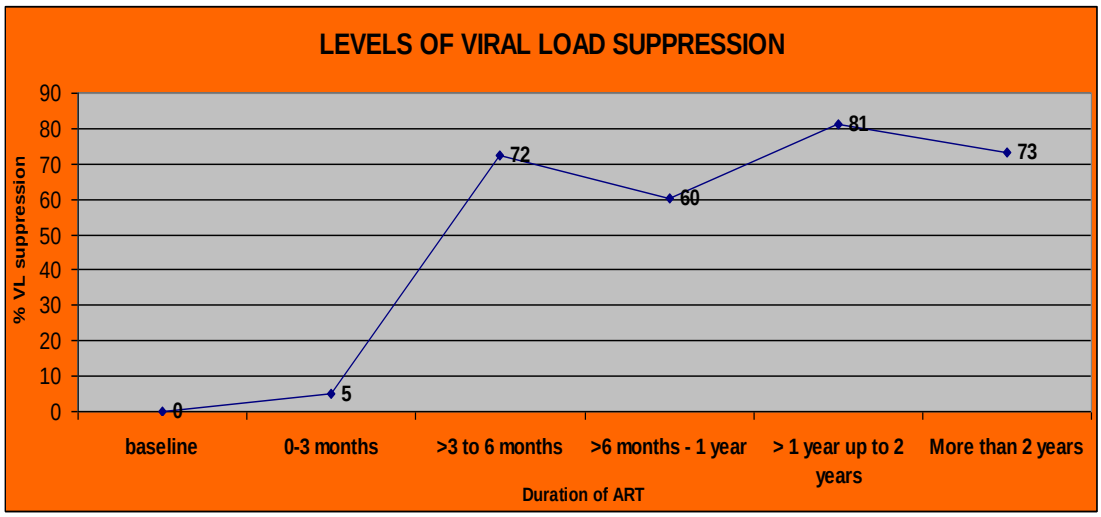

Figure 4.3: Viral Load suppression at different stages of ART

Figure 4.3 presents the patterns of viral load suppression, observed at different stages of ART. There is an irregular pattern observed at different stages of ART. The plasma viral load levels were measured as a routine monitoring of the effectiveness of treatment.

4.6 ADVERSE EFFECTS REPORTED WITH HAART

A number of adverse effects associated with the chronic use of HAART were reported by patients. The aim of this study was to study adverse events in patients on ART through identifying specific risk patient categories, establishing the rates of adverse events (i.e. establish the frequency of occurrence of specific adverse effects) and to characterize and describe the different adverse reactions.

Table 4.7 presents an overall picture of all adverse effects that were reported. The data presented in Table 4.7 is based on the 99 patients that were studied. A statistical analysis of the presented frequencies of adverse effects is presented in the coming sections.

Table 4.7: Types of events and the number of times they were reported during ART

Main Group	Description	Times reported	Percentage
Rash	Rash Grade III	3	2%
	Rash Grade I	8	5%
	Rash Grade II	10	7%
Total		**21**	**14%**
Gastrointestinal	Diarrhoea	1	1%
	Epigastritis	4	3%
	Nausea/vomiting	8	5%
	Abdominal discomfort	10	7%
Total		**23**	**16%**
Neurological	Insomnia/nightmares	2	1%
	Headache	4	3%
	Dizziness	5	3%
	Paraesthesia	11	7%
	P. neuropathy	27	18%
Total		**49**	**33%**
Metabolic	Gynaecomastia	1	1%
	Anaemia	2	1%
	IRIS	4	3%
	Pancreatitis	8	5%
	Hepatitis	10	7%
	Lipodystrophy	10	7%
	Lactic acidosis	20	14%
Total		**55**	**37%**
Grand Total times reported		**148**	**100%**

IRIS-Immune Reconstitution Inflammatory Syndrome

Metabolic (37%) and neurological adverse events (33%) the most. Of these neurological events, peripheral neuropathy (18%) appeared to be the most common event reported. From the main groups of adverse events reported, Immune Reconstitution Inflammatory Syndrome (3%) was the least reported event.

During ART, gastrointestinal events accounted for 16% of the events reported. Out of 148 times events reported, metabolic disorders associated with HAART such as pancreatitis (5%), lipodystrophy (7%) and lactic acidosis (14%) were reported. Rash was reported 21 times out of 148 times. Anaemia and Gynaecomastia were the least reported events, with both accounting for 1%.

Although causality assessment was a limitation in this analysis due to the retrospective nature of the study, and reliance on inscribed information in the patient files, suspected causes of reported ART adverse events were analysed as shown in Table 4.8. Table 4.8 below shows the association between drug class and reported ADR.

Table 4.8: Suspected causes of reported ART adverse events

	ARVs/ Combination	**AZT**	**D4T**	**EFV**	**NVP**	**Un-known**	**Total**
Abd discomf/cramps	2		8				10
Diarrhoea	1						1
Epigastritis	1		3				4
Nausea/vomiting	3		5				8
Hepatitis	5				5		10
Pancreatitis	2		6				8
Lactic acidosis	5		15				20
Lipodystrophy	1		9				10
Gynaecomastia			1				1
Anaemia		1				1	2
P. neuropathy	2		24			1	27
Insomnia/nightmares				2			2
Dizziness				5			5
Paraesthesia	6		5				11
Headache				3		1	4
IRIS	3		1				4
Grade I rash	1			1	5	1	8
Grade II rash	5				4	1	10
Grade III rash					3		3
Total (No of times)	**37**	**1**	**77**	**11**	**17**	**5**	**148**
Total (%)	**25%**	**1%**	**52%**	**7%**	**11%**	**3%**	**100%**

IRIS-Immune Reconstitution Inflammatory Syndrome; Abd discomf- Abdominal discomfort; P- Peripheral

The drug with the most number of events (52%) reported was D4T. These reported events included abdominal discomfort/cramps (eight times), lactic acidosis (15 times), and peripheral neuropathy (24 times). Events reported with EFV and NVP as suspected causative agents accounted for 7% and 11% respectively out of 148 events reported. Events reported due to suspected combinations accounted for 25% of the number of times the events were reported.

Although causality assessment results are not conclusive, it was observed that, D4T appeared to be the most offending agent in all the regimens. The least adverse events reported (one) were observed in patients taking AZT-containing regimens.

Table 4.9 below shows the action taken by prescribers upon a report of the adverse event as reported by the patients. Most of the actions were taken after investigations by the doctor. The action is mostly based on the standard treatment guidelines.

Table 4.9: Action taken

Event	**Changed NVP to EFV**	**Changed D4T to AZT**	**Continue treatment & monitored**	**Reduced dose of problem medicine**	**Stopped all ARVs**	**Not recorded**	**Total**
Abd discomf/cramps		7	3				10
Diarrhoea			1				1
Epigastritis		3	1				4
Nausea/vomiting		2	3	1	2		8
Hepatitis		2	7		1		10
Pancreatitis		6	2				8
Lactic acidosis		11	4	1	4		20
Lipodystrophy		8	2				10
Gynaecomastia		1					1
Anaemia			2				2
P. neuropathy		19	5			3	27
Insomnia/ nightmares			1	1			2
Dizziness			4	1			5
Paraesthesia		6	4		1		11
Headache			4				4
IRIS		2	2				4
Grade I rash			7			1	8
Grade II rash	1	1	7		1		10
Grade III rash	2		1				3
Total	**3**	**68**	**60**	**4**	**9**	**4**	**148**
Total (%)	**2%**	**46%**	**41%**	**3%**	**6%**	**3%**	**100%**

IRIS-Immune Reconstitution Inflammatory Syndrome; Abd discomf- Abdominal discomfort; P- Peripheral

For various adverse events that were reported, action was taken. Out of 148 events, 46% of those events reported, patients were changed from D4T to AZT. In another 41% of the events that were reported, it was recommended that the patients continue

with treatment and be monitored. No action was recorded in only four of the events that were reported as shown in Table 4.9.

From Table 4.9, out of 20 cases of lactic acidosis events that were reported, eight patients were changed from D4T to AZT. Nineteen cases also necessitated a change of D4T to AZT due to peripheral neuropathy experienced. Most patients i.e. seven out of 10 patients, who experienced abdominal discomfort and or cramps, were also changed from D4T to AZT. Nine patients were discontinued from taking ARVs further out of all the cases of adverse events reported. Changing D4T to AZT (46%) tended to be the most common action taken in all adverse effects reported.

4.7 ANALYSIS OF SPECIFIC ADVERSE EFFECTS REPORTED

4.7.1 Lactic acidosis

Table 4.10 below, shows the presentation of lactic acidosis by patients on HAART. The table also shows the baseline characteristics of patients at initiation of therapy with ARVs. It also provides information on the regimen that was prescribed for the patients and the length of ART when lactic acidosis was reported.

Table 4.10: Predisposing factors to the development of lactic acidosis during ART

BASELINE CHARACTERISTICS					LAB	ART REGIMEN				
Age	**Weight**	**Gender**	**pCD4**	**pVL**	**LACT**	**D4T**	**3TC**	**EFV**	**NVP**	**Duration in months**
39	139	F	76	24000	1.83	40	150	600		36
34	69	F	80	21700	6.60	40	150		200	41
39	65	F	120	11000	0.89	30	150	600		39
48	61	M	12	82700	3.60	30	150	600		42
40	63	F	52	11000	5.90	30	150		200	39
33	65	F	192	10000	2.73	40	150	600		37
38	81	M	62	370000	4.52	40	150		200	42
30	63	F	85	19000	5.00	30	150	600		35
51	60	F	112	30000	4.50	30	150	600		36
29	53	F	95	540000	3.30	40	150	600		33
60	67	F	39	330000	3.11	40	150	600		35
38	58	F	32	320000	8.00	30	150		200	36
41	67	M	32	1100000	5.00	40	150	600		33
39	57	F	17	250000	5.20	30	150		200	33
39	58	M	180	4000	3.00	30	150	600		59
39	60	F	182	39000	4.70	40	150	600		30
39	60	M	162	10000	3.70	30	150	600		35
39	74	F	49	45000	1.14	40	150	600		28
39	79	F	180	27000	4.30	40	150	600		25
39	94	F	123	150000	3.10	30	150	600		15
μ=40	**μ=70**	**n=20**	**μ=94**	**μ=169720**	**μ=4**	**40=10**	**n=20**	**n=15**	**n=5**	**μ=35.5**
		F=15(75%)				**30=10**				
		M=5 (25%)								
SD=7	**SD=19**		**SD=60**	**SD=268777**	**SD=1.8**					**SD=8.37**

T-total; F-female; M-male; SD-standard deviation; LAC-Lactate; D4T-Stavudine; 3TC-Lamivudine; EFV-Efavirenz; NVP-Nevirapine; μ – mean; n- sample size

In a sample of 99 patients, of those 20 patients that experienced lactic acidosis, 15 (75%) were females and 5 (25%) were males. The age of patients that developed elevated lactate levels ranged from 29 to 60 years and their weight ranged from 53 to 139 kg. The age of patients who did not experience lactic acidosis during ART ranged from 19 to 61 years and their weight ranged from 32 to 104 kg.

Although the two groups did not differ significantly as shown by their *p*-values of 0.130 and 0.119 for age and weight respectively (Table 4.11 below), the weight range for the group that experienced lactic acidosis tended to be greater than that of the group which did not.

There was a high inter-variability observed with the pCD4 and plasma viral load values as computed by their standard deviations (Table 4.10 and 4.11) in patients who experienced lactic acidosis.

From 20 subjects that experienced heightened lactate levels during ART, the mean lactate level computed was 4.006mmol/l and the levels ranged from 0.89 to 8 mmol/l. The duration of treatment was measured in months from the initiation of ART until the symptoms were reported and confirmed by lactate sampling. The mean duration of ART for patients who developed symptoms of lactic acidosis was 35.5 months.

Table 4.11 below shows a statistical test conducted for the two sample means of both the patients that reported lactic acidosis and those that did not. Measures of variability between the two sample means are also presented. A statistic measure of the relationship between the two groups is computed in terms of the p-values for various patient characteristics with respect to lactic acidosis.

Table 4.11: Characteristics of patients who experienced lactic acidosis

	LACTIC ACIDOSIS				
	YES (n = 20)		**NO (n = 79)**		**α = 0.05**
Characteristics	**Mean**	**SD**	**Mean**	**SD**	***P***
Female	15 (75%)		55 (70%)		0.786
Male	5 (25%)		14 (30%)		
Age (years)	40.10	7.15	37.19	7.63	0.130
Weight (kg)	69.65	18.98	62.35	13.73	0.119
pCD4 (cells/ mm^3)	94.10	59.55	100.80	63.57	0.669
ART duration (mons)	35.45	8.37	29.34	8.96	**0.007**

T-Test statistic and Fisher's Exact Test for two sample means: α- alpha (level of significance); *p* – probability value; SD- Standard Deviation; mons - months

According to the p-value (0.786), as computed using the Fisher's Exact Test, there were no significant differences between the female patients who experienced lactic acidosis and those who did not report lactic acidosis. Similarly, the male subgroups did not differ significantly as shown in Table 4.11.

There is evidence as computed by the p-value of 0.130 from the results of the t-Test statistic, that the population mean age (40.10 years) for patients who reported symptoms of lactic acidosis and the mean age (37.19 years) of those who did not report symptoms of lactic acidosis, did not differ significantly between the two sample groups.

According to the results of the t-Test statistic (Table4.11), the duration of treatment on ART of 35.45 months for the development of lactic acidosis was found to be significantly greater than the duration of 29.34 months (p = 0.007).

The mean lactate levels at different stages of ART for various sample sizes of patients who reported lactic acidosis at corresponding periods was analyzed as shown in figure 4.4 below.

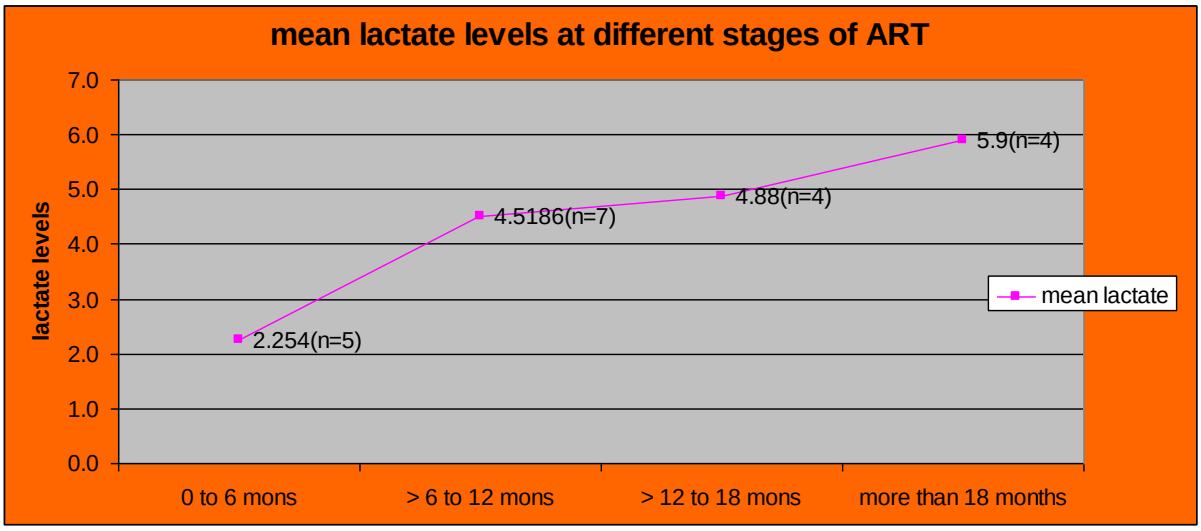

Figure 4.4: Mean lactate levels at different stages of ART (n- sample of test performed)

The mean lactate levels were arranged into numerically ordered class groupings based on different stages of treatment (as depicted in Figure 4.4.). A suitable width (6 months period) of the class groupings was determined and the boundaries of each class grouping to avoid overlapping.

There were 20 numerical values from the data and four class groupings were determined. From the graphical presentation above, the mean lactate levels

increased with the continuum of care (i.e. from 2.3 to 5.9 over a period of more than 18 months).

4.7.2 Lipodystrophy

Various possible factors that were suspected to be predisposing patients to develop lipodystrophy are presented in Table 4.12 below.

Table 4.12: Predisposing factors for the development of lipodystrophy during ART

BASELINE CHARACTERISTICS					
Gender	**Weight (kg)**	**Age (yrs)**	**pCD4 (cells/mm^3)**	**pVL (copies/mm^3)**	**Duration (months)**
F	62	38	150	15000	38
F	42	47	101	400	53
M	61	44	132	79000	39
F	63	40	52	11000	39
F	56	26	14	270000	2
F	65	33	192	10000	37
F	53	31	178	46000	37
F	60	51	112	30000	36
F	60	38	182	39000	30
F	56	56	205	29000	17
M = 1	**μ = 58**	**μ = 40**	**μ = 132**	**μ = 52940**	**μ = 32.8**
F = 9					

F-female; M-male; VL-viral load; ART-antiretroviral; μ – mean; yrs - years

As shown in Table 4.12, ten patients were assessed for the development of lipodystrophy. Of the ten that presented with symptoms of lipodystrophy, 90% were female and 10% were males. The mean duration of treatment for the development of lipodystrophy was found to be 32.8 months. The mean weight, age, and CD4 count at baseline was measured as 56.1kg, 42.1 years, and 132cells/mm^3 respectively.

Weight ranged from 32 to 139 kg in a group that did not report symptoms of lipodystrophy as compared to 42 to 65 kg for those that reported symptoms of lipodystrophy. Weight values for the group that reported lipodystrophy varied greatly (SD = 15.79) compared to that of those who did not report lipodystrophy (SD = 7.79).

Table 4.13: Characteristics of patients experienced lipodystrophy

	LIPODYSTROPHY				
	YES (n = 10)		NO (n = 89)		α = 0.05
Characteristics	**Mean**	**SD**	**Mean**	**SD**	***P***
Female	90.00		67.42		0.275
Male	10.00		32.58		
Age (years)	42.10	11.34	37.48	7.39	0.237
Weight (kg)	56.10	7.80	64.74	15.80	**0.009**
pCD4 (cells/ mm^3)	131.80	62.85	95.84	61.80	0.085
Duration (months)	32.80	14.00	30.22	8.79	0.582

T-Test statistic for two sample means: α- alpha (level of significance); *p* – probability value; SD- standard deviation

The mean values for age, pCD4 count and duration of treatment did not differ significantly between the group of patients who reported lipodystrophy and those that did not. For the *p*-value of 0.009, it is evident that the two groups differed significantly for weight. The mean weight of 56.10 kg differs significantly to the mean weight of 64.74 kg. Lipodystrophy appeared to be more prominent in patients with low baseline weight compared to patients with bigger baseline body weight. The body mass indices (BMI) were not computed for all the patients at baseline.

4.7.3 Pancreatitis

One of the metabolic complications that were reported with the use of HAART is pancreatitis. An analysis of the predisposing factors to the development of pancreatitis whilst taking ART is shown in Table 4.14.

Table 4.14: Predisposing factors to the development of pancreatitis during ART

BASELINE CHARACTERISTICS					LAB	ART REGIMEN				
Age (yrs)	**Weight (kg)**	**Gender**	**pCD4 (cells/mm^3)**	**pVL (copies/ mm^3)**	**AMYLASE (mmol/L)**	**D4T**	**3TC**	**EFV**	**NVP**	**Duration (months)**
39	139	F	76	24000	142	40	150	600		36
41	51	M	34	750000	119	30	150	600		40
39	65	F	120	11000	112	30	150	600		39
34	55	F	179	1500	181	30	150	600		45
33	65	F	192	10000	197	40	150	600		37
35	69	F	22	45000	133	30	150		200	37
45	60	M	162	10000	250	30	150	600		35
42	79	F	180	27000	99	40	150	600		25
μ=39	**μ=73**		**μ =121**	**μ=109813**	**μ= 154**	**40=3**	**8**	**7**	**1**	**μ=36.75**
		F=6(75%)			**SD=51**	**30=6**				
		M=2(25%)								

VL- Viral load; D4T- Stavudine; 3TC- Lamivudine; EFV- Efavirenz; NVP- Nevirapine; ART- Antiretroviral Therapy; SD- Standard Deviation; F-Female; M-Male; μ – mean

Table 4.14 presents the descriptive analysis of the measured serum amylase concentrations for eight patients that presented with symptoms of pancreatitis during ART.

Out of eight patients that reported symptoms of pancreatitis, 75% were females and 25% were males. All eight patients were treated on D4T containing regimen and one on nevirapine containing regimen. Of those who were on D4T, three were treated with D4T 40 mg and five with D4T 30 mg. The mean duration of treatment for the development of raised amylase levels after initiation of ART was 36.75 months. The baseline mean age and weight at the start of ART was 39 years and 73 kg respectively.

The age and weight ranges observed in groups that presented with symptoms of pancreatitis were 33 to 45 years and 51 to 139 kg respectively. The minimum (51 kg) and maximum (139 kg) values tended to be greater in the group that reported symptoms of pancreatitis as compared to that of the group that did not report pancreatitis (i.e. min = 32 kg and max = 104 kg). The mean baseline CD4 count and VL at the start of ART was 121 cell/mm^3 and 109 813 HIV RNA copies respectively.

Patients with pancreatitis presented with abdominal pain and increased amylase levels. The mean amylase computed for patients that presented symptoms of

pancreatitis was 154. Of the patients that reported symptoms of pancreatitis, serum amylase levels ranged from 99 to 250mmol/L (normal: 30-150mmol/L).

A further comparative study was carried out to measure the differences or the relationship between the group of patients that reported pancreatitis and the one that did not as shown in Table 4.15.

Table 4.15: Characteristics of patients experienced pancreatitis

	PANCREATITIS				
	YES (n = 8)		**NO (n = 91)**		**α = 0.05**
Characteristics	**Mean**	**SD**	**Mean**	**SD**	***p***
Male	6 (75%)		69.23		1.000
Female	2 (25%)		30.77		
Age (years)	38.50	4.21	37.90	8.18	0.839
Weight (kg)	72.88	28.06	63.08	13.73	0.360
pCD4 (cells/ mm^3)	120.63	68.62	97.62	62.04	0.321
Duration months	36.75	5.68	29.93	9.46	**0.048**

T-Test statistic and Fisher's Exact Test for two sample means: α- alpha (level of significance); *p* – probability value; SD- standard deviation

The results of the t-Test statistic show that there is no difference in the mean age, weight and pCD4 count of patients who experienced pancreatitis and that of those who did not experience pancreatitis. The two samples however differ significantly in the duration of treatment (*p*-value = 0.048). The mean duration of 36.75 months differs significantly from the mean duration of 29.93 months

4.7.4 Peripheral neuropathy

Table 4.16 below shows a further comparative study carried out to measure the relationship between the group of patients that reported peripheral neuropathy and the one that did not.

Table 4.16: Characteristics of patients experienced peripheral neuropathy

	PERIPHERAL NEUROPATHY				
	YES (n = 27)		NO (n = 72)		α = 0.05
Characteristics	**M**	**SD**	**μ**	**SD**	***p***
Female	18 (67%)		70.83		0.807
Male	9 (33%)		29.17		
Age (years)	36.78	6.03	38.15	8.11	0.425
Weight (kg)	63.67	10.80	64.18	16.68	0.858
pCD4 (cells/ mm^3)	91.37	54.64	102.50	65.35	0.396
Duration (months)	33.63	8.78	29.43	9.07	**0.041**

T-Test statistic for and Fisher's Exact Test two sample means: α- alpha (level of significance); *p* – probability value; μ- mean; SD- Standard Deviation

In a sample of 27 patients that experienced peripheral neuropathy during ART, 18 (67%) were females and 9 (33%) were males.

There was no significant difference between the mean ages, weight and pCD4 count of patients who experienced peripheral neuropathy and the means of those who did not experience peripheral neuropathy, as depicted by the computed p-values shown on Table 4.16. However, the two groups differed significantly (*p*-value = 0.041) for the mean duration of treatment.

Table 4.17 below shows the comparison between the two proportions of patients who reported symptoms of peripheral neuropathy during ART and those that did not with respect to the different dosages of D4T.

Table 4.17: Differences in patients with peripheral neuropathy on two different dosages of D4T

Peripheral Neuropathy					
	Outcomes of Observed Frequencies				
Dosage	**Yes**		**No**		**Total**
D4T 30mg	17	63%	48	67%	**65**
D4T 40mg	10	37%	24	33%	**34**
Total	**27**		**72**		**99**
Total (%)		**100%**		**100%**	
Results					
Level of Significance	0.05		**Joint Probabilities**		
Critical Value	3.841		P(D4T 30 and Yes)		0.32
Chi-Square Test Statistic	0.352		P(D4T 30 and No)		0.34
***p*-Value**	0.553		P(D4T 40 and Yes)		0.19
Do not reject the null hypothesis			P(D4T 40 and No)		0.17
Expected frequency assumption is met.					

D4T- Stavudine; P- Probability

Out of 27 patients that reported peripheral neuropathy, 63% were on D4T 30mg and 37% were taking D4T 40mg. In the remaining proportion (72) that did not report symptoms of peripheral neuropathy, 67% of the patients were taking D4T 30mg whilst 33% were on D4T 40mg. There was no difference in the occurrence of peripheral neuropathy between the two dosages of D4T.

4.7.5 Rash

Table 4.18: Development of rashes for patients on NNRTIs

EFV	**NVP**	**Mean Duration (weeks)**
1	**12**	**10.411765**
8%	**92%**	

Rashes were documented in 13 patients on NNRTIs (Table 4.17). The mean duration of treatment for the development of rash after initiation of ART was 10.41 weeks.

4.7.6 Other adverse effects

Gynaecomastia, anaemia, and IRIS were least reported and accounted for one, two, and four of adverse event episodes out of 148 episodes respectively.

4.8 ROUTINE LABORATORY DATA

4.8.1 NORMAL VALUES

Table 4.19: Normal laboratory values

	Reference ranges by gender	
Parameter	**Female**	**Male**
Haemoglobin	12-15	13-17
AST (mmol/L)	5-30	15-45
ALT (mmol/L)	5-40	5-40
S-Lactate (mmol/L)	0.3-2.4 (-1.8)	0.3-2.4 (-1.8)
S-Amylase (mmol/L)	30-150	30-150

The recorded laboratory values were compared to the published normal population reference ranges to assess any potential abnormalities. Table 4.18 presents the parameters that were analyzed during the study.

4.8.2 MEAN HAEMOGLOBIN VALUES

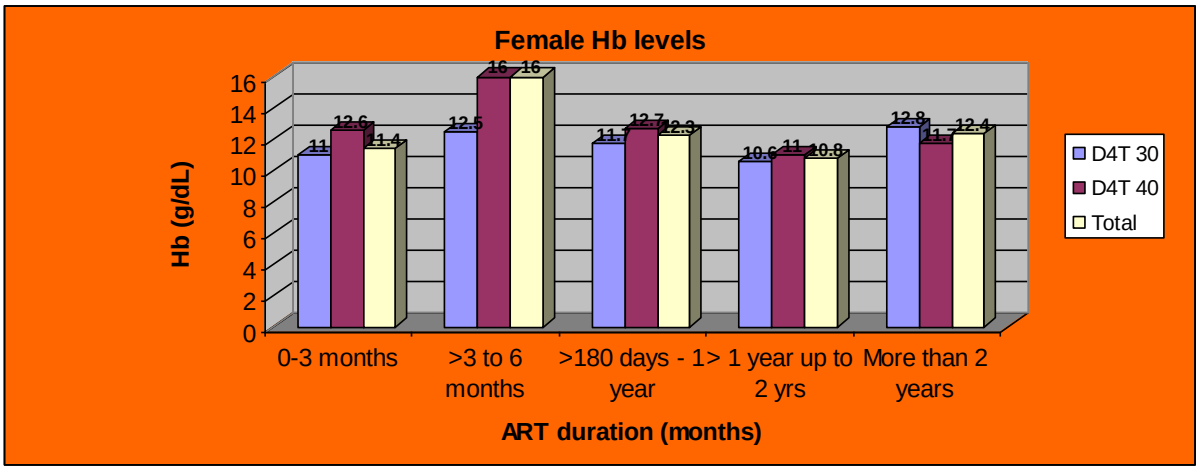

Figure 4.5a: Mean female haemoglobin levels

There was a slight increase in the mean Hb levels (i.e. above the reference range of 12-15 for females) during the period of more that three to six months of therapy.

Table 4.19 shows the descriptive statistics used to analyse the haemoglobin levels between a group of female patients taking D4T 30mg and that which is taking D4T 40mg.

Table 4.20: Female Haemoglobin t Test for Differences in Two Means

	Hb	
FEMALES	*p*-Value = 0.1969	
	D4T 30mg	D4T 40mg
Mean	11.68	12.46
SD	2.37	2.25
Minimum	8.00	9.00
Maximum	19.00	16.00
n	41.00	24.00

N- Sample size; D4T-Stavudine; SD-Standard Deviation; Hb-Haemoglobin

There were no significant variations in the frequency distribution of Hb levels around the mean. In addition, there were no significant differences in the mean levels of Hb between the patients receiving the two different dosages of D4T (i.e. D4T 30mg- and D4T 40mg-containing regimens). The computed p-value for the sample groups is 0.1969. The minimum and maximum Hb recorded for patients taking D4t 30mg is 8 and 19 and for patients on D4t 40mg was 5 and 18.

Figure 4.5b, shows the mean haemoglobin levels in male patients taking chronic ART at different stages of treatment.

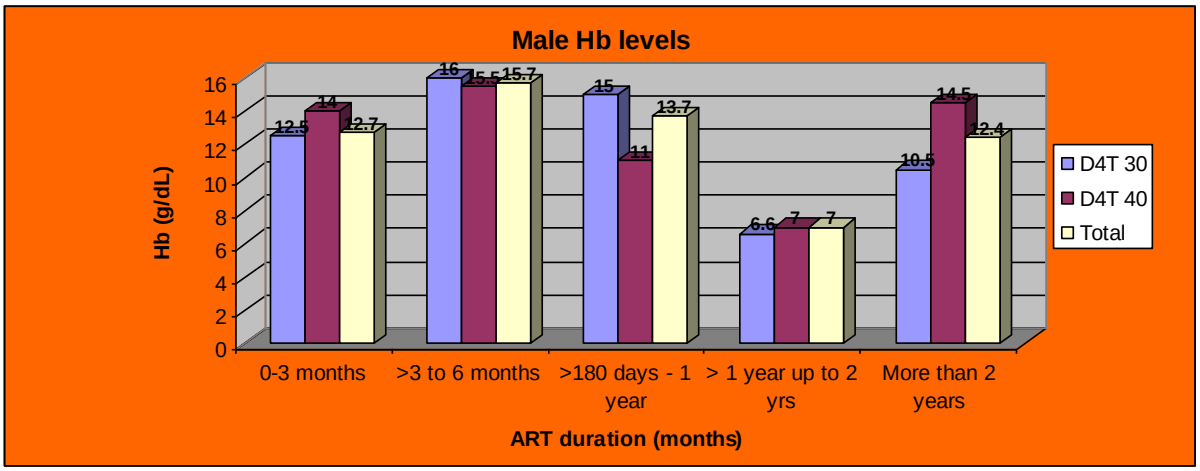

Figure 4.5b: Mean male haemoglobin levels

There was a slight increase in Hb levels (i.e. above the reference range of 12-15 for females) during the period of more that three to six months of therapy. The levels of Hb remained within the normal range of (13-17 for males) throughout the course of treatment. There were no significant variations in the frequency distribution of Hb levels around the mean.

Table 4.21: Male Haemoglobin t-Test for differences in two means

	Hb	
MALES	*p*-Value = 0.4712	
	D4T 30mg	D4T 40mg
Mean	12.37	13.30
SD	2.77	4.06
Minimum	8.00	5.00
Maximum	18.00	18.00
n	19.00	10.00

N- Sample size; D4T-Stavudine; SD-Standard Deviation; Hb-Haemoglobin

In addition, there were no significant differences in the mean levels of Hb between the patients receiving the two different dosages of D4T (i.e. D4T 30mg- and D4T 40mg-containing regimens) as shown by the p-value of 0.4712 in Table 4.20. No Hb levels were taken in male patients taking AZT containing regimen, from the initiation of treatment with AZT (i.e. 0 to 3 months) up to two years of ART.

4.8.3 MEAN ALANINE-AMINOTRANSFERASE (ALT) VALUES

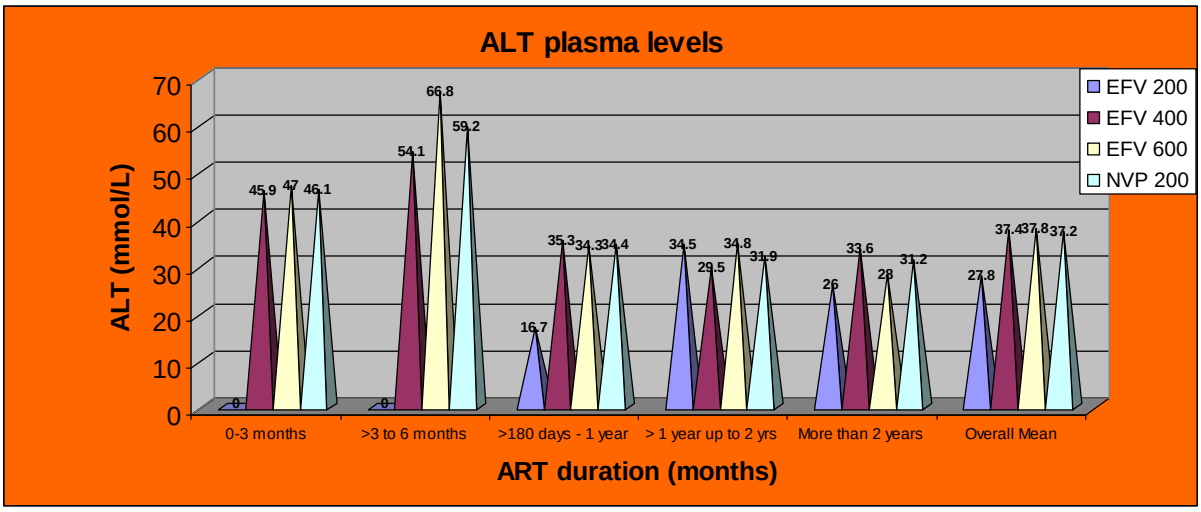

Figure 4.6: Mean ALT levels

The highest ALT levels observed during ART therapy were seen during the period of more than three months to six months. There was a slight increase in ALT above the reference range of 5-40 mmol/ml during the initiation period of therapy (i.e. from 0 to 3 months). After 3 to 6 months, ALT levels declined. The ALT levels remained constant from 180 days to more than two years of therapy. The overall ALT results recorded were (27.8, 37.4, 37.8 and 37.2) mmol/ml for EFV 200mg, EFV 400mg, EFV 600mg and NVP 200mg respectively.

4.8.4 MEAN LACTATE VALUES

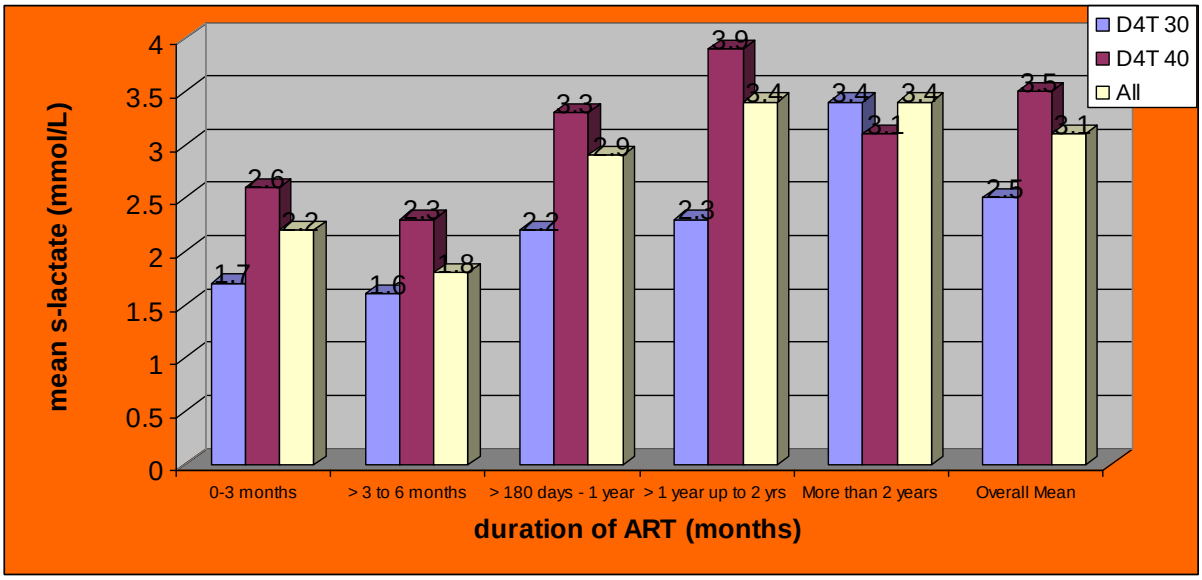

Figure 4.7: Mean plasma serum lactate levels

Of the patients in whom lactate, levels were measured, the highest mean lactate levels (i.e. 3.4) were observed at the duration of ART more than one year and up to two years or longer than two years. This highest mean lactate levels were observed from a sample of 49 patients and mostly were on a regimen containing D4T 40mg (n=33). In general, the highest mean lactate levels (3.5) were observed in 62 patients taking a regimen containing D4T 40 mg. No lactate levels were recorded for patients started on AZT containing regimen or mixed regimen 1a.

This chapter laid a fundamental analysis of the collated data regarding ART adverse effects reported by patients taking chronic ART. The next chapter seeks to match the findings of the study with the available literature. It provides an in-depth analysis and

discussion of these findings. It is from such fundamental context laid, that recommendations for future practice will be based.

CHAPTER 5

5. DISCUSSION

This chapter presents an interpretation of the results as presented in Chapter 4. It compares the findings of this report with those published in the literature. A thorough discussion of the presented results is undertaken to highlight problems that were identified. A brief discussion of the demographic data is presented and the rest of the Chapter focuses on the adverse effects that were reported and recorded during ART.

5.1 DEMOGRAPHIC DATA

There were more female (70%) participants in this study compared to their male (30%) counterparts. More female participants (37%) were from the age group 30-39 years and the least from the age group below 20 years. The occurrence of ART adverse effects were compared between both male and female categories.

5.2 PRESCRIBED DRUG REGIMENS

Treatment allocation was based on the standard treatment guidelines, where the demographics such as age and gender were taken into consideration (Department of Health, 2005). Although the guidelines have been revised, this study was conducted prior to the publication of the recent guidelines published by the Department of Health (2010).

Most of the patients were treated on regimen 1a where 38 out of 99 patients were placed on a combination of D4T 30mg/40mg, 3TC 150mg and EFV 600mg. Patients were monitored for tolerance and immunological response on a regular basis and where necessary some drug entities were switched to the possible available alternatives. Few patients were initiated on regimen 1b.

5.3 DURATION OF ART

By the time the study commenced, most of the patients had already completed more than six months of ART. Having tracked ART course and followed through the continuum of this study, most of the patients had completed 30 to 36 months duration on ART. Of the 23, 13 were females and 10 were males. Only eight had already been on ART for than 42 months.

The average duration, at which these ADRs presented were 34 months for peripheral neuropathy, 35 months for lactic acidosis, and 37 months for pancreatitis. The duration of treatment seemed to be the factor that warranted closer monitoring for patients who are chronically treated on ART.

5.4 CD4 CELL COUNT AND VIRAL LOAD MEASUREMENTS AS INDICATORS OF ART SUCCESS OR FAILURE

From Chapter 4 of this report, VL and CD4 cell counts results have been presented. These results are discussed in detail on the sections that follow. From a report by Jevtovic *et al.* (2005), they have alluded to the fact that, the introduction of HAART has indeed resulted in maximal control of viral replication and reconstitution of immune system functions among patients with HIV-induced immunodeficiency. To prove this beneficial effects referred to by the preceding authors, the levels of viral load suppression together with the levels of CD4 cell count recovery from baseline to more than two years been on ART were analysed.

Further in the literature as captured in the work of Phillips *et al.* (2008), for patients on the first line regimen of stavudine, lamivudine, and nevirapine the benefits of viral load or CD4 cell count monitoring over clinical monitoring alone are modest. For them, the development of cheap and robust versions of these assays was important.

5.4.1 Plasma CD4 count measurements

The mean duration of treatment to start observing an increase in CD4 cell count, although minimal, was after three months of treatment. In this period, the mean CD4

cell count increased from 100cells/mm^3 at baseline to 158cells/mm^3 after three months of ART. These were the first signs of effectiveness of ART as in line with the general findings of the published literature, as in the preceding quotations.

The overall immune recovery was observed from an average of 100cells/mm^3 at baseline to 374cells/mm^3 after two years of ART. Although this was a satisfactory situation according to World Health Organisation (2006) guidelines, the incremental rate stayed below 50% for the most part of the observed duration of treatment for patients on HAART. The highest incremental rate (58%) in plasma CD4 cell count was observed at the period from baseline to three months.

5.4.2 Plasma viral load measurements

A total of 488 viral load measurements (Table 4.5) have been recorded at different stages of ART. The pVL were monitored on a routine basis, as a measure of monitoring ART failure or success. Out of 41 measurements of VL taken after three months of ART (Table 4.6), only 2 (i.e. 5%) of the results were found to be below < 400 copies/mL. In the same corresponding period of zero to three months, the CD4 cell count increased from a mean of 100cells/mm^3 at baseline to 158cells/mm^3 after initiation of ART (Table 4.4).

Although the regression analysis was not computed in order to measure the relationship of VL decrease over ART duration and the relationship of CD4 cell count over the duration of ART, this analysis has revealed that over the duration of ART, CD4 cell counts increased from baseline and the VL has dropped after initiation of ART. This analysis has shown some consistency with the studies conducted by Jevtovic *et al*. (2005) and van Leth *et al*. (2005).

As indicated by this analysis, viral suppression and immune recovery has been observed throughout the continuum of care with chronic ART. However, this study acknowledges that adherence levels could have played a role in the variability of the results. In a study by van Leth *et al*. (2005), virologic failure has been defined as viral suppression not reaching pVL < 400copies/mL or a rebound to two consecutive values > 400copies/mL. In their analysis, van Leth *et al*. (2005) discovered that the

risk of virological failure was increased at very low CD4 counts compared to CD4 counts > 200 cell/L.

According to van Leth *et al*. (2005), the benefits of initiating HAART at a CD4 cell count > 300cells/L is marginal, at the most, and might depend on additional factors such as baseline pVL. It was shown that, regimens containing either NVP or EFV, together with stavudine and lamivudine were not statistically significantly different with respect to the proportion of patients with either treatment failure or a pVL < 50 copies/mL at week 48 (van Leth *et al*., 2005).

Patients with a baseline CD4 cell count < 25 cells/mm^3 had an increased risk for virologic failure when cut-off failure was 400copies/mL, although this risk did not reach statistical significance (van Leth *et al*. 2005). After a mean treatment duration of 33.1 months, 170 (38.2%) patients were found to have favourable both immunological and virological responses (Jevtovic *et al*., 2005).

Jevtovic *et al*. (2005) defined the favourable response to ART*,* as plasma VL levels below 400 copies per ml. After six months of ART, there was a decrease in the plasma VL (i.e. from 5% to 60% of VL measurements were < 400 copies/m/L as shown in table 4.6), indicating the effectiveness of treatment. This showed a favourable response to ART as per Jevtovic *et al*. (2005) and van Leth *et al*. (2005) assertions.

From three months to six months, the highest level of viral load suppression was recorded owing to the effectiveness of ART. In this period, out of 29 VL measurement results, 21 results had HIV RNA copies below a threshold of 400copies/ml, as set by the WHO for assessing ART effectiveness.

The level of viral load suppression declined during the period of six months to one year or 12 months from 72% to 60%. The levels of viral load suppression were inconsistent throughout the duration of treatment under study. This could be attributed to some degree of resistance of the virus to treatment due to poor adherence or some other host factors. Phillips *et al.* (2008) mentioned in their research that patients who have virological failure on treatment with stavudine,

lamivudine, and nevirapine are likely to continue to experience some benefit from that regimen, despite accumulation of resistance mutations.

This knowledge grounded statement is in line with the findings of this report where the mean CD4 cell count increased with every stage of therapy despite declining or rising VL levels. Although the levels of adherence in this research were not assessed, Phillips *et al.* (2008) attributed an underlying cause of virological failure to reduced or poor adherence to HAART regimens.

In support of the preceding arguments regarding the likely causes of treatment failure, Re *et al.* (2000) asserts that failure of a regimen may occur for many reasons, including viral resistance to one or more agents, altered absorption or metabolism of the drug, multi drug pharmacokinetics, poor patient adherence or partly related to the stage of disease.

After one year of treatment, there was a sharp increase in the level of VL suppression (i.e. from 60% to 81%). This sharp increase corresponded to the sharp increase in the proportions of mean CD4 cell count (i.e. from 243 to 336cells/mm^3). Although there was considerable increase in the proportions of CD4 cell count, this did not translate into significant incremental rate as expected (i.e. more than 50%, instead only 39% increase was observed). As expected by the World Health Organisation (2006) guidelines, this 50% rate of CD4 cell count increase, should translate to a mean CD4 cell count of ≥ 200cells/mm^3, considered the minimum effective level of immune protection.

Patients on antiretrovirals with partial viral suppression experience more favourable CD4 cell count changes than those off antiretroviral therapy, even for those with the same viral load (Phillips *et al.,* 2008). There was greater variability in the measurements of CD4 cell counts as measured by the standard deviation. The volatility observed with CD4 count measurement was seen despite increasing number of VL results < 400 copies.

While HAART allows for the reconstitution of immune functions in most treated HIV patients, discrepant responses including failure to achieve a significant increase in

circulating CD4+ cells despite undetectable plasma viral loads, or a good immunological response while not reaching undetectable viremia, may occur (Jevtovic *et al.,* 2005).

Although adherence was not assessed, this analysis could be pointing to possibilities of existing and persisting viral resistance to treatment that could be due to poor adherence or other host factors. It is important at this point, to highlight the fact that viral load is also used as an indicator of adherence. In the research report by Phillips *et al.* (2008), they found that viral load monitoring was used in high-income settings to minimise the time that patients who have virological failure in their first-line regimen remain on this failing regimen.

5.5 ADVERSE EFFECTS REPORTED WITH HAART

Limitations of antiretroviral therapies because of adverse events have been described and reported in literature. In this analysis a total of 148 adverse events have been reported by 99 patients that were studied. Although this has been reported in literature, this study in its findings brought evidence to the reality of occurrence of adverse effects in patients taking chronic ART. It is espoused in the literature, most aetiologies of adverse effects associated with the use of ARVs, particularly with the NRTIs could be explained by mitochondrial dysfunction associated with long-term toxicities of ART (Dagan *et al.,* 2002).

Amongst many, lactic acidosis, hepatic staetosis, myopathies, cardiomyopathies, neuropathies, and lipodystrophy are frequently attributed to mitochondrial toxicity (Dagan *et al.,* 2002). According to Dagan *et al.* (2002), since HAART toxicity is not well understood and could pose a major threat to the long term success of HIV therapy, there is an urgent need to examine the existing data on the association of HAART and its toxicities.

The remaining section of this chapter focuses in more detail, on the adverse effects that were reported.

5.6 ANALYSIS OF SPECIFIC ADVERSE EFFECTS REPORTED

5.6.1 Lactic acidosis

Elevations in lactic acid in the blood have been documented. A guideline terminology for elevated lactate has been defined by Brinkman (2000), as quoted by Dagan *et al.,* (2002) in their study;

1. Mild hyperlactatemia: serum lactate = 2.1-2.5mmol/L;
2. Serious hyperlactatemia: serum lactate ≥ 5mmol/L;
3. Lactic acidosis: serious hyperlactatemia and bicarbonate ≥ 20mmol/L.

In this study, lactic acidosis was reported in some patients on nucleoside reverse transcriptase inhibitors. From a count of 148 events that were reported, lactic acidosis accounted for 14% (Table 4.7). Ogedegbe *et al*. (2003), they reported in their study that hyperlactataemia was seen in 8-18.3% of HIV infected patients taking nucleoside reverse transcriptase inhibitors. During this study, the most common presenting symptoms that were reported were non-specific and included nausea, vomiting, abdominal pain, weight loss, malaise, and dyspnoea.

The use of D4T was found to be the most frequently identified risk factor for the development of hyperlactataemia during ART, as reported by Ogedegbe *et al.,* 2003. However, in this analysis, there was no control group to compare with the group of patients taking D4T. A randomised controlled analysis will be required in order to be able to draw statistical conclusions with respect to the use of D4T.

All patients studied in this report were initiated with a regimen containing D4T. Therefore, in this report, it can only be suspected that the likely offending agent was D4T as suggested by 15 cases of elevated lactate levels which pointed at D4T as the suspected cause of lactic acidosis (Table 4.8). Symptomatic hyperlactataemia in 114 (91.2%) was associated with receiving D4T in a study conducted by Manosuthi *et al*., (2008).

In the cases that D4T was suspected to be the problem agent in this report, 11 of them were changed from D4T to AZT, four patients were advised to continue treatment under close monitoring by the physician, ARVs were stopped in four patients and only in one patient the dose of D4T was reduced (Table 4.9). The symptoms were reported as improved in the patients that changed from D4T to AZT and those that stopped taking ART. In symptom-free patients, only serum lactate concentrations of or above 5.0 mmol/L warranted discontinuation of therapy (Ogedegbe *et al.,* 2003). They further mentioned that, prompt withdrawal of all NRTIs was the cornerstone in the management of hyperlactataemia with or without symptoms.

Geddes *et al.,* (2006) in their research report, further asserts that mild hyperlactataemia (lactate level of 2.1-5 mmol/l) is often asymptomatic or may cause symptoms as it was observed in this study. Figure 4.4 (i.e. five patients reported a mean lactate level of 2.3mmol/L and seven patients reported 4.5 mmol/L). Some of these patients who had mean lactate level of 2.3 mmol/L, they reported non-specific symptoms including dyspnoea, abdominal discomfort (nausea, vomiting and abdominal distension).

The mean duration of treatment that was reported in this study for patients to develop lactic acidosis was found to be 35.5 months, as shown in Table 4.10 and 4.11. This duration was seen in a sample of 20 patients that reported lactic acidosis as compared those that did not. These patients started presenting the signs and symptoms of lactic acidosis after having exposed to ART for a longer period. As such, the computed p-value on Table 4.11 indicated statistically significant differences in the two mean durations of treatment.

Relative to a study conducted by Caffrey (2000), the results of their study, showed that, as patients with HIV had a longer exposure to the NRTIs, more cases of lactic acidosis were reported. Eshum-Wilson *et al*. (2005) in their study mentioned that lactic acidosis and symptomatic hyperlactataemia can occur from one month to 20 months after commencing NRTIs. Eshum-Wilson *et al*. (2005) further mentioned that typical initial symptoms may develop over 1-6 weeks.

These assertions by Caffrey (2000) and Eshum-Wilson *et al*. (2005), reaffirms the need for closer monitoring of patients who are chronically treated on ART, especially with the D4T containing regimens. In this analysis patients taking ART were followed for periods of more than six months to more than 42 months (Table 4.2). For this duration of ART, lactic acidosis was reported 20 times, representing 14% of the total number of ART adverse effects reported (Table 4.7). Of these cases that were reported, D4T was the most likely suspected drug to cause lactic acidosis.

According to Eshum-Wilson *et al*. (2005), several factors may predispose a patient to the development of lactic acidosis/hyperlactataemia. Amongst these factors studied by Eshum-Wilson *et al*. (2005) that were found to predispose patients to the development of lactic acidosis were female sex, excellent compliance, duration of treatment of more than six months, chronic muscle or kidney disease, chronic hepatitis B or C infection, and the combination of D4T and DDI. The correlation between women with an increased BMI and lactic acidosis remains unproven (Eshum-Wilson *et al*., 2005).

From Table 4.11, the t Test statistic results indicated that there was no significant difference between the group that reported lactic acidosis and the one that did not in terms of their mean age, weight and pCD4 counts as measured by their presented p-values of 0.130, 0.119, and 0.669 respectively. However, the two groups differed significantly in terms of the duration of treatment (i.e. p-value of 0.007).

The longer the patients were treated on ART (i.e. mean duration of 35 months being on ART) the more likely they were to experience lactic acidosis. A similar finding with regards to duration of treatment has been reported in a study by Eshum-Wilson *et al*. (2005). Amongst the factors studied by Eshum-Wilson *et al*. (2005) that were found to predispose patients to the development of lactic acidosis was the duration of treatment of more than six months.

From a case report by Mokrzycki *et al*. (2000), after the mean duration of 9.4 months with stavudine therapy, the mean observed peak lactate level was 10.3mmol/L. After discontinuation of D4T treatment, lactic acidosis improved in four patients after 4-60 weeks (Mokrzycki *et al*., 2000). In this report, as mentioned already in the preceding

sections, a remission of lactic acidosis symptoms was observed after discontinuation of stavudine. The symptomatic serum lactate levels reported in a case study by Caffrey (2000:91) was 10.6mmol/L. The ARVs were also discontinued in this case report by Caffrey (2000:91). Figure 4.4 of this report showed that the mean lactate levels increased with different duration of ART (i.e. from 2.3 to 5.9mmol/L at 0 to 3 months and more than 18 months respectively).

Although, according to the findings of this analysis, the weight could not be seen as the predisposing factor (statistically insignificant with p-value=0.119), it has been observed that the weight range in patients who reported lactic acidosis was higher (i.e. 53 to 139 kg) as compared to those that did not (i.e. 32 to 104 kg).

From this study, out of 148 cases that were reported, lactic acidosis was reported 20 times. This accounted for 14% (Table 4.7) of the cases reported. Of the cases of lactic acidosis that were reported (20), five cases of lactic acidosis reported were associated with the use of ARV combinations and 15 times with the use of stavudine. There were no incidences associated with the use of AZT, EFV, and NVP. Lactic acidosis was reported the most times with the use of D4T.

In a similar study by Maulin *et al*. (1999) as quoted in a study by Caffrey (2000), they reported 11 cases of lactic acidosis in patients taking antiretroviral medication where D4T was common to all cases. Manosuthi *et al*., (2008) in their study, reported that, D4T was the most frequent etiologic drug of symptomatic hyperlactataemia. Manosuthi *et al*. (2008) further concluded that, the contribution of other NRTIs to the development of hyperlactataemia was relatively difficult to evaluate because the majority of patients received D4T due to the accessibility and affordability of this NRTI in their country.

Similarly, in this report following the standard treatment guidelines as shown in Table 4.1, out of 99 patients that were studied, 94 were treated on a regimen containing D4T. The remaining five were treated on a regimen containing AZT as the NRT of choice.

Although an inferential analysis was not performed in this instance, evidence from this study, consistent with the published literature, points to D4T as the major cause of lactic acidosis (i.e. for periods exceeding 2 years) treated on regimens containing D4T; lactic acidosis was reported 20 times with the use of D4T (Table 4.7).

John (2001) quoted by Dagan *et al.* (2002), further asserts that, increased lactate levels have also been shown to be associated with stavudine-containing combination therapy (vs. zidovudine) measured over an 18-month period in 349 patients. Lactic acidosis was also rarely reported in patients taking zidovudine (Caffrey, 2000). In this study, there was a statistically significant difference (i.e. p-value of 0.007) in the mean durations of treatment between patients who reported lactic acidosis and those who did not. The mean duration of treatment for patients who developed lactic acidosis was in this study 35.45 months.

From this study, one of the cases where lactic acidosis was reported, the female patient reported elevated ALT (112 mmol/L), abdominal cramps and distension, weight loss and the serum lactate ranging between 2.3 and 8.6 mmol/L recorded during the routine monitoring visits. This was a life-threatening event and all the ARVs were stopped. On ART re-challenge, the patient was started on AZT in place of D4T.

According to Bonet *et al.* (2003), and Moyle *et al.*(2002), as quoted by Geddes *et al.* (2006), they reported that the risk factors for developing lactic acidosis included being female, obese, pregnancy and having low CD4 count before starting a regimen containing a NRTI. This was found to be true for this study as 75% of the 20 patients that experienced lactic acidosis were females.

The mean age of 37.19 years did not differ significantly from the mean age of 40.10 years. This implied that, age was not a predictor for the development of lactic acidosis in patients taking ARVs for this study sample. Similarly, the two sample means did no differ significantly for weight and plasma CD4 count. The only result that showed the greatest significance between the two sample means was for the duration of treatment (i.e. *p*-value = 0.007).

Although the study groups of this analysis did not differ significantly with respect to age, weight, and pCD4 count when measured by their p-values (Table 4.11), the baseline characteristics of the group that reported symptoms of lactic acidosis were found to be similar to those that were studied by Manosuthi *et al*., (2008). The mean baseline age, weight, and pCD4 count as reported by Manosuthi *et al*. (2008), were 40 years, 59 kg, and 96cells/mm^3 respectively, whereas the mean baseline age, weight, and pCD4 count as presented in this report (Table 4.10) was found to be 40.1 years, 69.7 kg, and 94.1cells/mm^3 respectively.

5.6.2 Lipodystrophy

According to van Griensven *et al.* (2007), lipodystrophy can present as peripheral fat loss including hollowing of the cheeks, wasting of extremities or flatting of the buttocks (lipoatrophy), or relative/absolute accumulation of central fat in the abdomen, neck or breasts (lipo-hypertrophy).

This syndrome has also been observed in a few studies and has been described as a syndrome presenting as a combination of such morphologic and metabolic changes as hyperlipidemia, fat redistribution, and insulin resistance (Norris & Dreher, 2004:46). Out of 142 events that were reported in this study, lipodystrophy was reported 10 times, representing 7% in total of the events reported. In patients that reported lipodystrophy the following signs and symptoms were co-existing, i.e. thinning of the face and arms, elevated serum lactate, loss of fat on the lower limbs, increased breast size with or without secretions, flat butts and central obesity and abdominal distension.

From the case assessment of these 10 patients (Table 4.12) that experienced lipodystrophy, nine were females and one male. Lipodystrophy occurred more frequently in females as compared to males. A similar finding, although the sample sizes were not the same was observed in a study by Martinez *et al*. (2001). According to Martinez *et al*. (2001), they discovered that, after a median follow-up of 18 months, 85 (17%) of the 494 patients developed some type of lipodystrophy where an increased risk for lipodystrophy was found among women as compared with men.

From the analysis of this report, cases of lipodystrophy occurred more frequently in the female group as compared to males. This finding is further supported by a study conducted by Bonfanti *et al*. (2003), where the lipodystrophy syndrome was detected in about 25% of the patients and the multivariate analysis showed that the risk of lipodystrophy was correlated with female sex, older age, homosexuality, overt disease and with the duration of treatment before entering this study. Among patients receiving concomitant antiretroviral therapy the risk of lipodystrophy was greater with stavudine.

However, in this analysis, it has been found that the risk factor for the development of lipodystrophy was the low mean body weight of 56.10 kg. There was a statistically significant difference ($p = 0.009$) in the mean weight between the group that reported lipodystrophy and the one that did not.

However this report wishes to acknowledge that, anthropometric indices were found to be insufficient as a diagnostic tool for lipodystrophy. Upon diagnosis, body fat changes were not associated with technical investigations, e.g. screening for serum glucose, cholesterol and triglycerides. Body mass indices were also not computed at baseline and monitored throughout therapy. Although significant research has been done in the bodily morphologic changes, there are no conclusive causes of lipodystrophy (Norris & Dreher, 2004).

5.6.3 Pancreatitis

Acute pancreatitis is a common cause of morbidity in patients with HIV (Bush and Kosmiski, 2003). Moreover, the spectrum of potential risk factors for pancreotoxicity is expected to significantly change over time, especially after the introduction of combined antiretroviral therapy (Manfredi *et al*., 2004). Hypertriglyceridemia is a well-established cause of acute pancreatitis in the general population (Bush and Kosmiski, 2003).

Specific medications associated with the use of HAART cited by Bush and Kosmiski (2003) as the cause of acute pancreatitis included DDI, D4T, 3TC and DDC. As cited to be one of the causes of pancreatitis in the study by Bush and Kosmiski (2003), it

has been observed in this analysis that D4T was the most suspected cause of pancreatitis out of eight cases that were reported as shown in Table 4.8.

Bush and Kosmiski (2003) discovered that retrospective studies have suggested that acute pancreatitis occurred 35 to 800 times more frequently in HIV-infected patients than in the general uninfected population. In this analysis, the incidence of pancreatitis was reported eight times (i.e. 5% times reported as compared to other events, Table 4.7). From Table 4.14, it has been observed that pancreatitis occurred more frequently in the female (75%) patients than males (25%).

Patients that reported pancreatitis presented with symptoms of abdominal pains, nausea and vomiting. This is worrying as Reisler *et al.* (2005) reported that acute pancreatitis is a potentially life-threatening condition characterised biochemically by elevations of lipase and/or amylase.

Manfredi *et al*. (2004), in their study when comparing 334 patients who experienced at least one episode of confirmed serum pancreatic abnormality with 586 control subjects who did not, found that the only variables which showed a significant relationship with the development of occasional pancreatic disturbances were the overall duration of known HIV seropositivity, prior or concurrent diagnosis of full blown AIDS, more severe immunodeficiency as expressed by a greater frequency of a CD4+ lymphocyte count <200 cells/mm^3 and the duration of protease inhibitor-based HAART.

The mean CD4 count of the patients that reported pancreatitis in this report was 121cells/mm^3 as shown on table 4.14. Although the mean CD4 cell count was below 200 cells/mm^3, the t-Test statistic result for the two sample means of patients that reported pancreatitis and those that did not, did not differ significantly with respect to pCD4 count as measured by their p-value of 0.321 (Table 4.15).

However, in the very same analysis by Manfredi *et al*. (2004), no significant correlation was shown with all considered demographic and epidemiological parameters (age, gender, type of risk for HIV infection), the percentage of patients

treated with antiretroviral drugs, and the comprehensive duration of nucleoside analogue administration.

In comparison to the analysis by Manfredi *et al*. (2004), this study suggests that there has not been a statistically significant relation between the study groups that presented with pancreatitis and those that did not in terms of age, weight, and pCD4 count. This reaffirms the finding by Manfredi *et al*. (2004). However, in contrast to Manfredi *et al*. (2004), the longer the patients were exposed to ART, the more likely they were to develop pancreatitis.

The two groups differed significantly for the mean duration of treatment with the p-value of 0.048 (Table 4.15). The mean duration of treatment reported for the development of pancreatitis was 36.75 months on ART. This finding suggest that, the duration of treatment is the predictor for pancreatitis which warrants closer monitoring of patients who have taken ART for periods equal to or exceeding 36.75 months. Manfredi *et al*. (2004) found that patients with at least one episode of serum pancreatic enzyme abnormality had 26.2 months of comprehensive duration of antiretroviral therapy including a nucleoside analogue as compared to 24.5 months for patients who never experienced serum pancreatic enzyme abnormality.

The finding by Manfredi *et al*. (2004) supports the finding of this report where the mean duration of treatment for patients who reported symptoms of pancreatitis was found to be 36.75 months and those that did not was 29.93 months (Table 4.15). This was the only significant relationship discovered for pancreatitis. A further assertion to this finding has been reported by Bush and Kosmiski (2003), where they discovered that cases of acute pancreatitis specifically attributed to antiretroviral agents were not significantly different between the groups.

Bush and Kosmiski (2003) reported that the mean age was not statistically different between the groups, but median CD4 cell count was significantly higher in the patients presenting with pancreatitis. In this analysis, there were no significant differences between the group that reported symptoms of pancreatitis and those that did not, with respect to gender, age, weight, and pCD4 cell counts as measured by the computed p-values shown in Table 4.15.

Only three patients from those that reported symptoms associated with pancreatitis (eight), had elevated serum amylase levels (i.e. 181, 197 and 250mmol/L) above reference levels upon assay results. In a report from a study by Manfredi *et al*. (2004), 128 patients out of 334 (38% of subjects with at least one episode of pancreatic laboratory abnormality), experienced at least three-fold increase of serum pancreatic enzymes persisting for six months or more. The mean amylase reported in this study was 154 mmol/L and the minimum and maximum amylase levels recorded were 99mmol/L and 250mmol/L respectively.

The normal laboratory value for serum amylase in adults is 30 to 150mmol/L. However there was greater variability in the frequency distribution of the reported amylase levels as measured by their standard deviation of 51%. Serum amylase is expected to rise above normal in episodes of pancreatitis. This is an important indicator for the diagnosis and monitoring of ART induced pancreatitis. Patients treated for longer periods on ART should be identified as potential risk category for the development of pancreatitis.

The clinical presentation of NRTI-associated pancreatitis is similar to a mitochondrial inherited genetic disorder 'Pearson's syndrome' that suggests that mitochondria may be part of the aetiology (Dagan *et al.,* 2002:397). In only 53% of causes of acute pancreatitis was serum triglyceride levels analysed as part of the evaluation of acute pancreatitis (Bush and Kosmiski, 2003). In this report, serum triglycerides levels were not measured for patients that reported pancreatitis. However, all patients were treated on an NRTI based regimen, with D4T identified as the likely offending agent.

The retrospective design of this study and the relatively small number of index cases (i.e. small sample size) of acute pancreatitis had a bearing on the accurate analysis of the reported cases of pancreatitis. In addition, the determination of causal factors in each case was dependent on the quality of documentation and triglyceride levels were not checked in most if not all of the reported cases of pancreatitis. Medication re-challenge was not used in the cases of pancreatitis deemed to be secondary to medications.

The ability to compare different pancreatitis rates by ARV treatment combinations was limited to some extent by the sample size, duration of follow up, the retrospective nature of the study. Because of the retrospective nature of the study, patient data from the files were not collected in a uniform and systematic fashion by the examining physicians, hence the need for a more comprehensive and standardised pharmacovigilance approach.

Although acute pancreatitis is a common reason for emergency hospital admissions, there is a paucity of information about the disease in a South African context and to what extent disease severity and outcomes compare with published literature (Anderson *et al*., 2008).

5.6.4 Neurological disorders

The neurological disorders that were commonly reported (33%) by patients included insomnia (1%), dizziness (3%), headache (3%), paraesthesia (7%) and peripheral neuropathy (18%), and as shown in Table 4.7.

Apart from it being likely to be caused by chronic ingestion of ARVs, sensory neuropathy (SN) has been recognised as one of the commonest neurological complications of HIV infection since early 1980s (Cherry *et al.,* 2003). Distal symmetrical peripheral neuropathy is a common adverse experience in persons with HIV infection. This condition, which presents as a pain, numbness, burning and/or dysaethesia initially in the feet, is often multi-factorial in its origin Moyle and Sadler (1998).

Effective viral suppression and prevention of disease progression might prevent the development of neurological disorders, or even allow regression of existing cases of sensory neuropathy. The study by Cherry *et al.* (2003) appeared to confirm previous findings of an increased risk of sensory neuropathy with lower CD4 cell counts and higher viral loads, as well as increasing age or a prior diagnosis of AIDS. Out of 27 cases of peripheral neuropathy reported in our study, 33.33% were males, and 66.67% were females.

The mean CD4 count of the sample was 91cell/mm^3 and the mean viral load was 308 829. This CD4 count is 55% less than the recommended level of CD4 count for consideration of initiation of ART. From the study by Browne *et al.* 1993, quoted by Cherry *et al.* (2003), sensory neuropathy was the dose limiting toxicity of D4T and that the incidence of sensory neuropathy (SN) related to both the dose and duration of D4T.

High doses of D4T were associated with SN in more than 70% of study participants (Cherry *et al.,* 2003). From a count of 27 peripheral neuropathy events reported in this study, 24 events were from patients taking a regimen containing D4T, two on ARV combinations and one on AZT-containing regimen. Moyle and Sadler (1998) reported that nucleoside analogue reverse transcriptase inhibitors represent an important contributor to peripheral neuropathy.

From the 27 events of peripheral neuropathy reported in this report, 19 of the patients were changed from D4T to AZT and seven continued treatment. Ten percent of patients receiving stavudine or zalcitabine and 1 to 2% of didanosine recipients had to discontinue therapy with these agents due to neuropathy as reported by Moyle and Sadler (1998). Most of the symptoms had improved after D4T was changed to AZT. This is an indication that D4T was the problematic agent in the ART combination. The same result has been observed in the study by Moyle and Sadler (1998), where prompt withdrawal of these therapies enabled gradual resolution of signs and symptoms in most patients, although a period of symptom intensification may occur shortly after withdrawal.

A comparison between the proportion of patients who reported peripheral neuropathy and those that did not report symptoms of peripheral neuropathy with respect to different dosages of D4T (i.e. 30mg and 40mg) was performed. The results of the comparison based on the Chi-square test (Table 4.17), shows that there were no significant differences (i.e. p-Value = 0.553) between the two proportions. Patients developed neuropathy irrespective of the D4T dosage.

The dosage of D4T appeared not to be the predictor for the development of peripheral neuropathy in this study sample. However, a systematic review by WHO

(2006) of nine randomized trials and six observational cohort studies strongly suggests that stavudine-containing regimens maintain clinical and virologic efficacy when stavudine is dosed at 30 mg twice daily, and that this reduced dose is associated with lower rates of toxicity, especially peripheral neuropathy, compared to the 40 mg twice-daily dose.

The two groups were also compared with respect to gender, age, weight, pCD4 count and duration of ART. The computed t-Test statistic (Table 4.16) indicated that there were no significant differences between the two proportions with respect to gender, age, weight, and pCD4 cell count. However the two groups differed significantly for the duration of ART (p-Value = 0.041). The neuropathy is dose and exposure-time related and generally improves with discontinuation of the precipitating drug (Dagan *et al*., 2002). Although dose could not be established as a predictor of neuropathy in this analysis, the duration ART has been found to be the predictor.

Amongst the risk factors for developing peripheral neuropathy during nucleoside analogue therapy that were reported by Moyle and Sadler (1998) included low CD4+ cell count (<100 cells/mm^3). There were no significant differences in the two groups that reported peripheral neuropathy and those that did not with respect to CD4 count in this analysis, however the group that reported peripheral neuropathy had mean baseline CD4 count less than 100 cells/mm^3 (i.e. 91.37 cells/mm^3 as shown in Table 4.16), which is consistent with the findings of Moyle and Sadler (1998).

In this analysis, the correlation between the two groups with respect to duration indicates that the longer the patients were exposed to ART the greater the chances that they would develop peripheral neuropathy. Cherry *at al*. (2003), reported that the incidences of SN were related to both the dose and duration of D4T used. Sensory neuropathy was observed after a mean duration of 33.63 months with the use of D4T-containg regimen (Table 4.16).

Table 4.9 shows the action taken for most of the reported adverse effects and changing D4T to AZT (46%) accounted for the most of the actions taken. Out of the 27 cases of SN, 19 were changed from D4T to AZT and only five patients were advised to continue with treatment and be monitored. After changing from D4T to

AZT, a remission of symptoms was observed. Removal of D4T mitigated the symptoms.

By the time of the study it was already known that the dosage of D4T was central to the development of peripheral neuropathy, therefore fewer patients were put on D4T 40mg. In this analysis, the sample representation for D4T 40mg tended to be smaller as compared to that of D4T 30mg. However, an interesting finding in this analysis was that there were no significant differences between the two groups and that the duration of treatment was the main predictor for the prognosis of peripheral neuropathy during the course of chronic ART.

The duration of treatment, seemed to be the predictor for the development of peripheral neuropathy. Patients treated longer on ART (i.e. mean duration = 33.63 months) are more likely to present peripheral neuropathy. The minimum and maximum weight for patients who experienced peripheral neuropathy was 36 and 86 kg respectively and that of those who did not experience peripheral neuropathy was 32 to 139 kg respectively. Thus, patients at increased risk of peripheral neuropathy should potentially avoid the use of the neurotoxic nucleoside analogues or be more carefully monitored during therapy Moyle and Sadler (1998).

5.6.5 Rash

Consistent with the study by Caffrey (2000), NNRTIs rash was found to be the common adverse event. From a study by Carr and Cooper as quoted by Carr (2000), they made mention that ART hypersensisitivity, typically manifest as an erythematous, maculopapular, pruritic, and confluent rash with or without fever. The rash is most prominent on the body and arms and usually begins after 1-3 weeks of therapy (Carr 2000).

In this research, out of 13 patients that experienced rash during ART, 12(92%) were treated with nevirapine containing regimen and 1 (8%) efavirenz containing regimen. The mean duration of treatment when the rash incidences were reported was 10 weeks. Rash was graded into three grades as moderate to severe.

Severe cases presented as a red maculopapular rash and was generalised. In these cases, nevirapine was changed to efavirenz. Only one incident was reported with rash on the face, lips, eyes, and whole body with slight swelling of the lips. This patient therapy was changed from nevirapine to efavirenz.

From the study by Carr (2000), the rates of rash development for patients on different ART components were found to be as follows, nevirapine=17%, delavirdine=18%, efavirenz=10%, abacavir=3% and amprenavir=20%. From our analysis of the occurrence of rash with ART, NVP appeared the likely cause of rash, accounting for 92% of the reported cases compared to 8% by EFV.

The mean duration of treatment for the development of rash with the suspected use of NNRTIs was found to be 10.4 weeks. In this study, the mean duration (10.4 weeks) of treatment for the development of rash with ART is not consistent with that mostly published in the literature. However, evidence points to the NNRTIs as the likely causative agent. Most cases resolved spontaneously despite continuation of therapy.

Van Leth *et al.* (2005), in their study, found a relationship between baseline CD4 cell count and the incidence of rash, but further cautioned that subgroup analyses for adverse events should be interpreted with caution.

The preceding study by van Leth *et al.* (2005), was inconclusive as to whether the baseline CD4 count could be used as an assessment for the predictor of the development of rash prior to ART initiation. Even though the causes could be known, currently there is no demographic, metabolic, or immunological factor, including history of hypersensitivity, which predicts the development of antiretroviral hypersensitivity (Carr 2000).

5.6.6 Hepatitis

Of the adverse events that were reported, elevation in serum liver enzymes was reported 10 times. ALT was recorded for patients taking ART. Studies by Sulkowski *et al.* (2002) revealed that in approximately 6% to 30% of treated patients,

antiretroviral therapy was associated with significant increases in serum liver enzymes. In some studies, ALT elevations were observed with co-infection with hepatitis viruses.

Sulkowski *et al.* (2002) also reported this in their study, where 30% and 10% of HIV-infected persons were co-infected with hepatitis C virus (HCV) and hepatitis B virus (HBV) respectively. In our study, ALT was computed for different stages of ART and for different doses of EFV and NVP. From this analysis, the highest ALT levels recorded during ART were 66.8 and 52.9 mmol/L for EFV 600mg and NVP 200mg respectively during the period of 3 to 6 months on ART.

The normal reference ranges for the serum ALT is 5-40mmol/L for both males and females (Table 4.18). Subsequent to the period of 3 to 6 months, the ALT levels stabilised between 30 and 40mmol/L on continuation of treatment. For most of these episodes, the initial elevation of the ALT levels was asymptomatic; hence, there were no treatment interruptions for all the cases.

In a study by Sulkowski *et al.* (2002), they observed severe hepatotoxicity in 15% of patients prescribed NVP and 8.0% of those prescribed EFV. In contrast, this study, reported 32% of NVP and 50% of EFV-associated episodes of hepatitis during the first 12 weeks of therapy.

However, from the studies by Verdom *et al.* (2001), Peytavin *et al.* (2001), and Reisler *et al.* (2001), as quoted by Sulkowski *et al.* (2002), it has been acknowledged that, although reported, little published information is available regarding the risk of hepatotoxicity among patients receiving EFV.

Patients treated with EFV containing regimen were more i.e. represented 65% of the study population as compared to those treated with NVP containing regimen (i.e. represented 35% of the study population). This could be a reason why more episodes of elevated serum ALT were observed for EFV compared to NVP.

Although the chances (i.e. P (D4T 30 and Yes) = 0.32) of developing peripheral neuropathy tended to be high for patients taking D4T 30mg as compared to the

chances of developing peripheral neuropathy with D4T 40mg (i.e. P (D4T 40 and Yes) = 0.19), there were no statistically significant differences (*p*-Value = 0.553) between the two proportions as computed by the Chi-square test.

CHAPTER 6

6. LIMITATIONS

There were several limitations identified in this study that affected the analysis of the events associated lipodystrophy, pancreatitis and peripheral neuropathy. The first limitation associated with this study was that, on diagnosis, body fat changes were not associated with technical investigation (e.g. screening for serum glucose, cholesterol and triglycerides). Body mass indices were also not computed at baseline and monitored throughout therapy. Therefore, the quality or accuracy of the diagnosis of reported incidences of lipodystrophy could not be verified and qualified by technical investigation, since the study relied mostly on the recorded patient information.

The second limitation of this study included was its retrospective design and the relatively small number of index cases of acute pancreatitis. In addition, the determination of causal factors in each case was dependent on the quality of documentation and triglyceride levels were not checked in most if not all of the reported cases of pancreatitis. Medication re-challenge was not used in the cases of pancreatitis deemed to be secondary to medications.

Thirdly, the sample representation for D4T 40mg tended to be smaller as compared to that of D4T 30mg. The reason was that by the time of the study, it was already known that the dosage of D4T was central to the development of peripheral neuropathy, therefore fewer patients were put on D4T 40mg and many of them were initiated or changed to D4T 30mg. However, an interesting finding in this analysis was that, there were no significant differences between the two groups and that the duration of treatment was the main predictor for the prognosis of peripheral neuropathy during the course of chronic ART.

Information bias is possible as case data for some reported adverse effects were collected retrospectively from hand-written patient records. From the prospective point of view, data that was collected retrospectively on patients who were enrolled was confirmed as patients were followed through.

CHAPTER 7

7. RECOMMENDATIONS

Although there is a cost to routine laboratory monitoring of ART, lactate levels should be used routinely as a measure for the optimal monitoring and management of NRTI toxicity on a regular basis, as opposed to current practice where lactate levels are only measured in those patients presenting with suggestive or pointing clinical symptoms of lactic acidosis.

Any unusual elevation during the monitoring should be considered as a clinical indicator for possible poor prognosis in the management of HIV or ART complication, and this should warrant review of the treatment regime. ADR reporting systems should be standardized as normal practice and as a way of improving the management of ART adverse events at all levels of care. Prevention, detection, and management of ADR should happen at the primary health care level.

The knowledge embedded in this report, could be used as a bases of guiding future practice in managing patients on ART. In this era of a highly resource strained circumstances due to HIV/AIDS burden, further analysis of the opportunity costs of treating ART ADRs, could be explored, to assess our cost saving versus cost benefits.

More clinical pharmacists employed in the primary health care settings will add value to money in the care and management of HIV/AIDS with ART. There is a need for specialized pharmaceutical care skills to complement the current health care team in the primary health care system.

There is a need to revise the current HIV/AIDS guidelines concerning suitable treatment combinations, especially the use of NRTIs, which are individualized to meet specific patient categories. From this analysis, D4T has been suspected to be consistently the NRTI mostly associated with lactic acidosis, lipoatrophy, and peripheral neuropathy. These toxicities have proven to be cumulative and often irreversible, and have the potential to affect adherence in the long term.

The South African programmes which are mostly resource strained, are dependent on D4T-based regimens. This points to the overhaul of the government strategies on expanding ART to the poor majority, since D4T even in its lower doses has proven to be toxic over a long term (WHO, 2006). D4T containing regimens may remain the most accessible option for people in urgent need of treatment in resource-limited settings, but should be used sparingly and for a medium term.

Most of the patients do not have courage to report unusual events during ART, and resort to report when the condition is debilitating and affecting their ability to perform their routine functions. Most of these events are reported at a late stage, and therefore affects accurate recording of the events. To improve accuracy of the duration of treatment when events occurred after initiation of therapy, can only happen through encouraging spontaneous reporting of events by patients.

A set of requirements for ADR reporting and recording should be established at Primary Health Care (PHC) establishments that provide ART. From the set of requirements, there will be a need to develop a more comprehensive and consolidated ART reporting and recording system (e.g. Appendix B). To sustain and ensure that the system functions sufficiently, more human resource capital has to be developed through training and capacity building.

According to Phillips *et al.,* (2008:1443), the development of cheap and robust assays to measure viral load and CD4 cell count in settings where antiretroviral therapy is an important priority for the HIV research community should be considered

Although the results of this report might not be extrapolated to the bigger population, the general findings are that out of 100 patients that were studied, 61 were on D4T 30mg, 34mg on D4T 40mg and 5 on AZT. This analysis provoked questions as to what is the best baseline CD4 count to initiate HAART in order to avert its side effects during the continuum of care. To rule out pancreatitis in all patients that present with severe gastrointestinal symptoms, serum amylase assay should be performed.

Clinical pharmacist monitoring the adverse events associated with the chronic use of ART should identify patients treated for periods exceeding 33 to 36 months as more

they are more probable of developing lactic acidosis, pancreatitis and peripheral neuropathy. This recommendation follows evidence based on the computed p-values.

This analysis has shown that duration of treatment is a predictor for the development of ART adverse effects.

CHAPTER 8

8. CONCLUSIONS

The main aim of this study was to analyze the adverse events in adult HIV-infected patients receiving antiretroviral therapy for more than six months at a public health treatment site, and to quantify the frequency of adverse events in different patient subgroups. The objectives of this analysis included an establishment of a data base of adverse effects experienced during ART, recording of adverse effects in patients on ART, identifying specific risk patient categories, establishing the rates of adverse events and characterizing and describing the different adverse reactions.

In this chapter, we assess the achievement of this analysis with respect to the stated objectives. The conclusions are based on the findings of the study and on the statistical result presented.

8.1 A data base of adverse effects experienced during ART

From a pharmacovigilance point of view, the general focus of this research has managed to establish a database of adverse effects experienced during ART (Appendix A). Although that was achieved, a challenge remains, to integrate this into our current practice. There is a need for a more consistent and a standardised practice in the recording and analysis of adverse events.

This database will serve as an integral and useful hands-on source of information in making treatment decisions during pharmaceutical care. The data, which was captured for individual patients as shown in Appendix B, could be retrieved and analysed at a later stage when making treatment decisions.

8.2 Recording of adverse effects in patients on ART

All the medicine problems that were reported and recorded for 99 patients on the study were recorded (Appendix A and B). It is important for the health care provider

who is recording the events to understand what should be recorded as an adverse event and what should not be recorded as an adverse event.

This will require a proper causality assessment by the clinician attending the patient. Knowledge of event classification is also required. The process of recording should occur during the continuum of care on a routine basis so that a proper link of the event to the likely offending drug could be established.

8.3 Analysis of CD4 cell count and VL during ART

From the analysis of the results, there are favourable responses observed after taking ART. This was proven by an upward movement in the proportions of CD4 cell counts measured during the chronic ART use by the enrolled HIV-positive patients. Apart from the rising CD4 cell count in general, dropping levels of VL were also observed with the use of ART.

Based on the analysis of the presented data in this report, both subpopulations that reported adverse events associated to HAART use and those that did not report any events are not statistically significantly different from each other with respect to baseline CD4 cell count.

For the studied population, baseline CD4 cell count is not a predictor for the development of adverse effects associated with HAART. However, the subpopulation of patients who reported adverse events in this report had some similarities with those that were reported in the literature (e.g. CD4 cell counts <100 cell/mm^3 in the subgroups that reported peripheral neuropathy and pancreatitis).

Although there were generally observed increases in pCD4 count, the benefits of ART seemed generally minimal for the study sample. This was true for the rates of increase in the proportions of CD4 cell counts (i.e. 58% after three months, 46% after six months, 5% after 12 months, 39% after 24 months, and 11% after more than two years), which were lower than the 50% specified by the World Health Organisation (2006). This could be due in part to low levels of adherence to the HAART, which did not form part of the scope of this study.

8.4 The study of adverse events in patients on ART

The most commonly reported adverse events in this report were neurological disorders (34%), gastrointestinal toxicity (16%), rash (14.8%), lactic acidosis (12%), hepatitis (7%), hyperlipidemia/lipodystrophy (7%), pancreatitis (4%), IRIS (2.8%), anaemia (1.4%), and gynaecomastia (0.7%).

Lactic acidosis is a rare, life-threatening adverse event of the class of antiretroviral known as NRTIs. In this analysis only 14% of the incidences of lactic acidosis were reported.

Based on the analysis of the presented data in this report, age, weight, gender, and pCD4 count are not the predictors for the development of lactic acidosis. However this analysis suggests that, the duration of treatment is the predictor of lactic acidosis in patients chronically treated on HAART. The longer these patients are exposed to HAART, the more likely that they will experience lactic acidosis, especially with the NRTI-based, D4T regimen. From our study population, lactic acidosis occurs more frequently in females (75%) than in males (25%).

Although the most likely predisposing factors to the development of ART ADRs were analysed, the challenge remains as the long-term use of the NRTI-stavudine is associated with most of the adverse events reported. This makes it essential that all attending physicians, health care providers and patients are trained to recognize this condition early, especially when they have been on ART for longer periods. Furthermore, this report supports the current revision of the role of D4T as a preferred companion NRTI in the recently revised and published treatment guidelines.

Although the normal frequency distribution analysis was not performed, different adverse events were seen occurring most frequently across certain different gender categories (e.g. 75% cases of lactic acidosis reported in females and 67% cases of peripheral neuropathy as compared to their male counterparts). Individualisation of therapy at initiation based on the baseline characteristics prior to therapy should be emphasised and encouraged as a best practice.

Pancreatitis has been associated with longer use of ART and for most of the reported cases it was life-threatening. For this study sample, age, gender, pCD4 count and weight are not predictors for the development of pancreatitis. It will also be wise for good clinical practice not to view this problem in isolation to lactic acidosis, since both are metabolic complications of mitochondrial toxicity by HAART. Occurrence of one should instigate investigation of another. This shows the value of pharmacovigilance in the monitoring of ART.

Routine monitoring of these parameters (i.e. CD4 cell count and Viral Load) remains crucial to the assessment of treatment failure and success. Although this could prove a best practice in successful management of patients taking chronic ART, it could be a setback in resource-limited settings, where expansion of the scale of treatment to the population might be a priority.

ADR reporting can assist health care practitioners in better managing ART to avert the complications of chronic use of ART. Amongst many aims of the pharmacovigilance practices, are to detect problems related to the use of medicines, to communicate the findings in a timely manner, and to contribute to the assessment of harm and maximization of benefits of ART.

Spontaneous reporting is limited by human resource capital available in South African health establishments. This translates into lack of adequate staff to handle the numbers and poorly trained or lack of trained staff to record adverse events.

For this study population the mean age, weight, pCD4 count, and gender appeared not to be the predictors for the development of lactic acidosis, pancreatitis and peripheral neuropathy. However long-term treatment with ART tended to be the significant predictor for the development of lactic acidosis, pancreatitis and peripheral neuropathy. It therefore calls for clinicians to monitor closely those patients that are relatively been exposed to ART for longer periods.

The longer the patients are on ART, the more probable that they will experience lactic acidosis, irrespective of their age, weight and pCD4 count. In monitoring for the

development of ART side effects, clinicians should monitor closely for patients who are longer on ART.

These data highlight the urgent need for access to more affordable and less toxic ART regimens in resource-limited settings.

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10. APPENDICES

APPENDIX A: ART ADR DATABASE

Pt No	AGE	WEIGHT	GENDER	pCD4	pVL	ALT	OTHER LABS	ARV 1	ARV 2	ARV 3	MEDICINE PROBLEMS	CAUSALITY	ART started	DATE REPORTED	ART DURATION	ART stopped
1111996	35	62	F	159	630000	17	8	D4T 30	3TC 150	NVP 200	DRY ITCHY RASH 2-4WEEKS 3/5/06 STARTED EFV. PAINFUL FEET FELL PREG STOP EFV	NON	2005/09/06		35.5	2008/08/05
1176343	41	51	M	34	750000	18	8	D4T 30	3TC 150	EFV 600	EPIGASTRITIS (S-LAC=1.58, S-AMY=118) S-AMY ELEV. PANCREATITIS SECONDARY TO REG 1A D4T FOR AZT. HEPATITIS 2/2/06 ALT=60	SECONDARY TO ARVs REG 1A D4T		7/12/06 (PANC) 2/206 (HEP)		
1222254	37	66	M	106	800000	26	15	D4T 40	3TC 150	EFV 600	PAINFUL FEET OCCASIONALLLY (8/8/06) PARASTHESIA REPORTED. REASSESS PN. ?? EPIGASTRIC PAIN,			8/8/06		
1270655	48	60	M	57	1200000	48	11	D4T 30	3TC 150	EFV 600	OCCASIONAL DIARRHOEA 28/9/06. SEB DERMAT 26/10/06. HEPATITIS (ALT=74)24/1/07. PN (PAINFUL FEET 19/6/07 D4T 40 -30)	D4T		24/1/07 PN 19/6/07		
1212486	35	69	F	22	45000	45	12	D4T 30	3TC 150	NVP 200	SE HEADACHE 22/11/05. GI SE-VOMIT17/1/06.HEPATITIS ALT=183 8/07/08.			22/11/05		

1206905	32	69	F	43	11000	22	12	D4T 40	3TC 150	NVP 200	IIMMUNE RECONSNTITUTION INFLAMMATORY SYNDROMERS (-)? PARASTHESIA IRS (-) 11/1/06. GRADE 1 PARASTHESIA. PAINFUL FEET 12/4/06					
1189353	44	61	M	132	79000	43	12	D4T 40	3TC 150	EFV 200	ALT=56 ASYMPTOMATIC. LYPODYSTROPHY SWOP D4T TO AZT					
1198140	30	56	F	61	53000	60	9	D4T 40	3TC 150	NVP 200	ITCHY FACE MILD RASH 27/09/05. BURNING FEET 08/02/06. PN GRADE I.SWOP D4T TO AZT	NVP D4T, D4T				
1275910	31	63	F	121	1010	66	14	D4T 40	3TC 150	NVP 200	NO COMPLAINTS	NIL				
1190382	34	53	M	11	20000	35	10	D4T 30	3TC 150	EFV 600	PRURITIS? PNUSTRISIA AND FEET 16/11/05. PARASTHESIA GRADE I RES NO. SLIGHTLY PAINFUL FEET. PN? PPSENSITIVE 1/3 OF BOTH FEET (PI SURFACE ONLY) PN GRADE II 13/09/06. SWOP D4T TO AZT DUE TO PN			16/11/05		
1295796	25	62	F	103	71000	38	14	D4T 30	3TC 150	NVP 200	PARASTHESIA + PN 13/12/07. SWITCH D4T TO AZT. RASH ON SWITCH EFV TO NVP 30/08/07			13/12/07		

1233951	48	51	M	46	120000	22	13	D4T 30	3TC 150	EFV 600	VIROLOGICAL FAILURE. SWITCH TO REG II AZT-DDI-KAL04/09/07. NO S/E					
1263047	36	57	M	142	21000	25	18	D4T 30	3TC 150	EFV 600	NOCTENAL DIZZINES AFTER TAKING EFV? 11/10/06			11/10/06		
1142931	35	80	F	25	33000	15	13	D4T 40	3TC 150	NVP 200	NONE, VIROLOGICAL FAILURE CHANGED TO REG 2					
1198253	46	67	F	116	25000	37	15	D4T 40	3TC 150	NVP 200	S-LAC=3 25/10/06 ASYMPTOMATIC	NONE				
1305175	56	56	F	205	29000	19	9	D4T 30	3TC 150	EFV 600	MODERATE LIPODYSTROPHY SWOP TO AZT 01/08/08			01/08/08		
1262995	29	60	F	193	170000	21	10	D4T 30	3TC 150	NVP 200	VIROLOGICAL FAILURE SWOP TO REG II KAL+AZT+DDI 06/02/08					
1303718	19	32	M	182	800000	13	10	D4T 30	3TC 150	EFV 600	DIZZINESS+NIGHT DREAMS EFV 600 REDUCED 400 NOCTE VOMITING AFTER EFV REDUCE TO 200. CONCOMITANT EAR PROBLEM. D4T 30 TO 20 LACTATE28/08/07	EFV 600		09/05/07		
1198469	34	55	F	179	1500	12	12	D4T 30	3TC 150	EFV 600	CHRONIC PANCREATITIS AMYLASE=181 07/02/07. IRS 01/11/05 S-AMY=196 ASYMPT MILD PN PAINS & NEEDLE SENSATION. SWOP TO D4T-AZT			07/02/07		

1222231	41	67	M	32	1100000	16	11	D4T 40	3TC 150	EFV 600	IRIS 04/04/06. RESP DISTRESS HYPER S-LAC LAC AC > 5.0 PAINFUL ENLARGEMENT OF BREAST, GYNAECOMASTIA SWOP D4T TO AZT	D4T GYNAECOMASTIA	06/02/06	03/01/07		
1181363	39	65	F	120	11000	40	16	D4T 30	3TC 150	EFV 600	GRADE II SKIN RASH10/10/05. ABD CRAMPS-VOMT S-AMY, S-LAC19/10/05 IRIS			10/10/05		
1311453	45	67	F	161	6800	29	19	D4T 30	3TC 150	EFV 600	NONE	NON				
1115940	39	65	F	324	1600000	25	15	D4T 30	3TC 150	EFV 600	IRIS 18/07/06	ARV's				
1254440	25	69	F	99	310000	47	14	D4T 40	3TC 150	NVP 200	23/10/06 RASH ON FACE AND LIPS EYES AND WHOLE BODY. SIGHT SWELLING OF THE LIPS SWOP NVP FOR EFV. BACTRIM TO DAPSONE	NVP, BACTRIM		23/10/06		
1189400	29	62	F	14	180000	13	14	AZT 300	3TC 150	NVP 200	VIROLOGICAL FAILURE SWOP TO DDI-AZT-KAL					
1176330	35	57	M	174	200000	14	16	D4T 30	3TC 150	EFV 600	GRADE I SKIN RASH 30/11/05, PN GRADE III PN PINS AND NEEDLES			30/11/05		
1321401	36	94	F	123	150000	15	12	D4T 30	3TC 150	EFV 600	EPIGASTRIC PAINS ON EFV SWOP TO NVP. S-LAC 3.1 SWOP TO AZT LOSS OF WEIGHT		25/09/07	20/08/08		

1205470	43	61	F	140	320000	30	9	D4T 40	3TC 150	NVP 200	RASH ON FACE NVP 8/05/07				
1193010	48	61	M	12	82700	37	12	D4T 30	3TC 150	EFV 600	GRADE II RASH ITCHY 01/11/05 NAUSEA AND VOMITING ABD PAINS ASYMPTOMATIC SWOP D4T TO AZT INCREASENIN LACTATE		04/05/05	01/11/05	
1253182	45	60	M	162	10000	28	11	D4T 30	3TC 150	EFV 600	ABD PAINS 24/05/06, PAINFULL FEET, HEADACHES, HIGH AMY 25/07/06 SEE AMYLASE LEVELS- PANCREATITIS. PARASTHESIA 25/07/06. S-LAC. SWOP D4T TO AZT.PN		24/01/06	24/05/06	
1305171	38	58	F	71	420000	27	11	D4T 30	3TC 150	EFV 600	NONE				
1205411	42	59	F	49	2000000	23	12	D4T 30	3TC 150	EFV 600	ABD PAIN 15/05/07, VOMIT S-AMY				
1241844	39	61	F	124	2000000	20	9	D4T 40	3TC 150	EFV 600	BURNING PAINFUL FEET @ NIGHT-PN 21/02/07. PN ++. SWOP D4T TO AZT				

1176334	47	42	F	101	400	25	13	D4T 30	3TC 150	EFV 600	LIPODYSSTROPHY NOTICED ON THE FACE 08/05/08. SWOP D4T TO AZT. 3YRS ON HAART			08/05/08		
1228452	34	51	M	186	18000	29	14	D4T 30	3TC 150	EFV 600	NONE					
1206895	36	57	F	133	700000	20	12	D4T 30	3TC 150	EFV 600	NONE					
157595	51	38	F	64	430000	27	15	D4T 30	3TC 150	EFV 400	NONE					
1241787	35	45	F	19	50000	13	8	D4T 30	3TC 150	EFV 600	GRADE I RASH ON FACE 10/04/06. MODERATE ANAEMIA HB=8.2 23/05/06 CHECK HB LEVELS					
1263005	32	68	F	122	34000	136	13	D4T 40	3TC 150	EFV 600	HEADACHE @ NIGHT EFV 24/08/06 PERSISTENT HEADACHE. DRY EYES ON EXPOSURE TO SUNLIGHT 01/03/07. PN O7/04/08 SWOP D4T TO AZT.			07/04/08		
1298263	29	60	F	1	88000	69	10	D4T 30	3TC 150	EFV 600	PN 14/06/07. SWOP D4T TO AZT. SWOP TO REG II VL FAILURE			14/06/07		
1205382	30	64	F	80	130000	44	12	D4T 40	3TC 150	NVP 200	NONE					
1293613	34	50	F	127	790000	8	8	D4T 30	3TC 150	EFV 600	NONE					
1183935	43	72	F	135	170000	14	13	AZT 300	3TC 150	EFV 600	GRADE II PN CHANGE D4T TO AZT 3/05/06			3/05/06		

1263015	44	74	F	49	45000	42	14	D4T 40	3TC 150	EFV 600	INSOMNIA 21/09/06. ADB CRAMPS, LOSS WT S-LAC DONE. PN ON TRYPTANOL 07/02/07 SWOP D4T TO AZT		24/08/06	21/09/06		
1176325	42	93	M	80	2500	18	17	D4T 40	3TC 150	EFV 600	NONE	NONE				
1194425	40	63	F	52	11000	22	11	D4T 30	3TC 150	NVP 200	SEB DERMATITIS 26/07/06. S-LAC HIGH SWOP TO AZT. ASYMPTOMATIC 3/01/08. LIPODYSTROPHY 24/04/08		25/08/05	26/07/06 AND 24/04/08		
1233895	43	59	M	19	39000	36	14	D4T 30	3TC 150	EFV 600	DIZZINESS ON EFV 3/3/06. SELF LIMITING	EFV		3/3/06		
1170714	40	56	M	123	750000	32	14	D4T 30	3TC 150	EFV 600	CONFUSION DIZZINESS 27/07/05 SELF LIMITING			27/07/05		
1250424	38	58	M	180	4000	113	16	D4T 30	3TC 150	EFV 600	BURNING FEET 02/05/06 PN GRADE II. ALT 113 17/10/06. RAISED LACTATE NAUSEA, ABD PAIN. RAISED LIVER ENZYMES		31/01/04	02/05/06		
1275854	42	79	F	180	27000	46	9	D4T 40	3TC 150	EFV 600	ELEVATED ALT 112 20/11/06. ABD CRAMPS WT LOSS RAISED LACT 11/10/07 8.6 STOP ARVs. ABD DISTENSION. SWOP TO AZT		23/10/06	20/11/06		
1148244	39	139	F	76	24000	44	15	D4T 40	3TC 150	EFV 600	ELEVATED AMYLASE AND LAC 27/01/06. HYPERLACTATAEMIA STOP ARVs 07/07/06		01/11/05	27/01/06		

125924	45	74	M	104	710	27	14	D4T 40	3TC 150	EFV 600	PARASTHESIA ON FEET 21/12/05. BURNING FEET & PAIN GRADE II PN SWOP TO AZT			21/12/05		
1205374	46	67	F	162	370000	21	12	D4T 40	3TC 150	EFV 600	NONE					
1198480	33	65	F	192	10000	21	14	D4T 40	3TC 150	EFV 600	20/06/06 ABD CRAMPS, NAUSEA INCREASED S-LAC 2.73 ASYMPTOMATIC. LIPODYS-LOSS OF FAT BUTS INCR FAT ON BRST 22/02/07 INCRS BRST SIZE SWOP D4T TO AZT	D4T	03/10/05	20/06/06 & 22/02/07		
1263060	43	98	M	8	40000	134	16	D4T 40	3TC 150	EFV 600	ABD PAINS. INCRS ALT 198 ESP GGT 16/08/06. ALCOL? HEPATITIS ELEVATED LIVER ENZYMES LFTs DONE	ARVs		16/08/06		
1346172	38	71	F	171	51000	22	14	D4T 30	3TC 150	EFV 600	NONE	NONE				
1195273	26	56	F	14	270000	28	8	D4T 30	3TC 150	NVP 200	MILD HYPERSENSITIVITY-RASH ON FACE & ABD 10/01/06 MACULOPAPULAR ITCHY. GRADE II RASH. LYPODYS SYNDR(THIN FACE & ARMS) 19/12/07 SWOP TO AZT	NVP OR BACTRM AND D4T		10/01/06 AND 19/12/07		

1221150	29	58	F	129	280000	18	11	D4T 30	3TC 150	NVP 200	ITCHY SKIN (PRURITIS)- 11/01/06 MILD. PARASTHESIA GRADE II 22/09/06. BURNING FEET AT NIGHT. D4T TO AZT. FEET RESOLVING	NVP & D4T		11/01/06 & 22/09/06		
1206305	31	53	F	178	46000	23	13	D4T 30	3TC 150	NVP 200	GRADE III ALT 15/12/05. LYPODYS(FLAT BUTT & CENTRAL OBESITY) 10/01/08			10/01/08		
1181624	39	63	M	7	48000	43	10	D4T 30	3TC 150	EFV 600	NONE	NONE				
1215895	29	53	F	95	540000	284	15	D4T 40	3TC 150	EFV 600	LOSS OF WEIGHT WITH INCRS S-LAC 17/04/07. SWOP TO AZT. PN ++ & INCRS S-LAC. ADD TRYPTANOL. ANAEMIA 2 SECONDARY TO AZT NEED FOR BLOOD TRANSAFUSION HB=5.6 INCRS S-LAC,PN, ANEMIA	D4T-AZT	23/02/06	17/04/07 TO 21/08/07		
1325384	35	79	F	147	30000	17	12	D4T 30	3TC 150	NVP 200	CLINICALLY STABLE	NONE				
1206895	36	57	F	151	700000	20	12	D4T 30	3TC 150	NVP 200	CLINICALLY WELL	NONE				
1233936	39	57	F	17	250000	27	13	D4T 30	3TC 150	NVP 200	NO COMPLAINTS. VIROLOGICAL FAILURE. VOMITING, LOSS OF WT INCRS S-LAC 5.2 ASYMPTOMATIC VOMITING 14/08/08	D4T TO DDI	13/03/06	14/08/08		
1238726	44	61	M	17	390000	47	10	D4T	3TC	EFV	CINICALLY STABLE	NONE				

								30	150	600						
1215926	33	53	F	144	1200000	26	12	D4T 30	3TC 150	NVP 200	NO PROBLEMS REPORTED	NONE				
1211166	30	64	F	95	25000	18	13	D4T 30	3TC 150	EFV 600	GRADE II RASH ON FACE 07/03/06 INCRS S-LAC ASYMPTOMATIC 11/12/06 S-Lac=5. ABD PAINS VOMIT RESP SYMPTMS SWOP TO AZT		13/12/05	11/12/06		
1146537	38	84	F	85	19000	33	10	D4T 40	3TC 150	NVO 200	BURNING FEET. GRADE II PN OVER FEET 22/11/05. PARASTHESIA GRADE I. S-LAC INCRSD 8.1 NAUSEA & VOMIT. STOP ARVs. SWOP TO AZT	D4T	17/11/05	02/01/07		
1122216	40	58	F	32	320000	20	9	D4T 30	3TC 150	NVP 200	GRADE II RASH ON FACE 20/02/06 PN GRADE II 05/04/06	NVP AND D4T		20/02/06		
1272925	29	104	F	174	15000	21	11	D4T 40	3TC 150	NVP 200	PATIENT STABLE. NO PROBLEMS REPORTED	NIL				
1253534	33	41	F	61	120000	29	11	D4T 30	3TC 150	NVO 200	NO PROBLEMS WERE REPORTED. CLINICALLY STABLE	NIL				
1233943	30	56	F	5	71000	38	10	D4T 30	3TC 150	NVP 200	MAC/PAP RASH ON FACE 20/03/06. ELEVATED ALT 108 GRADE I. ASYMP NO CMPLTS	NVP		20/03/06		

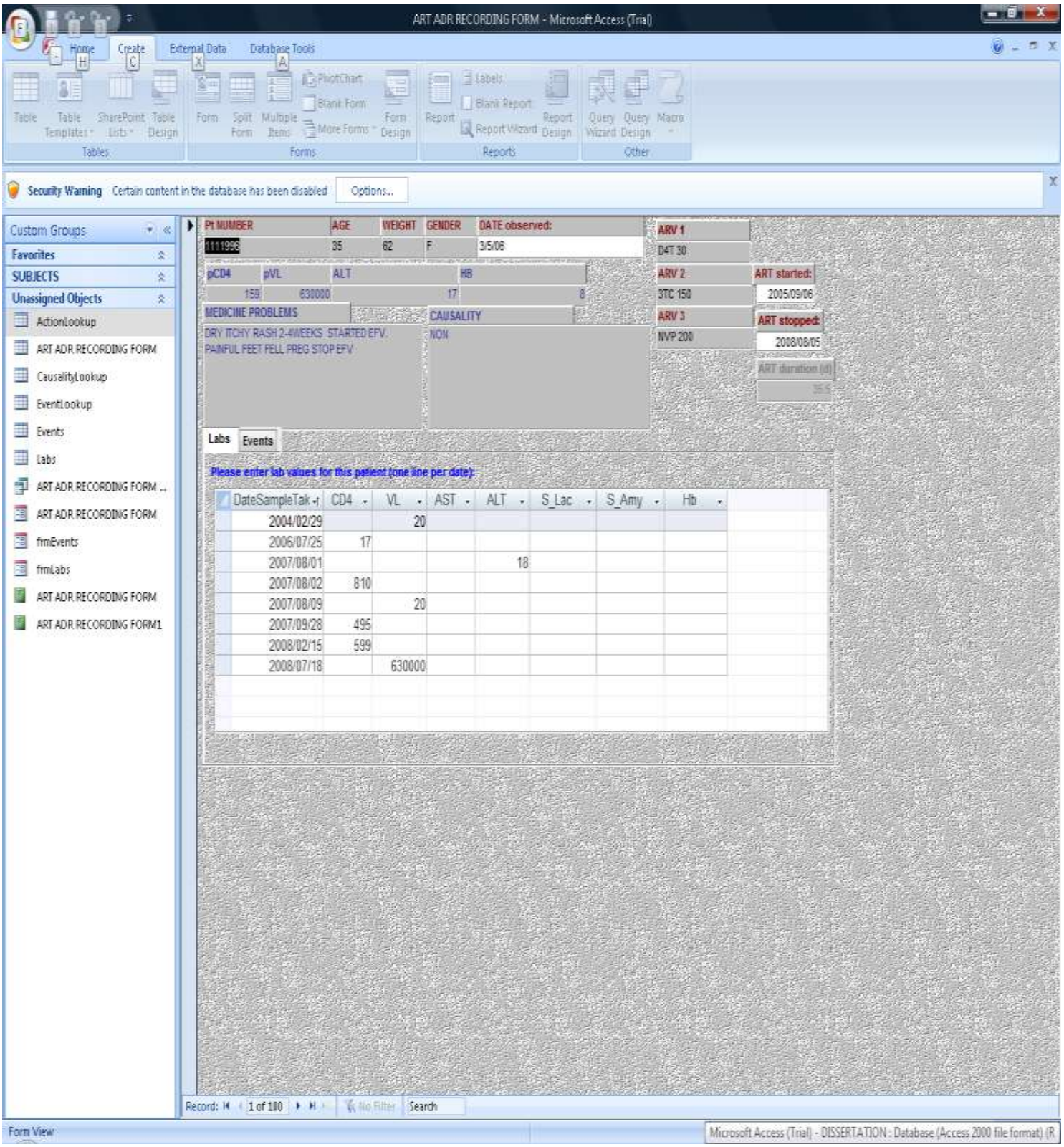
1282173	45	74	M	72	920000	40	5	D4T 40	3TC 150	EFV 600	PN REPORTED 28/08/08. SWOP D4T TO AZT. RAISED LFTs	D4T		28/08/08		
1360484	40	100	F	152	16000	61	12	D4T 30	3TC 150	EFV 600	NONE. CLINICALLY WELL	NIL				
1259931	28	59	F	156	190000	16	9	D4T 40	3TC 150	EFV 600	NONE. CLINICALLY WELL	NIL				
1263046	41	86	F	57	180000	61	9	D4T 30	3TC 150	NVP 200	PN++15/03/07. SWOP TO AZT.	D4T		15/03/07		
1199459	40	58	M	112	59000	52	11	D4T 30	3TC 150	EFV 600	NONE	NIL				
1179699	34	69	F	80	21700	11	16	D4T 40	3TC 150	NVP 200	INCRSD ALT GRADE II 20/12/05. PARASTHESIA 04/10/06. SWOP D4T TO AZT. ASYMPTOMATIC HYPERLACTATAEMIA 16/01/06		28/06/05	16/01/06		
1253168	38	60	F	182	39000	13	14	D4T 40	3TC 150	EFV 600	DIZZINESS, ABD DISTENSION ASYMPT S-LAC 14/05/07 SWOP D4T TO AZT. LIPODYS 08/08/08		14/06/06	14/05/07		
1206258	34	81	F	78	280000	18	12	D4T 30	3TC 150	NVP 200	NONE	NIL				
1207518	50	61	M	42	1600000	25	16	D4T 30	3TC 150	EFV 600	PARASTHESIA OF FEET 16/11/06 SWOP D4T AZT					
925622	61	63	F	189	340000	16	13	AZT 300	3TC 150	EFV 600	NONE. C'LINICALLY WELL	NIL				
1314484	50	45	F	90	320000	26	8	D4T 30	3TC 150	NVP 200	RASH ON FACE 18/09/07	NVP		18/09/07		

1275855	22	46	F	57	380000	31	8	AZT 300	3TC 150	EFV 600	NONE. NO COMPLAINTS REPORTED	NIL				
1213205	51	60	F	112	30000	47	11	D4T 30	3TC 150	EFV 600	10/01/06 M/P RASH ON THE FACE MILD. ABNORMAL LIPID PROFILE 21/11/06. VOM, ABD PAINS, S-LAC=4.5 ASYMPTOMATIC SWOP D4T TO AZT LOS WEIT. MONITOR LAC. DYSLIP. INCRSD CHOLES & TRIGLY. DIARRHOEA & VOMIT	NVP	11/11/05	10/01/06 & 21/11/06		
1122852	38	62	F	150	15000	24	13	D4T 30	3TC 150	NVP 200	INCRSD BREAST SIZE, LIPODYS 03/09/07	D4T		03/09/07		
1096642	31	60	F	27	220000	15	13	D4T 30	3TC 150	EFV 600	PN GRADE III 04/07/06	D4T		04/07/06		
1275857	33	64	M	29	1100000	30	9	D4T 40	3TC 150	EFV 600	NONE	NIL				
1215891	38	84	M	132	110000	90	16	D4T 40	3TC 150	NVP 200	GRADE II INCRSD ALT 20/03/06					
1206901	42	70	F	102	2400	29	12	D4T 30	3TC 150	EFV 600	HEADACHES 17/01/06	EFV				
1226278	30	61	M	93	44000	114	12	D4T 30	3TC 150	EFV 600	14/02/06 GRADE I INCRS IN ALT=103			14/02/06		

1220238	60	67	F	39	330000	31	14	D4T 40	3TC 150	EFV 600	28/02/06 LACTIC ACIDOSIS. STOP ALL ARVs. MONITOR LACTATE LEVELS	D4T 40	12/12/05	28/02/06		
1323429	33	41	F	14	450000	44	14	D4T 30	3TC 150	NVP 200	NO PROBLEMS REPORTED	NIL				
1270619	38	59	M	48	950000	45	12	AZT 300	3TC 150	EFV 600	CLINICALLY WELL	NIL				
1198515	38	81	M	62	370000	61	18	D4T 40	3TC 150	NVP 200	RAISED S-LAC 07/09/06. MONITOR LAC.ASYMPT.SWOP D4T TO AZT	D4T	18/05/05	07/09/06		
1180795	31	68	F	167	46000	34	13	D4T 40	3TC 150	EFV 600	NO PROBLEMS REPORTED	NIL				
1206907	43	79	F	155	37000	22	13	D4T 40	3TC 150	EFV 600	GRADE II RASH 15/11/05. MAC/PAP RASH GENERALIZD. BURNING FEET 07/02/06 PN SWOP D4T TO AZT	EFV 600		15/11/05		
1224617	37	53	F	106	1100000	26	10	D4T 30	3TC 150	EFV 600	11/04/06 PN BOTH FEET. PARASTHESIA			11/04/06		
1283326	29	54	F	185	110000	15	12	D4T 30	3TC 150	NVP 200	GRADE II RASH GENERALISED 20/11/06. EXTENDING FRM ABD TO ARMS LEGS PAPULAR RASH + VOMIT. VOLUNTARILY STOP ARVs DUE TO S/E	NVP		20/11/06		

1307406	39	36	M	46	29	172	9	D4T 30	3TC 150	EFV 600	PN +++ 18/07/07 SWOP D4T TO AZT. TEGRETOL + TRYPTANOL	D4T		18/07/07		

APPENDIX B: ART ADR RECORDING FORM – Microsoft Access



APPENDIX C: CONSENT FORM

"Drug adverse effects in Human Immunodeficiency Virus-infected patients receiving antiretroviral therapy- a pharmacovigilance approach"

Participation in this research project is voluntary. Only data from subjects who provided consent shall be used for the purpose of the study. The information provided shall be treated with privacy and confidentiality. A participant has the right to withdraw from the project at any stage of the study.

PURPOSE OF THE STUDY

AIM

To study the adverse effects of antiretroviral drugs in HIV-infected patients.

OBJECTIVES

- To establish a data base for recording adverse effects
- To identify and record adverse effects in patients on ART
- To identify specific adverse effect patterns of ARVs
- To identify specific risk patient categories

STATEMENT OF CONSENT-SUBJECT

The purpose of the proposed study was explained to me and read out to me in a language that I understand. I was also given the opportunity to re-think and ask questions regarding the aim and objectives of the study. No pressure was put on me to partake in the proposed study.

I understand that, from withdrawing from the study I will not be disadvantaged in whatsoever way from receiving comprehensive treatment that holds for my condition; neither will it influence the care that I receive from my regular pharmacist.

I know that the Research, Ethics, and Publication Committee of the University of Limpopo (Medunsa Campus) and by the Sedibeng District health authorities have approved the study. I am fully aware that the results of this study will be used for

scientific purposes and may be published. I agree to this, provided my privacy is guaranteed.

I hereby give consent to participate in this study.

……..	…….	.	……
Name of participant	**Date**		**Signature of patient/guardian**

…….	…….	.	……
Place	**Date**		**Witness**

Statement by Researcher

I provided verbal and written information regarding this study to the participant. I agree to answer any future questions concerning this study as best as I am able. I will adhere to the approved protocol.

……	……..	……..	……
Name of Researcher	**Signature**	**Date**	**Place**

APPENDIX D: ETHICS COMMITTEE APPROVAL

UNIVERSITY OF LIMPOPO
Medunsa Campus

MEDUNSA CAMPUS RESEARCH & ETHICS COMMITTEE

CLEARANCE CERTIFICATE

P O Medunsa
Medunsa
0204
SOUTH AFRICA

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

MEETING: 02/2008

PROJECT NUMBER: MCREC/H/18/2008: PG

PROJECT :

Title:	Drug adverse effects in HIV-infected patients receiving antiretroviral therapy – A pharmacovigilence approach
Researcher:	Mr. M.D. Gaula
Supervisor:	Prof. A.G.S. Gous
Co-supervisor:	Ms. M. Leteka
Department:	Pharmacy
School:	Health Care Sciences
Degree:	MSc (Med) (Pharmacy)

DATE CONSIDERED: March 05, 2008

DECISION OF THE COMMITTEE:

MCREC approved the project.

DATE: March 05, 2008

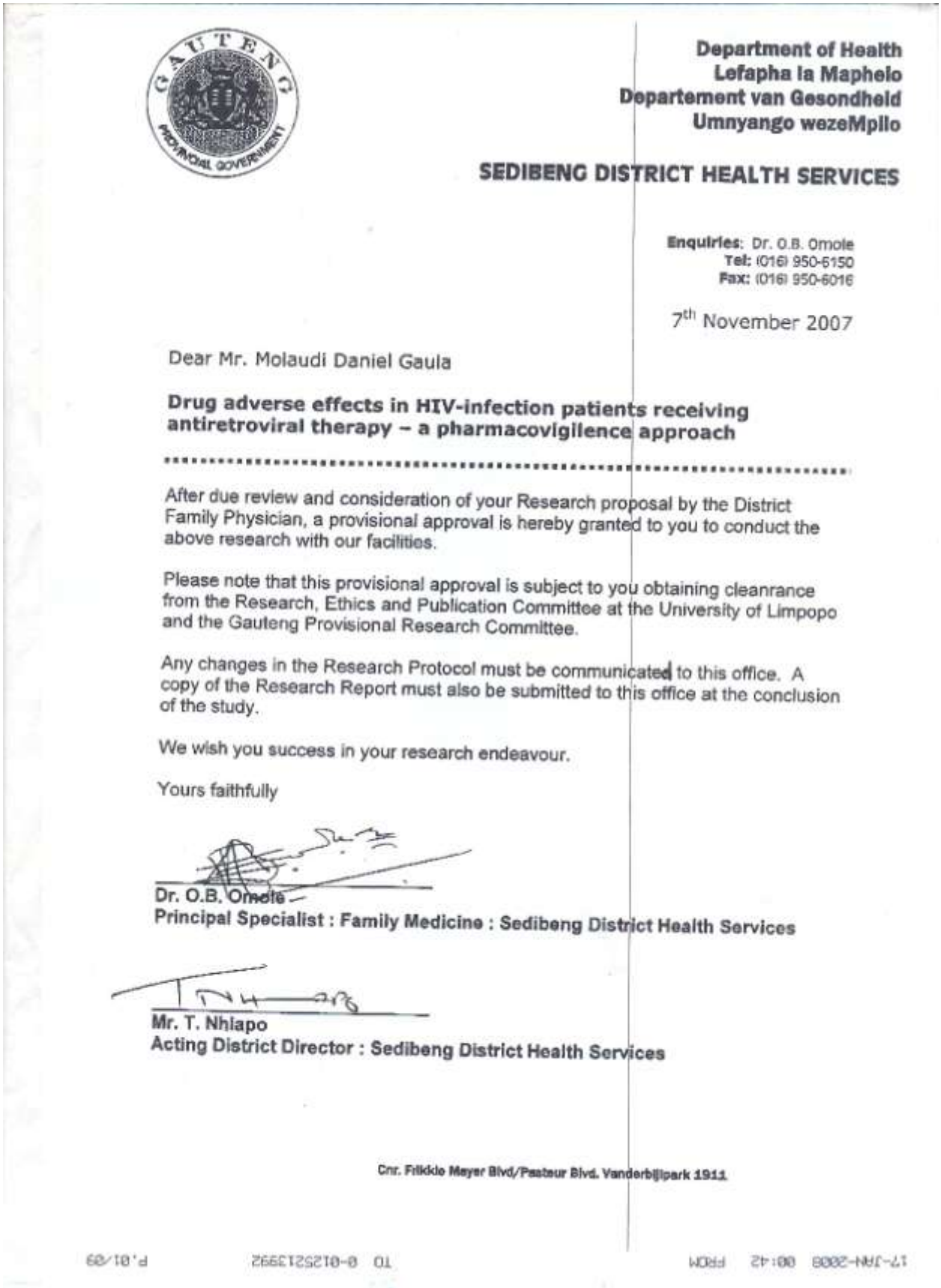
UNIVERSITY OF LIMPOPO
2008 -03- 05
RESEARCH
Medunsa Campus

PROF GA OGUNBANJO
DIRECTOR: RESEARCH & CHAIRPERSON MCREC

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.

African Excellence - Global Leadership

APPENDIX E: SEDIBENG DISTRICT HEALTH SERVICES APPROVAL



Department of Health
Lefapha la Maphelo
Departement van Gesondheid
Umnyango wezeMpilo

SEDIBENG DISTRICT HEALTH SERVICES

Enquiries: Dr. O.B. Omole
Tel: (016) 950-6150
Fax: (016) 950-6016

7th November 2007

Dear Mr. Molaudi Daniel Gaula

Drug adverse effects in HIV-infection patients receiving antiretroviral therapy – a pharmacovigilence approach

After due review and consideration of your Research proposal by the District Family Physician, a provisional approval is hereby granted to you to conduct the above research with our facilities.

Please note that this provisional approval is subject to you obtaining cleanrance from the Research, Ethics and Publication Committee at the University of Limpopo and the Gauteng Provisional Research Committee.

Any changes in the Research Protocol must be communicated to this office. A copy of the Research Report must also be submitted to this office at the conclusion of the study.

We wish you success in your research endeavour.

Yours faithfully

Dr. O.B. Omole
Principal Specialist : Family Medicine : Sedibeng District Health Services

Mr. T. Nhlapo
Acting District Director : Sedibeng District Health Services

Cnr. Frikkie Meyer Blvd/Pasteur Blvd. Vanderbijlpark 1911