Assessment of adverse drug reactions caused by HAART at antiretroviral clinics in the Maseru district, Lesotho

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It all starts here ™

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ABSTRACT

TITLE: Assessment of Adverse Drug Reactions caused by HAART at Antiretroviral Clinics in Maseru District.

KEYWORDS: HIV/AIDS, antiretroviral (ARV) drugs, adverse drug reactions, pharmacovigilance, laboratory monitoring.

Antiretroviral drugs are successful in controlling HIV/AIDS and reducing disease progression. Antiretroviral regimens are stopped in up to 25% of all patients during their initial treatment therapy as a result of adverse drug effects, failing treatment and nonadherence within the initial eight months of treatment (Sharma *et al.*, 2007: 235). A pharmacovigilance surveillance system makes it possible for physicians, pharmacists and other healthcare providers to report suspected ADRs. The purpose of this system is to operate as a guide in identification of new ADRs and predisposing risk factors to known ADRs.

The objective of this study was to assess the prevalence and documentation of adverse drug reactions (ADR) in the private and public antiretroviral clinics in Maseru district, with special reference to zidovudine (AZT) and tenofovir (TDF) - based regimens. The empirical investigation was divided into two phases. The first phase was a cross-sectional quantitative retrospective drug utilisation review study which focused on the occurrence of adverse drug reactions in patients taking zidovudine (AZT) and tenofovir (TDF). The second phase, a survey in a form of questionnaires for the health professionals.

Drug utilisation review: The sample size of patients was 300. Of the 44 patients who experience ADRs, 72.73% (n = 32) were female and 27.27% (n = 12) were male. A greater number of patients who experienced ADRs were females with 43.18% (n = 19) presenting with skin rash, 27.27% (n = 12) with nausea/vomiting, and 2.27% (n = 1) with diarrhoea. In male patients, 2.27% (n = 1) had peripheral neuropathy, 18.18% (n = 8) skin rash, 2.27% (n = 1) Fanconi syndrome, 2.27% (n = 1) nausea/vomiting, and 2.27% (n = 1) diarrhoea. Patients whose ART regimen changed due to ADRs were five. 60% (n = 3) of the patients were females and 40% (n = 2) were males. There was an estimated increase of 0.0025 cell/mm^3, 0.0026 cell/mm^3, 0.0024 cell/mm^3, 0.0025 cell/mm^3, and of 0.0019 cell/mm^3 in CD4 cell count per day according to sex, age group, weight group, initial ART regimen, and ADRs, respectively. An estimated increase of 0.00021 g/dL, 0.00022 g/dL, 0.00018 g/dL, 0.00022 g/dL, and of 0.00020 g/dL in Hb profile per day occurred according to sex, age group, weight

group, initial ART regimen, and ADRs, respectively. There was an estimated increase of 0.000062%, 0.000046%, 0.000068%, 0.000062%, and of 0.00017% in neutrophil count according to sex, age group, weight group, initial ART regimen, and ADRs per day, respectively. There was an estimated increase of 0.000044 IU/L, 0.000043 IU/L, 0.000046 IU/L, and of 0.000028 IU/L in ALT according to sex, age group, weight group, and initial ART regimen per day, respectively. An estimated decrease of 0.000013 IU/L in ALT according to ADRs per day also occurred. There was an estimated decrease of 0.00038 µmol/L, 0.00039 µmol/L, 0.00040 µmol/L, 0.00040 µmol/L, and of 0.00028 µmol/L in serum creatinine per day according to sex, age group, weight group, initial ART regimen, and ADRs, respectively. There was an estimated decline of 0.00023 mmol/L, 0.00022 mmol/L, 0.00023 mmol/L, 0.00024 mmol/L, and of 0.00015 mmol/L per day in urea according to sex, age group, weight group, initial ART regimen, and ADRs, respectively.

Health professional's questionnaire: 49 health professionals responded to the questionnaire. **100% (n= 49) of the participants showed that they did not use the yellow card scheme to report ADRs. 34.65% (n = 17) use the individual case safety reports. 57.14% (n = 28) used the structured databases to report ADRs. 85.71% (n = 42) documented in the patient bukana, and 6.12% (n = 3) used the HIV/AIDS ART card to document ADRs occurrence. 91.84% (n = 45) of the health professionals never filled the ADR reporting form in their working environment.**

In conclusion, adverse drug reactions occurring in a hospital or healthcare facility should be recorded and reported by the medical practitioners, nurses, pharmacists, and the pharmacy technicians. Therefore, it is important to assess the continuous evaluation of the benefits and harm of medicines which will help in achieving the ultimate goal of making safer and more effective treatment available for patients. As well as to help the health professionals to participate in the very important process of continuous surveillance of safety and efficacy of pharmaceutical products used in clinical practice.

OPSOMMING

TITEL: Assessering van Ongewensde Geneesmiddelreaksies Veroorsaak deur HAART in Antiretrovirale Klinieke in die Maseru-Distrik.

SLEUTELWOORDE: MIV/VIGS, antiretrovirale (ARV) geneesmiddels, ongewensde geneesmiddelreaksies (OGR), geneesmiddel-veiligheidsmonitering, laboratorium-monitering.

Antiretrovirale geneesmiddels is suksesvol in die beheer van MIV/VIGS en die vermindering in die siekte se voortskryding. Antiretrovirale geneesmiddels is gestaak by tot 25% van alle pasiënte tydens hul aanvanklike behandelingsterapie as gevolg van ongewensde geneesmiddel-effekte, faling van behandeling en nie-nakoming binne die eerste agt maande van behandeling (Sharma *et al*. 2007:235). 'n Geneesmiddel-veiligheidsmonitering-waarnemingstelsel maak dit vir dokters, aptekers en ander gesondheidsorgvoorsieners moontlik om vermeende OGR aan te meld. Die doel van hierdie stelsel is om as 'n gids in die identifisering van nuwe OGR en predisponerende risikofaktore vir bekende OGR te dien.

Die doel van hierdie studie was om die voorkoms en dokumentasie van OGR in die private en openbare antiretrovirale klinieke in die Maseru-distrik te evalueer, met spesiale verwysing na zidovudien- (AZT) en tenofovir- (TDF) gebaseerde riglyne. Die empiriese ondersoek is in twee fases verdeel. Die eerste fase was 'n deursnee-opname, kwantitatiewe, retrospektiewe medisyneverbruik-evalueringstudie wat op die voorkoms van OGR in pasiënte wat zidovudien (AZT) en tenofovir (TDF) neem, gefokus het. Die tweede fase was 'n opname in 'n vorm van vraelyste vir die gesondheidswerkers.

Medisynegebruik-oorsig: Die monstergrootte van pasiënte was 300. Van die 44 pasiënte wat OGR ervaar, was 72.73% (n = 32) vroulik en 27.27% (n = 12) manlik. 'n Groter aantal pasiënte wat OGR ondervind was vroue met 43.18% (n = 19) wat met veluitslag, 27.27% (n = 12) met naarheid/braking, en 2.27% (n = 1) met diarree presenteer. By manlike pasiënte het 2.27% (n = 1) het perifere neuropatie, 18.18% (n = 8) veluitslag, 2.27% (n = 1) Fanconi-sindroom, 2.27% (n = 1) naarheid/braking, en 2.27% (n = 1) diarree getoon. Vyf pasiënte se ART regimen het verander as gevolg van OGR. 60% (n = 3) van die pasiënte was vroue en 40% (n = 2) mans. Daar was 'n geskatte toename van 0.0025 selle/mm³, 0.0026 selle/mm³, 0.0024 selle/mm³, 0.0025 selle/mm³, en van 0.0019 selle/mm³ in CD4-telling per dag volgens geslag, ouderdomsgroep, gewigsgroep, aanvanklike ART-regimen, en OGR, onderskeidelik.

'n Geskatte toename van 0.00021 g/dL, 0.00022 g/dL, 0.00018 g/dL, 0.00022 g/dl, en van 0.00020 g/dl in die Hb profiel per dag het plaasgevind volgens geslag, ouderdomsgroep, gewigsgroep, aanvanklike ART-regimen, en OGR, onderskeidelik. Daar was 'n geskatte toename van 0.000062%, 0.000046%, 0.000068%, 0.000062%, en van 0.00017% in neutrofieltelling volgens geslag, ouderdomsgroep, gewigsgroep, aanvanklike ART-regimen, en OGR per dag, onderskeidelik. Daar was 'n geskatte toename van 0.000044 IU/L, 0.000043 IU/L, 0.000046 IU/L, en 0.000028 IU/L in ALT volgens geslag, ouderdomsgroep, gewigsgroep, en die aanvanklike ART-regimen per dag, onderskeidelik. 'n Geraamde afname van 0.000013 IU/L in ALT volgens OGR per dag het ook voorgekom. Daar was 'n geskatte afname van 0.00038 µmol/L, 0.00039 µmol/L, 0.00040 µmol/L, 0.00040 µmol/L, en van 0.00028 µmol/L in serum-kreatinien per dag volgens geslag, ouderdomsgroep, gewigsgroep, aanvanklike ART-regimen en OGR, onderskeidelik. Daar was 'n geskatte afname van 0.00023 mmol/L, 0.00022 mmol/L, 0.00023 mmol/L, 0.00024 mmol/L, en van 0.00015 mmol/L per dag in ureum volgens geslag, ouderdomsgroep, gewigsgroep, aanvanklike ART-regimen en OGR, onderskeidelik.

Gesondheidswerker se vraeIys: 49 gesondheidswerkers het op die vraelys gereageer. 100% (n = 49) van die deelnemers het aangedui dat hulle nie gebruik maak van die geelkaartskema om OGR aan te meld nie. 34.65% (n = 17) gebruik die individuele geval-veiligheidsverslae. 57.14% (n = 28) het die gestruktureerde databasisse om OGR aan te meld, gebruik. 85.71% (n = 42) het in die pasiënt-bukana gedokumenteer, en 6.12% (n = 3) het die MIV/VIGS-ART-kaart gebruik om OGR -voorkoms te dokumenteer. 91.84% (0 = 45) van die gesondheidswerkers het nooit die OGR -verslagdoeningsvorm in hul werksomgewing ingevul nie.

Ongewensde geneesmiddelreaksies wat in 'n hospitaal of mediese fasiliteit voorkom, moet aangeteken word en aan die mediese praktisyns, verpleegsters, aptekers, en die apteektegnici gerapporteer word. Daarom is dit belangrik om die deurlopende evaluering van die voor- en nadele van medisyne te doen, wat sal help om die uiteindelike doel, naamlik die beskikbaarstelling van veiliger en meer doeltreffende behandeling van pasiënte, sowel as om die gesondheidspersoneel te help om deel te neem aan die baie belangrike proses van deurlopende toesig oor die veiligheid en doeItreffendheid van farmaseutiese produkte wat gebruik word in kliniese praktyk.

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List of abbreviations in the text

Abbreviations related to disease and medication

ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
AEFI	Adverse Events Following Immunization
AZT	Zidovudine
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
cART	Combination Antiretroviral Therapy
CD4 cell	T-lymphocyte bearing CD4 receptor
DF	Degree of Freedom
ICSR	Individual Case Safety Reports
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
EFV	Efavirenz
FBC	Full Blood Count
FI	Fusion Inhibitor
GFR	Glomerular Filtration Rate
gp41	Glycoprotein 41
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B virus
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HSR	Hypersensitivity Reaction
HR1	Homology region 1
HR2	Homology region 2
IPT	Isoniazid Prophylaxis Therapy
LFT	Liver Function Tests
NVP	Nevirapine
NRTI	Nucleoside/nucleotide Reverse Transcriptase Inhibitor
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
RNA	Ribonucleic Acid

STI	Sexually Transmitted Disease
TB	Tuberculosis
TST	Tuberculin Skin Test
TDF	Tenofovir

Abbreviations related to institutions

CHAL	Christian Health Association of Lesotho
CNPV	National Centre for Pharmacovigilance
DPL	Direction de la Pharmacie et des Laboratoires
DGPML	Direction Générale de la Pharmacie, du Médicament et des Laboratoires
DHMT	District Health Medical Teams
FDA	Food and Drug Administration
GOL	Government of Lesotho
MCC	Medicines Control Council
MOHSW	Ministry of Health and Social Welfare
NGO	Non-Governmental Organisations
NACL	National AIDS Commission Lesotho
NAFDAC	National Agency for Food and Drug Administration and Control
NADEMC	National Adverse Drug Event Monitoring Centre
NMRA	National Medicines Regulatory Authority
NDSO	National Drug Supply Organisation
PHPs	Public Health Programme
SPS	Strengthening Pharmaceutical Systems
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
TADATIS	Tanzania Drug and Toxicity Information Services
TIPC	Therapeutics Information and Pharmacovigilance centre
UNAIDS	Joined United Nations Programme on HIV/AIDS
UNIDO	United Nations Industrial Development Organisation
UNGASS	United Nations General Assembly Special Session
UMC	Uppsala Monitoring Centre (WHO)
WHO	World Health Organisation

Definitions

- ***Antiretroviral drugs*** are medications used for the treatment of infection by retroviruses, mainly HIV.
- ***Adverse drug reaction*** is any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy (WHO, 2002b: 5).
- The ***cohort event monitoring*** (CEM) is a prospective, observational, cohort study of adverse events associated with one or more medicines (WHO, 2009: 3).
- ***Highly active antiretroviral therapy*** is a combination of antiretroviral drugs used for the treatment of HIV infection. This drugs attack the virus at three different sites.
- ***Monitoring laboratory tests*** are routine laboratory tests carried out with the purpose of monitoring treatment response in terms of toxicities and success.
- ***Pharmacovigilance*** is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems (WHO, 2002a: 7).
- As defined by the World Health Organisation (2007b), a ***spontaneous report*** is an unsolicited communication by health care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme.
- ***Tenofovir-based regimens*** are regimens that contain three antiretroviral medicines with tenofovir as a back bone. The regimen may contain lamivudine with efavirenz or nevirapine.
- ***Zidovudine-based regimens*** are regimens that contain three antiretroviral medicines with zidovudine as a back bone. The regimen may contain lamivudine with efavirenz or nevirapine.

Synonymous terms in the text

Drugs, medicines, medication

Medical records, medical files

Weight, body mass

> Greater than

< Less than

= Equal

≤ Less than and/or equal to

≥ Greater than and/or equal to

% per cent

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

The research focused on assessment of adverse drug reactions in HIV/AIDS patients caused by highly active antiretroviral therapy (HAART) and also on how health professionals handle reporting or recording of adverse events in Maseru district, Lesotho. This chapter discusses the problem statement, research objectives and research methodology.

1.2 PROBLEM STATEMENT

Antiretroviral drugs have been successful in controlling HIV/AIDS and reducing disease progression. Antiretroviral regimens are however stopped in up to 25 per cent of all patients during their initial treatment therapy as a result of adverse drug effects, failing treatment and nonadherence within the initial eight months of treatment (Sharma *et al.*, 2007: 235). Adverse drug reactions (ADR) occurring in a hospital or healthcare facility should be recorded and reported by medical practitioners, nurses, pharmacists and pharmacy technicians. They should also be documented by the healthcare organisation to a wider audience by means of regional or national reporting method (World Health Organisation, 2005: 7).

Adverse drug reactions cause a financial burden on a country because of monitoring, treatment and equipment used to manage the ADR. As a result of either having patients being hospitalised or extension of hospitalisation for patients already in the hospital because of ADRs, financial burden increases significantly (Davies *et al.*, 2007: 83). The costs of drug-related morbidity and mortality exceeded USD 177 billion in 2000 in the United States (Ernst & Grizzle, 2001); the total estimated annual cost to society due to ADRs in the European Union (EU) is 79 billion euros (European Commission, 2008).

A pharmacovigilance surveillance system makes it possible for physicians, pharmacists and other healthcare providers to report suspected ADRs. The purpose of this system is to operate as a guide in identification of new ADRs and predisposing risk factors to known ADRs. According to the Centre for Health Policy Research, more than 50 per cent of the approved drugs in the United

States were related to adverse effect not detected before approval (Rabbur & Emmerton, 2005: 92). At least one adverse drug reaction occurs in 10 to 20 per cent of hospitalised patients (Rao *et al.*, 2006: 293).

The World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring, Uppsala, promotes pharmacovigilance at country level and 134 countries were part of the World Health Organisation pharmacovigilance programme in 2010 (World Health Organisation, 2013). They are responsible for gathering information on drug safety and circulating it to all member countries. The 98th full member country of the international drug monitoring centre founded by World Health Organisation is Kenya (Pharmacy and Poisons Board, 2010: 1). Kenya accomplished this in a year of the official opening of its national pharmacovigilance system.

Nonadherence to long-term drug therapy is one of the reasons for deprived health outcomes and escalating healthcare costs (Lindsay & Heaney, 2013: 329). Some of the risk factors of poor adherence in HAART include adverse effects caused by ART which differ in severity and the complexity of the ART regimen. A pooled analysis of North American studies in 2001 reported adherence of 55 per cent (95 per cent CI 49 to 62 per cent) while for African studies adherence was 77 per cent (95 per cent CI 68 to 85 per cent) (Abaasa *et al.*, 2008: 2, Mills *et al.*, 2006: 1). Nonadherence to HAART leads to treatment failure and increased risk of transmission of a drug resistant virus to other members of the population thus rendering nonadherence a major public health issue (Srikanth *et al.*, 2012: 16).

Initiation of ART, monitoring of antiretroviral treatment effectiveness and disease progression is carried out with the help of CD4 cell counts (World Health Organisation, 2007: 12). There are different laboratory tests used to assess patients on different ART regimens. HIV-positive patients on zidovudine-based regimens are at greater risk of anaemia as a result of zidovudine, low body mass and low CD4 cell counts. Anaemia monitoring is conducted by checking the haemoglobin (Hb) profile one month after AZT commencement followed by every three months (World Health Organisation, 2010: 65). Patients on tenofovir-based regimens are prone to renal failure as an adverse effect. Renal function monitoring using creatinine clearance is suggested for these patients and also for those with diabetes, hypertension, low body mass, and for those of older age group. Creatinine clearance is calculated for patients on TDF-based regimens prior to initiation and every six months

(World Health Organisation, 2010: 65). Pharmacovigilance programmes in developing countries are very limited (Palaian *et al.*, 2010: 180). There is very little information available on medicine safety in Nepal and these concerns are frequently not communicated (Palaian *et al.*, 2010: 180). It is important to record and report non-serious adverse events particularly if they could be risk factors to poor adherence (World Health Organisation, 2007: 6).

Antiretrovirals toxicity profile is not well known in developing countries. The spectrum of adverse effects related to HAART in developing countries may differ from that in developed countries because of the high prevalence of conditions such as anaemia, malnutrition, and tuberculosis and frequent initial presentation with advanced HIV/AIDS disease (Subbaraman *et al.* 2007: 1093). Therefore, it is important for a study to be carried out to assess the continuous evaluation of the benefits and harm of medicines which will help in achieving the ultimate goal of making safer and more effective treatment available to patients, as well as to help health professionals to participate in the very important process of continuous surveillance of safety and efficacy of pharmaceutical products used in clinical practice.

1.3 RESEARCH QUESTIONS

The following research questions were formulated on the basis of the preceding recognitions:

- How should a pharmacovigilance programme be developed and implemented specifically for antiretrovirals in a developing country such as Lesotho?
- What are the prescribing patterns of ARVs and other medicines in the health care sector in Lesotho?
- Is proper documentation of the ADR of antiretroviral drugs being carried out in Lesotho?

1.4 RESEARCH OBJECTIVES

The research includes a general as well as various specific research objectives.

1.4.1 General research objective

The general research objective of the study was to assess the prevalence and documentation of ADR in the private and public antiretroviral clinics in Maseru district, with special reference to zidovudine (AZT)-based regimens (AZT/3TC/NVP and AZT/3TC/EFV) and tenofovir (TDF) - based regimens (TDF/3TC/NVP and TDF/3TC/EFV).

1.4.2 Specific research objectives

The study consists of a literature review and empirical investigation. The research objectives of the two phases above include the following:

1.4.2.1 Literature review

The specific research objectives of the literature review include the following:

- To outline the treatment protocols as stated by the Lesotho (2010) and World Health Organisation (2010) antiretroviral treatment guidelines and other related treatment guidelines.
- To describe ARV drugs according to different classification systems and possible side effects.
- To emphasise the importance of adverse drug reactions reporting on antiretroviral drugs.
- To determine from the literature how proper documentation of ADR can be done and maintained to improve patient safety.
- To evaluate the role of health professionals in recording and reporting of adverse drug reactions.

1.4.2.2 Empirical investigation

The specific research objectives of the empirical investigation are as follows:

- To assess the frequency at which adverse drug reactions (ADRs) occur in patients taking either tenofovir or zidovudine based regimens.
- To evaluate the laboratory tests (e.g. CD4 cell count, viral load, haemoglobin profile, neutrophil count, alanine aminotransferase (ALT) and creatinine clearance) results for any reflection of the presence of adverse drug reactions.
- To evaluate how documentation of adverse drug reactions is being done by health professionals.
- To assess health professionals understanding of adverse drug reactions recording or reporting.
- To determine how health professionals manage adverse drug reactions.

1.5 RESEARCH METHOD

The study consists of two phases namely: the literature review which will be elaborated on in chapter two and an empirical investigation which will be discussed in detail in chapter three. The report and discussion of the results obtained from the empirical investigation will be dealt with in detail in chapter four.

1.5.1 Literature review

The literature review consists of the following subtopics:

- **Antiretroviral treatment**. In this subtopic the emphasis is on the classification of antiretroviral drugs, their specific side effects or adverse reactions and also on HAART regimens.
- **Treatment protocols as stated by Lesotho and World Health Organisation 2010 antiretroviral treatment guidelines**. The focus is on the treatment of HIV/AIDS. It comprises of when to initiate, which regimens to start with and also how to monitor a patient on a specific ART regimen.
- **Laboratory monitoring**. The emphasis is on how laboratory monitoring can be used to identify potential ADRs.
- **Pharmacovigilance**. The focal point is on the importance of recording or reporting adverse drug reactions by health professionals and the different reporting systems available.

1.5.2 Empirical investigation

1.5.2.1 Research design

Firstly, the study was a cross-sectional quantitative retrospective drug utilisation review study which focused on the occurrence of adverse drug reactions in patients taking zidovudine (AZT) and tenofovir (TDF) –based regimens. Patients' medical records were used to capture demographic data, medical history, laboratory results and adverse drug effects. Secondly, a survey in a form of questionnaires involving health professionals was conducted.

1.5.2.2 Method

The study population, research instruments and implementation in the two phases of the study were as follows:

1.5.2.2.1 Study populations

In phase one, the preliminary total population of HIV-positive adult patients in Sankatana ART clinic was estimated to be 1 423 by the clinic statistician. Data was collected retrospectively from the medical files of patients on both AZT- and TDF- based regimens. All patient files on the mentioned regimens were used for data collection by the researcher. In phase two, the study sample consisted of all health professionals (doctors, nurses, pharmacists and pharmacy technicians) working at Sankatana ART centre, Khanya Medical centre, Healthy lifestyle and diabetes centre, Baylor College of Medicine, and St. Joseph's hospital. The total number of these health professionals was 65.

1.5.2.2.2 Research instruments

In phase one, data was captured by the researcher from the patient medical records using a drug utilisation data collection form *(refer to appendix C)*. Data from the patient files was captured from Sankatana ART centre. A structured health professional's questionnaire was used to interview health professionals in the second phase of the study *(refer to appendix E)*.

1.5.2.2.3 Implementation

Data was collected retrospectively by the researcher from the medical files of patients on both AZT- and TDF- based regimens using the drug utilisation data collection form in the first phase of the study. All patient files on the mentioned regimens were used for data collection. The data collected from the patients' medical files was for the periods 1st January 2010 to 31st December 2010 and 1st January 2011 to 31st December 2011. The type of information gathered included patient demographic data, medical history, adverse effects and laboratory data which included CD4 cell count, haemoglobin profile, creatinine clearance, neutrophil count and alanine aminotransferase (ALT). In phase two, the health professionals' questionnaires were distributed to different health workers by the researcher and collected after a week to give them time to answer all questions.

1.5.2.3 Data analysis

Captured data were entered on an excel spread sheet. Statistical Analysis System®, (SAS 9.1®) programme was used for analysis. For the statistical analysis, the following descriptive and inferential tools were used: frequency, arithmetic mean, standard deviation, confidence intervals, and t-test; and Proc Mixed procedure used for computation of Linear mixed models. Body mass and laboratory tests (creatinine clearance, haemoglobin profile, CD4 cell

count and ALT) were the measurements used to assess the clinical well-being of patients and ADRs that may be experienced.

1.5.2.4 Ethical consideration

Patient numbers were used instead of patient names not to breech patient confidentiality in phase 1. The consent letters were given to health professionals participating in the study before handing out questionnaires in phase 2. The protocol, informed consent, data collection form and health professionals' questionnaire were first submitted for approval to the Ministry of Health and Social Welfare in Lesotho. Once this local approval was obtained, the letter of approval was sent to Sankatana ART clinic. All the documents sent to the Lesotho Ministry of Health and Social Welfare together with the letter of approval was submitted to the North West University ethics committee.

1.6 CHAPTER SUMMARY

In this chapter, an outline of the importance of conducting the study and the methods used to carry it out were supported clearly in different sections namely: problem statement, research questions, research objectives and research methodology.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

This chapter focuses firstly on the population, HIV/AIDS prevalence and the health care system of Lesotho. Secondly, it covers the classification of antiretroviral drugs and their specific side effects/adverse effect, and the role of pharmacovigilance in HIV/AIDS treatment. Thirdly, treatment protocols of HIV/AIDS as stated by the Lesotho and World Health Organisation 2010 antiretroviral treatment guidelines will be looked at. Lastly, laboratory monitoring of patients on different highly active antiretroviral therapy (HAART) regimens will also be included.

2.2 POPULATION OF LESOTHO

Lesotho is located in the south eastern region of Southern Africa and has an area of approximately 30,000 square kilometres. It is completely surrounded by the Republic of South Africa (World Vision, 2005: 3). The country is segregated into 10 districts which are Maseru, Berea, Leribe, Butha-Buthe, Mokhotlong, Thaba-Tseka, Qacha's Nek, Quthing, Mohale's Hoek, and Mafeteng. Since Lesotho's independence in 1966, the government in collaboration with the Bureau of Statistics carried out five modern population censuses the latest being in April 2006 (Ministry of finance and development planning & Bureau of statistics, 2008: 7). As reflected by Lesotho's de jure census 2006, the population of Lesotho was 1,876,663 and it was slightly lower than the preliminary figure by 0.2 per cent (Bureau of Statistics, 2009: 1).

Table 2.1: Lesotho districts and their population

DISTRICTS	POPULATION 2006
Maseru	**429 823**
Butha-Buthe	**109 529**
Leribe	**298 352**
Berea	**256 496**
Mafeteng	**193 682**
Mohale's Hoek	**174 924**
Quthing	**120 502**
Qacha's Nek	**71 876**
Mokhotlong	**96 340**
Thaba-Tseka	**129 137**
TOTAL	**1 880 661**

Adopted from Bureau of Statistics 2009: 3

Figure 2.1 below adapted from Ministry of finance and development planning & Bureau of statistics (2008: 7) shows that the de jure population of Lesotho was about four times bigger in 2006 than in 1911, when the de jure population was counted for the first time.

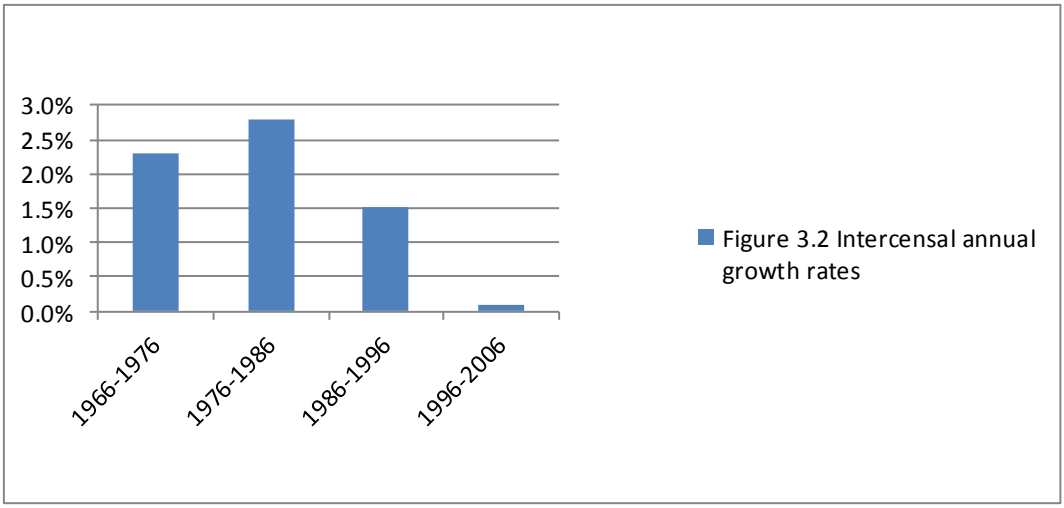

Figure 2.1: Intercensal annual growth rates

According to the Ministry of finance and development planning & Bureau of statistics (2008: 7), after 1956 the annual growth rate increased to reach 2.6 per cent from 1976 to 1986. The declining growth rate thereafter was due to changes in fertility, mortality, migration and the HIV/AIDS pandemic.

2.3 HIV/AIDS PREVALENCE IN LESOTHO

A total of 2.7 million people were infected with HIV in 2010, a decline from 3.1 million in 2001 in developing countries adding to the total number of 34 million people living with HIV in 2010 (World Health Organisation, 2011a: 2). Access to antiretroviral therapy increased from 400 000 in 2003 to 6.65 million in 2010 with 47 per cent coverage of people qualifying for treatment (World Health Organisation, 2011a: 2). The countrywide adult HIV/AIDS prevalence rates in Botswana, Lesotho and Swaziland were 24.1 per cent, 23.2 per cent and 33.4 per cent correspondingly in 2006 (Bokazhanova & Rutherford, 2006: 4). Lesotho has the third highest HIV/AIDS prevalence in the world. The epidemic persists in being most severe in southern Africa, with South Africa having more people living with HIV/AIDS (an estimated 5 600 000) in 2009 than any other country in the world (Joined United Nations Programme on HIV/AIDS, 2011: 7). In 2007, estimates showed that there were approximately 260,000 HIV-positive adults (15 to 49 years); an estimated 21,000 HIV-positive children (0 to 14 years) bringing the total HIV-positive population to approximately 280,000 in Lesotho (United Nations General Assembly Special Session report, 2008: 4).

According to the National AIDS Commission of Lesotho (2012: 11), in 2011, Lesotho's HIV/AIDS prevalence rate for adults (15 to 49 years) remained at 23 per cent signalling a continuing stabilisation of the epidemic. However, gender disparities in HIV infection rate remain: 26.7 per cent of all adult women are HIV-positive as compared to 18 per cent of all adult men. Linking 2008 and 2011, the incidence of new HIV infections reduced from approximately 21,000 to 17,500 (National AIDS Commission of Lesotho, 2012: 11). In addition, the numbers of AIDS-related deaths decreased by 16 per cent from an approximately 12,000 in 2008 to 8,500 in 2011. Also, an estimated 252,669 HIV-positive adults within age range of 15 to 49 years and 37,172 HIV-positive children within the age range of 0 to 14 years were living in Lesotho in the same year (National AIDS Commission of Lesotho, 2012: 11).

2.4 LESOTHO HEALTH SYSTEMS

According to the National AIDS of Commission Lesotho (2006: 16), a decentralisation approach was implemented in dealing with HIV/AIDS challenges as it guarantees effectiveness from national, district, community, and village levels. In addition, the foundation of an organisation comprising public and private sector representation presented a potentially enhanced coordination of the national reaction. The spread of access to ART to

the health centre level in each district of the country has resulted in a significant increase in the rate at which HIV-positive patients have been enrolled on ART.

Decentralisation is used to describe a wide variety of resource and power transfer arrangements as well as accountability systems and has become the driving force for health sector reform and is driven by the wider sectorial reform efforts (Government of Kenya, 2008: 11). Ministry of Health and Social Welfare Lesotho supported the health delivery strategy under the conditions of the Local Government (Amendment) Act (5 0f 2004). They implemented the 10 districts as the official health planning and governance boundaries, and formed the District Health Management Teams (DHMT) to manage health services delivery at district level (Government of Lesotho, Ministry of Health and Social Welfare, 2009: 1). Health care services are provided chiefly by the Government of Lesotho (GOL) and the Christian Health Association of Lesotho (CHAL). According to the United Nations General Assembly Special Session report (2008:6), 180 of 216 ART service points have been accredited and accreditation of the remaining 36 sites is in progress. There are 18 health service areas and 160 health centres of which 52 per cent are government owned and 48 per cent are managed by the Christian Health Association of Lesotho and other Non-Governmental Organisations (NGO) (United Nations General Assembly Special Session, 2008: 6).

There is a signed memorandum of understanding between CHAL and the Government of Lesotho, and Lesotho has adopted the primary health care strategy: thus all structures operate in a form of multisectorality (Ministry of Health and Social Welfare, 2007). National AIDS Commission has expanded and strengthened its ability to collect and share information on district and local level interventions through district level technical officers.

Table 2.2 Reported number of sites that are providing antiretroviral therapy in Lesotho

2005	2007	
22	110	TOTAL

Adopted from Joined United Nations Programme on HIV/AIDS & World Health Organisation, 2008

Table 2.3 Estimated numbers of people receiving antiretroviral therapy in Lesotho

	2004	2005	2006	2007
Both sexes	**74 000**	**78 000**	**81 000**	**85 000**
Low estimate	**56 000**	**59 000**	**62 000**	**66 000**
High estimate	**89 000**	**94 000**	**98 000**	**100 000**

Adopted from Joined United Nations Programme on HIV/AIDS & World Health Organisation, 2008

According to the Lesotho ART guidelines 2010, all patients on ARVs were required to collect their medicines on a monthly basis from different health facilities. HIV-positive patients on ART who collected their medicines in December 2010 were 80,695 while approximately 83,624 patients collected their ARVs in December 2011 (National AIDS Commission of Lesotho, 2012: 17). As a result, the overall ART coverage was 58 per cent with 66 per cent (75,793) being adults and 21 per cent (4,902) children below the age of 15 years. Recently, the coverage is estimated to be 61 per cent with adults being 63 per cent and children 43 per cent. Decentralisation of ART at health centre level is frequently being reinforced by the country using teams of mentors in individual districts to support health care providers (National AIDS Commission of Lesotho, 2012: 17).

Medical practitioners based at the district hospitals visit several health centres located in that district to help with supervision and mentoring of nurses. At the community level, there are village health workers and traditional healers, and community health workers. There are approximately 8,600 personnel working in the health sector in Lesotho, excluding traditional healers and traditional birth attendants, of these personnel, only 44 per cent or approximately 3,790 are employed in the formal health sector operated by the Government of Lesotho (GOL), the Christian Health Association of Lesotho (CHAL), other Non-Governmental Organisations (NGOs) and the private-for profit sector (Ministry of Health and Social Welfare, 2009: 3).

2.4.1 State of Lesotho antiretroviral treatment

In developing countries, an estimated six million people need ART treatment without delay, but treatment was offered to only 400,000 in 2003 (Osewe *et al.*, 2005: 1). According to the Ministry of Health and Social Welfare (2010: 1), the number of people ever started on ART

was 31, 584 adults and 2, 335 children in December 2007, this brought the total number of people ever enrolled for ART to 33, 584 representing 59 per cent coverage.

2.4.1.1 Lesotho antiretroviral drug supply

The Ministry of Health and Social Welfare through the Directorate for HIV/AIDS started a procurement office for HIV/AIDS health products. It controls the procurement of antiretroviral medicines. The National Drug Supply Organisation (NDSO) manages storage and distribution to different hospitals and health centres country wide. Forecasting and budgeting for ARV drugs is done centrally (World Health Organisation, 2005: 2). The National Drug Supply Organisation also serves as the central store in the country. Most of the government's primary health clinics drug orders are delivered to the District Health Medical Teams (DHMTs) situated in the main district hospitals all over the country (World Bank, 2009: 6). The DHMTs work as cost centres for specific functions mainly for operations and maintenance such as expenditures for transport, medicines and other recurrent costs (Government of Lesotho, Ministry of Health and Social Welfare, 2009: 1).

The average monthly consumption reports on ARV drugs are submitted to NDSO for the different clinics by the DHMT Pharmacists in different districts. These reports enable NDSO to quantify and deliver according to their delivery schedule. In the health centres, inventory stock level is monitored using stock cards, on which the quantity received or issued is shown, supplier name, invoice number, balance, date, name of drug, strength and form of drug, and remarks. Each and every item has its own stock card.

2.5 CLASSIFICATION OF ANTIRETROVIRAL DRUGS

The availability of antiretroviral therapy for HIV-positive people allows them to enjoy a normal healthy life. Increased access to combination antiretroviral therapy (cART) has led to a considerable decrease in morbidity and mortality among HIV-positive patients in resource-limited situations (Brinkhof *et al.*, 2009: e1000066). Prolonged survival has allowed HIV-positive patients on cART to support their family and contribute to local economies and social structure (Leisegang *et al.*2009: e1000189).

2.5.1 Antiretroviral treatment

The first antiretroviral drug to be developed was zidovudine. A clinical drug trial phase I/II on HIV-infected patients in the United States in 1986 revealed promising results and the

placebo arm was stopped ahead of time (Weiss, 2008: 204). A risk of rapid emergence of zidovudine resistant HIV mutations was observed. This led to the development of more reverse transcriptase inhibitors and also protease inhibitors. Lately, fusion inhibitors and Integrase inhibitors have been approved (De Clercq, 2010: 507). This was achieved through the understanding of the HIV replication cycle (Zhu *et al.*, 2004: 5045).

2.5.1.1 Classification of antiretroviral drugs and their side effects/adverse effects

According to Shibuyama *et al.* (2006: 1075), antiretrovirals are categorised according to their mechanism of action. The different drug classes include (De Clercq, 2010: 507):

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors
- Fusion inhibitors

Certain drug classes may be more efficacious than others by virtue of greater sigmoidicity of the concentration-response curve, with some protease inhibitors alone exhibiting greater than nine log suppression of viral replication in CD4+ T cells (Shen *et al.*, 2008: 762). All antiretroviral drugs can have both short-term and long-term adverse events. The possibility of specific side effects differs from drug to drug, from drug class to drug class, and from patient to patient (Montessori *et al.*, 2004: 229). The patient should carefully be monitored by the prescriber of ART for any possible side effects related to the combination of medications being in use. Additionally, there are four drug classes consisting of many antiretroviral drugs. As a result, there is a vast number of possible HAART combinations and selecting a suitable regimen greatly depends on knowledge of antiretroviral toxicities. The use of routine blood tests in measuring CD4 cell counts and HIV viral load should be used as prognostic markers for disease progression. The goal is to get the CD4 cell count as close to normal as possible, and to suppress the HIV viral load to an undetectable level (Gilks *et al.*, 2006: 505).

Table 2.4: Different classes of antiretroviral drugs and their examples.

Brand name	Generic name	Commonly used abbreviations
Nucleoside/tide reverse transcriptase inhibitors		
Emtriva®	**Emtricitabine**	**FTC**
Epivir®	**Lamivudine**	**3TC**
Hivid®	**Zalcitabine**	**ddC**
Retonavir®	**Zidovudine**	**AZT, ZDV**
Videx®	**Didanosine**	**ddI EC**
Viread®	**Tenofovir**	**TDF**
Zerit®	**Stavudine**	**D4T**
Ziagen®	**Abacavir**	**ABC**
Non-nucleoside reverse transcriptase inhibitors		
Sustiva®	**Efavirenz**	**EFV**
Virammune®	**Nevirapine**	**NVP**
Rescriptor®	**Delavirdine**	**DLV**
Protease inhibitors		
Lexiva®	**Fosamprenavir**	**£APV**
Crixivan®	**Indinavir**	**IDV**
Fortovase®	**Saquinavir-soft gel**	**SQV-sgc**
Invirase®	**Saquinavir-hard gel**	**SQV-hgc**
Kaletra®	**Lopinavir + ritonavir**	**LPV/r**
Norvir®	**Ritonavir**	**RTV**
Reyataz®	**Atazanavir**	**ATV**
Viracept®	**Nelfinavir**	**NFV**
Aptivus®	**Tipranavir**	**TPV**
Fusion inhibitor		
Fuzeon®	**Enfuvirtide**	**T-20**

Adopted from Hartmann & Enk (2007: A1099), Kumarasamy *et al.* (2011: 789) & Orrell (2011: 235)

2.5.1.1.1 Nucleotide and nucleoside reverse transcriptase inhibitors (NRTIs)

Zidovudine was the first nucleoside reverse transcriptase inhibitor with in vitro anti-HIV activity (De Jonge *et al.*, 2005: 2176). From the time of its approval in 1987, a total of 13 NRTI drug products are now available for clinical application: eight individual NRTIs, four fixed-dose combinations of two or three NRTIs, and one complete fixed-dose regimen containing two NRTIs and one non-nucleoside reverse transcriptase inhibitor (Cihlar & Ray, 2010: 39-40). NRTIs are analogues of the naturally occurring blocks of DNA, the purine nucleosides, adenosine (A) and guanosine (G), and the pyrimidines, thymidine (T) and cytidine (C) (Shibuyama *et al.*, 2006: 1076). These drugs are identified by the reverse

transcriptase enzyme after the phosphorylation stage in their mechanism of action and thus integrated into embryonic viral DNA. The addition of cellular nucleosides is then prohibited and further viral DNA synthesis cannot occur (Hoffman & Landovitz, 2004: 2).

Treatment with nucleoside reverse transcriptase inhibitors can cause several long-term adverse effects due to mitochondrial toxicity (Montaner *et al.*, 2004: S73). Mitochondrial DNA (mtDNA) polymerase ɣ utilizes NRTIs and disrupts replication of mtDNA leading to depletion of mtDNA and faulty assembly of proteins essential for oxidative phosphorylation (Maagaard *et al.*, 2008: 1474). The hierarchy of mitochondrial DNA polymerase-γ inhibition is as follows: zalcitabine greater than didanosine greater than stavudine greater than zidovudine greater than lamivudine equal to abacavir equal to tenofovir (Lee *et al.*, 2003: 14712). The class-specific side effects seen with NRTIs include lactic acidosis, hepatic steatosis, and lipoatrophy; and drug specific side effects include anaemia, cardiomyopathy, gastrointestinal (GI) distress, drug-induced hypersensitivity, myopathy, nephrotoxicity, pancreatitis, ototoxicity, peripheral neuropathy, and retinal lesions (Lee *et al.*, 2003: 14712).

2.5.1.1.1.1 Lipoatrophy

Lipoatrophy is a syndrome included under the general term of lipodystrophy. Lipodystrophy is linked with the development of a group of metabolic and morphologic disorders. They consist of fat wasting in the face, arms, legs and buttocks; fat accumulation in the abdomen, dorsocervical region and breasts in women; hyperlipidemia, hyperglycemia and insulin resistance (Puttawong *et al.*, 2004: 605). Risk factors for lipodystrophy in patients on NRTIs include accelerated age, abnormal lipid profile prior to therapy, and a low CD4 cell nadir (Shibuyama *et al.*, 2006: 1076). Stavudine is the commonly used NRTI with the highest tendency for lipoatrophy (Velsor *et al.*, 2004: 10). Prevention of lipoatrophy may be accomplished by using an NRTI with a lower affinity to DNA polymerase-α. Non-drug treatment may include dietary techniques and exercise.

2.5.1.1.1.2 Lactic Acidosis

Lactic acidosis is a serious NRTI-related mitochondrial toxicity, with or without hepatic microsteatosis (Shibuyama *et al.*, 2006: 1077). The diagnosis of lactic acidosis is not easy as the presenting symptoms such as nausea, emesis, abdominal pain, increased fatigue, and unexpected body mass loss can be vague (Wester *et al.*, 2007: 319). Preventive measures comprise avoidance of combinations of NRTIs with a high incidence for the reaction. Lactate

levels should also be monitored in patients with unclear initial symptoms such as unexplained nausea, vomiting, abdominal pain, hepatic steatosis or elevated transaminases (Calza *et al.*, 2005: 5).

2.5.1.1.1.3 Peripheral Neuropathy

Peripheral neuropathy is commonly associated with the development of chronic pain. It is regarded as the most recurrent neurological complication of human immunodeficiency virus (HIV)-1 infection (Simpson *et al.*, 2008: 299). HIV/AIDS associated sensory neuropathy pathogenesis involves deterioration of peripheral nerve fibres where the clinical features of antiretroviral toxic neuropathy are identical to those of distal sensory polyneuropathy (Valcour *et al.*, 2009: 104). All NRTIs are neurotoxic to a varying degree and in a dose-dependent manner. As a result, peripheral neuropathy is most commonly seen with zalcitabine, didanosine and stavudine (Cossariza & Moyle, 2004: 139). Patients may express some symptoms of neuropathy such as burning, numbness, pins-and-needles, aching sensation, cramping, and impaired temperature sensation in the feet and legs (Marchettini *et al.*, 2006: 175). Severe peripheral neuropathy may lead to discontinuation of the medication and substitution of other drugs.

2.5.1.1.2 Non-nucleotide reverse transcriptase inhibitors (NNRTIs)

Non-nucleoside reverse transcriptase inhibitors, in combination with other antiretroviral drugs have formed the basis for the treatment of HIV-1 infection in ART commencement. Nevirapine and efavirenz were initially discovered and developed in the late 1980s and more research led to the discovery and development of other NNRTIs with increased genetic barrier to the development of resistance (De Clercq, 2005: 57). Non-nucleoside reverse transcriptase inhibitors bind directly to reverse transcriptase, non-competitively inhibiting enzymatic activity (Hoffman & Landovitz, 2004: 2). They are different from NRTI structurally and thus have distinct toxicities, despite a common enzymatic target; the main side effects induced by NNRTIs are cutaneous problems (rash) and hepatotoxicity (Wit *et al.*, 2008: 933). Efavirenz commonly has central nervous system (CNS) side effects which include vivid dreams, insomnia, hallucinations, and drowsiness (Shibuyama *et al.* 2006: 1082). These side effects are very common and could to the patients' discontinuation of treatment therefore leading to treatment failures.

2.5.1.1.2.1 Dermatologic Adverse Reactions

Skin rashes are more common with non-nucleoside reverse transcriptase inhibitors than with other antiretroviral drugs. Self-determining risk factors which may led to the development of cutaneous reactions include female sex, CD4 cell counts less than 100 cells/mm^3 and age greater than 40 years (Shibuyama *et al.*, 2006: 1081). The NNRTIs spectrum of cutaneous reactions can vary from a mild morbilliform rash to Stevens-Johnson syndrome (Jay & Marshall, 2007: 221). Patients on nevirapine experience severe cutaneous reactions when compared to those on efavirenz resulting in more patients being stopped from taking nevirapine as opposed to efavirenz (Borras-Blasco *et al.*, 2008: 883). Depending on the severity of the cutaneous reaction, the drug may be discontinued and never re-challenged and the NNRTI class replaced with another class of antiretroviral drugs (Orrell, 2011: 234).

2.5.1.1.2.2 Hepatotoxicity

All classes of antiretroviral therapy are correlated with elevations in serum hepatic enzymes. Basic mechanisms suggested include: mitochondrial toxicity in association with several NRTI; hypersensitivity reaction in association with NNRTI and immune reconstitution disease in association with underlying chronic viral hepatitis (Law *et al.*, 2003: 2192). Hepatotoxicity is caused by most drugs as their metabolism occurs in the liver. The NNRTIs are implicated in hypersensitivity reactions with NVP-containing regimens being more hepatotoxic than EFV- and DLV- containing regimens, at least for the first two to three months of therapy (Kontorinis & Dieterich, 2003: 173). There are other associated risk factors which could influence the patient's vulnerability to hepatotoxic effects such as alcohol use, underlying diseases, and concomitant drugs (Dieterich *et al.*; 2004: S81). Treatment of hepatotoxicity includes the removal of the offending drug when ALT and/or AST increases to levels greater than 5 to 10 upper limit of normal, followed by supportive care until the enzymes normalise (Shibuyama *et al.*, 2006: 1082).

2.5.1.1.3 Protease inhibitors (PIs)

The action of protease inhibitors occurs at a very late stage in the HIV replication process. PIs prevent the HIV-1 protease from cleaving the two Gag and GagPol precursor proteins by binding precisely to the active side of the enzyme resulting in the formation of immature non-infectious virus particles (Wynn *et al.*, 2004: 263). They are therefore selective, competitive inhibitors of protease which is an enzyme vital to viral maturation, infection, and replication. All PIs are associated with some risk of lipodystrophy, hepatotoxicity, hyperglycaemia,

increased bleeding episodes among patients with haemophilia, gastrointestinal disturbances (e.g. nausea, vomiting, and diarrhoea) and lipid irregularities (Shibuyama *et al.*, 2006: 1082).

2.5.1.1.4 Fusion inhibitors (FIs)

The most recent group of ARVs to be developed is fusion inhibitors. The only member of this class, Enfuvirtide (Fuzeon®), was approved by food and drug administration (FDA) for use in patients with significant viral loads despite being on HAART regimens (Lalezari *et al.*, 2003: 2176). It is administered parenterally as it is a bulky polypeptide. Enfuvirtide acts on the HR1 domain of HIV-1 envelope gp41 thus stopping binding of the distal HR2 region and subsequent gp41 structural rearrangement that facilitates virus–cell fusion (Clotet *et al.*, 2004: 1137). Adverse effects experienced by patients on enfuvirtide encompass injection site reactions, hypersensitivity reactions, and an increased risk of pneumonia (Greenberg & Cammack., 2004: 335).

2.5.2 Highly active antiretroviral therapy (HAART) regimens

Highly Active Antiretroviral Therapy (HAART) was introduced in 1996 and combines at least three antiretrovirals (ARVs) (Rajesh *et al.*, 2010: 84). Increased lifespan and quality of life of HIV-infected patients was tied to an impact HAART had on the course and treatment of disease and disease-related morbidity (Borras-Blasco *et al.*, 2008: 879). A swift reduction in viral load plasma, cerebrospinal fluid (CSF) and lymphatic tissue is experienced by HIV-positive patients on HAART (Girard, 2009: 127). Nevertheless, HAART has quite a few vital problems yet to be solved which include: the emergence of new drug-resistant HIV mutants, the need to take the large dosages of drugs, and drug side effects (Ohrui, 2011: 53).

Table 2.5: The South Africa antiretroviral treatment guidelines

REGIMEN TYPES		CLASSES OF DRUGS
First line		
All new patients needing treatment, including pregnant women	TDF + FTC (or 3TC) + EFV FDC preferred	**Replace EFV with NVP in patients with significant psychiatric co-morbidity or intolerance to EFV and where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.**
Contraindications to EFV	TDF + (FTC or 3TC) + NVP	**Use NVP based regimen: In patients with significant psychiatric comorbidity or intolerance to EFV and where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.**
Contraindication to TDF	AZT+ 3TC +EFV or (NVP)	**Renal disease or the use of other nephrotoxic drugs e.g.** **aminoglycosides**
Contraindication to TDF and AZT	d4T + 3TC+ EFV (or NVP)	**Renal disease and anaemia or the use of other nephrotoxic drugs, aminoglycosides**
Contraindication to TDF, AZT and d4T	ABC + 3TC + EFV (or NVP)	**Renal disease, anaemia, peripheral neuropathy, the use of other nephrotoxic drugs**
Currently on d4T-based Regimen	TDF + FTC(or 3TC) + EFV FDC preferred	**Mandatory if patients experience toxicity and patients who are at high risk of toxicity (high BMI or pregnant). Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if well tolerated.**
Second line		
Management of virological Failure		**If plasma HIV RNA >1000 copies, Check for adherence, compliance, tolerability and drug- drug interaction and assess psychological issues.** **Repeat VL test 2 months later.** **If plasma VL confirmed >1000copies change regime to second line therapy**
Failing on a TDF-based 1st line Regimen	AZT+3TC+ LPV/r	**Patients with anaemia and renal failure** **switch to ABC**
Failing on a d4T-based 1st line Regimen	TDF+3TC (or FTC) and LPV/r	
Dyslipidaemia or diarrhoea associated with LPV/r	**Switch LPV/r to ATV/r**	

VL = viral load

Adopted from the Republic of South Africa Department of Health (2013).

2.5.3 Drug specific side effects/adverse effects

Drug side effects, regimens complexity, co-morbidities, life-long pill consumption and the life quality in patients on HAART may limit the outcome of ART (AIDS support and technical assistance resources, 2010: 6). The range of adverse effects caused by HAART in

developing and developed countries may vary due to the high prevalence of conditions such as anaemia, malnutrition, and tuberculosis and frequent initial staging with advanced HIV disease (Subbaraman *et al.*, 2007: 1093).

Table 2.6: Specific side effects of different antiretroviral medicines

ANTIRETROVIRAL DRUG	COMMON ASSOCIATED TOXICITY
TDF	-Asthenia, headache, diarrhoea, nausea, vomiting, flatulence -Renal insufficiency, Fanconi syndrome (risk factors: background renal disease, concomitant use of nephrotoxic medications, conditions associated with potential nephrotoxicity e.g. diabetes mellitus, hypertension)[3, 5] -Osteomalacia[2, 4] -Decrease in bone mineral density[2,3,4,5]
AZT	-Bone marrow suppression[2] -Macrocytic anaemia or neutropaenia[3,5] -Gastrointestinal intolerance[3], headache, insomnia, asthenia, skin and nail pigmentation[2, 4] -Lactic acidosis with hepatic steatosis[3]
EFV	-Persistent and severe CNS toxicity (dizziness, vivid dreams, depression, confusion)[3, 5] -Rash, hypersensitivity reaction Stevens-Johnson syndrome[1] -Hepatitis[2, 4] -Hyperlipidaemia[2, 4] -Male gynaecomastia[2, 4] -Potential teratogenicity (first trimester of pregnancy)[3]
NVP	-Hypersensitivity reaction[1] -Stevens-Johnson syndrome rash[1] -Hepatic toxicity[3, 5] -Hyperlipidaemia[4]
3TC	Pancreatitis, Lactic Acidosis and Severe Hepatomegaly with Steatosis, nausea and vomiting, and diarrhoea[6]

AZT (zidovudine); TDF (tenofovir); EFV (efavirenz); NVP (nevirapine); 3TC (lamivudine)
Adopted from Hartmann & Enk (2007)[1], Kumarasamy *et al.* (2011: 791)[2], Ministry of Health and Social Welfare (2010: 53)[3], Orrell (2011: 235)[4], World Health Organisation[5] (2010:66) & GlaxoSmithKline (2011: 6-8)

2.5.3.1 Zidovudine (AZT)

Zidovudine is an NRTI that has anaemia as one of its adverse effects. Anaemia significantly impacts the quality of life because of its association with nausea, fatigue and weakness (Agarwal *et al.*, 2010: 387). Zidovudine-related anaemia is normally experienced by patients

on AZT within three months following therapy initiation (Subbaraman *et al.*, 2007: 1095). Some of the risk factors to anaemia include high zidovudine dosage, increased treatment duration, low CD4 cell count, and pre-existing anaemia. Zidovudine causes anaemia by a mechanism which involves inhibition of haemoglobin synthesis and globin gene transcription (Omoregie *et al.*, 2008: 34). In practice, treatment alternatives for anaemia caused by zidovudine include recombinant human erythropoietin, blood transfusion and replacement zidovudine with another antiretroviral agent (King *et al.*, 2009: 22).

2.5.3.2 Tenofovir disoproxil fumarate (Tenofovir DF)

One of the members of the NRTI drugs is tenofovir DF. Patients on tenofovir-based regimens commonly experience mild to moderate gastrointestinal events which may include diarrhoea, nausea, flatulence and vomiting (Kumarasamy *et al.*, 2011: 791). Nephrotoxicity, including renal insufficiency and Fanconi's syndrome, has been reported infrequently but the incidence, risk factors, and time to resolution remain uncertain (Nelson *et al.*, 2007: 1274). Older age patients with or without diabetes and hypertension, those with low body mass, and patients on renal toxicity associated drugs are at higher risk of tenofovir-induced toxicity (World Health Organisation, 2010: 33). As a result renal monitoring is required for patients on TDF-based regimens.

2.5.3.3 Lamivudine (3TC)

Lamivudine is well tolerated. It always forms part of the ART regimen combination used in first-line regimens. The toxicity profile of lamivudine is low toxicity with minimal drug-drug interactions (Gilks *et al.*, 2006: 507). Comparison of lamivudine to emtricitabine revealed commonly occurring ADRs such as: nausea, increased appetite, headache, rash and dry skin (Shibuyama *et al.*, 2006: 1080).

2.5.3.4 Nevirapine (NVP)

Nevirapine is an NNRTI associated with hypersensitivity reactions and hepatotoxicity. According to Wit *et al.* (2008: 933), six to seven per cent of patients initiated on NVP-containing regimens had to stop NVP due to hypersensitivity reactions. Gender and CD4 cell count are of use in preventing NVP-associated adverse effects. Nevirapine should not be given to adult females or males with CD4 cell counts greater than 250 cells/mm^3 or greater than 400 cells/mm^3 respectively unless the benefit outweighs the risk (World Health

Organisation, 2006: 3). Most hypersensitivity reactions (HSRs) are experienced within the first 18 weeks after beginning NVP therapy (Wit *et al.*, 2008 934).

2.5.3.5 Efavirenz (EFV)

Efavirenz is a member of NNRTI class with central nervous system (CNS) side effects. According to Shibuyama *et al.* (2006: 1082), insomnia, dizziness, light-headedness, nervousness, irritability, impaired concentration, abnormal or vivid dreaming, and hallucinations occur more frequently with efavirenz than with comparator arms. They normally resolve after a few weeks of efavirenz therapy (Gutierrez *et al.*, 2005: 1652). These side effects may be reduced by implementing the following strategies: administration of efavirenz at bedtime and no alcohol consumption.

2.6 TREATMENT PROTOCOLS OF HIV/AIDS AS STATED BY LESOTHO AND WORLD HEALTH ORGANISATION 2010 ANTIRETROVIRAL GUIDELINES AND OTHER RELATED GUIDELINES

The World Health Organisation (WHO) assists countries with continuing assistance, tools and support in providing and scaling up antiretroviral therapy within a public health approach (World Health Organisation, 2010: 17). These guidelines are generated with an expectation that each country will adapt the suggestions to suit its own situation.

2.6.1 World Health Organisation 2010 treatment guidelines

New emerging scientific evidence on HIV/AIDS treatment may lead to the revision of the guidelines for ART for HIV infection in adults and adolescents. The recommendations in the 2010 ART guidelines came about as a result of new evidence being provided on when to initiate ART, optimal ART regimens, the management of HIV co-infection with tuberculosis and chronic viral hepatitis, and the management of ART failure (World Health Organisation, 2010: 8).

According to the World Health Organisation (2010: 20), the adolescent and adult antiretroviral treatment guidelines state that:

- All HIV-positive adolescents, adults and pregnant women with CD4 cell counts of less than and/or equal to 350 cells/mm^3, should be initiated on ART, irrespective of the presence or absence of clinical symptoms. Patients with severe or advanced

clinical disease (World Health Organisation clinical stage 3 or 4) should start ART irrespective of their CD4 cell count.

- NNRTI plus two NRTIs combination forms the first-line regimens. One of the NRTIs should either be zidovudine (AZT) or tenofovir (TDF) in addition to lamivudine (3TC). Stavudine (d4T) use as part of first-line regimens should be reduced because of its toxicities.
- Ritonavir-boosted protease inhibitor (PI) plus two NRTIs forms second-line ART therapy. Either AZT or TDF should be included as one of the NRTIs, with reference to what was used in first-line therapy. The favoured PIs are ritonavir-boosted atazanavir (ATV/r) or lopinavir/ritonavir (LPV/r).
- CD4 cell count testing should be done in all patients to optimise pre-ART care and ART management. HIV-RNA (viral-load) testing is recommended to confirm suspected treatment failure.

2.6.2 Lesotho 2010 antiretroviral treatment guidelines

The Lesotho national guidelines for HIV/AIDS care and treatment were revised to reproduce the new World Health Organisation ART guidelines and guarantee that Lesotho offers HIV/AIDS services in line with the regional and international standards. The ART guidelines are intended to aid healthcare providers in managing HIV/AIDS infected patients in all health facilities to guarantee that treatment is the same country wide (Ministry of Health and Social Welfare, 2010: 4).

According to the Ministry of Health and Social Welfare (2010: 15), patients diagnosed with HIV/AIDS should be clinically evaluated, given cotrimoxazole prophylaxis for prevention of opportunistic infections, prophylactic isoniazid for Tuberculosis (TB) prevention and baseline laboratory monitoring conducted. Clinical evaluation consists of staging of clinical disease, screening for TB, STIs and pregnancy, and recognition of any current opportunistic infections and co-morbid conditions. CD4 cell count for immunologic staging, haemoglobin, ALT and creatinine are baseline laboratory investigations to be done before ART initiation (Ministry of Health and Social Welfare, 2010: 15). Lesotho is one of the third world countries striving for better care for HIV-positive patients. Implementation of up to date antiretroviral treatment guidelines in Lesotho was carried out and stated early initiation of treatment (less than 350

cells/mm³), tenofovir in first line, and nurse-initiated and managed HIV care, including antiretroviral therapy (ART), at primary health care level (Cohen *et al.*, 2009: 5).

In Lesotho, the first-line drugs available are zidovudine, abacavir, tenofovir, lamivudine, nevirapine and efavirenz. Second-line drugs include lopinavir/ritonavir and atazanavir/ritonavir and the backbone will be determined by which drugs the patient was on during first-line treatment. Lastly, third-line drugs consist of darunavir, ritonavir as a pharmacokinetic booster; raltegravir and etravirine (Ministry of Health and Social Welfare, 2010: 48-59).

2.6.3 Tuberculosis treatment guidelines and other related guidelines

Other diseases are seen with HIV-positive patients and guidelines were developed to give guidance on treatment and laboratory monitoring of these co-morbid diseases. These guidelines enable safe treatment of HIV-positive people, as antiretroviral drugs interact with a lot of medicines and also to prevent the occurrence of adverse drug events.

2.6.3.1 Tuberculosis/HIV co-infection treatment guidelines

People with HIV infection should be examined on a regular basis for TB during every clinical visit to a health facility (Kranzer, 2011: 419). HIV-positive adults and adolescents with a positive or unknown tuberculin skin test (TST) status and who are unlikely to have active TB should be on IPT for at least six months as part of a wide-ranging package of HIV care (World Health Organisation, 2011b: 5-6). All HIV-infected patients with active TB should be put on ART within eight weeks after TB treatment initiation regardless of the CD4 cell counts and the regimen will consist of AZT or TDF, 3TC (or FTC) and EFV (World Health Organisation, 2010: 22).

2.6.3.2 Cotrimoxazole prophylaxis guidelines

In developed countries, data have clearly verified the success of cotrimoxazole at decreasing the morbidity and mortality rates in HIV-infected individuals, including those on ART, particularly from *Pneumocystis jiroveci* pneumonia (PCP) formerly known as *Pneumocystis carinii* pneumonia (World Health Organisation, 2008:13). Cotrimoxazole prophylaxis also decreases the frequency of clinic visits and hospitalisations, reduces body mass loss, may slow the decrease in CD4 cell counts and the increase in HIV viral loads, and is cost-effective (Lowrance *et al.*, 2007: 56).

The rational for prescribing cotrimoxazole prophylaxis is to prevent *Pneumocystis jiroveci* pneumonia and toxoplasmosis. In addition, it has antimicrobial activity against a wide range of pathogens including *Pneumococcus*, non-typhoidal *Salmonella*, *Isospora*, *Cyclospora*, *Nocardia*, *Plasmodium falciparum*, *Toxoplasma gondii* and PCP. It is recommended that all clinical stages 3 and 4 adults and adolescents and those in clinical stages 1 and 2 with CD4 cell count less than and/or equal to 350 cells/mm^3, and all patients with a history of PCP should be put on cotrimoxazole prophylaxis (World Health Organisation, 2006b: 19). Additionally, all adults and adolescents taking TB treatment should also be given cotrimoxazole (Ministry of Health and Social Welfare, 2010: 23). Patients, who experienced severe adverse reaction (grade 4) to cotrimoxazole or other sulphur drugs in the past, should not be given cotrimoxazole prophylaxis (Zachariah & Massaquoi, 2006: 36). Dapsone should be used as an alternative in patients with a history of allergic reactions to cotrimoxazole because it should not be re-challenged (World Health Organisation, 2006a: 19).

2.6.3.3 HIV/AIDS and co-morbid diseases treatment guidelines

Hepatitis B virus (HBV) infected patients requiring treatment should be initiated on ART despite their CD4 cell counts or World Health Organisation clinical staging (World Health Organisation, 2010: 27) with their regimens containing TDF and either emtricitabine or lamivudine (World Health Organisation, 2010: 20). HIV/AIDS disease is associated with an increased risk of kidney diseases irrespective of the extensive use of HAART (Winston *et al.*, 2008: 1449). Diabetes, hypertension and some antiretroviral drugs are associated with kidney diseases in the setting of HIV infection (Scherzer *et al.*, 2012: 1). There are some ARV drugs that also cause renal failure due to their toxic effects. There is doubt as to whether all patients on TDF-based regimens should be monitored for renal function or whether only a certain population with other risk factors associated with renal diseases should be screened and monitored for renal function (World Health Organisation, 2010: 33).

2.7 LABORATORY MONITORING OF PATIENTS ON ANTIRETROVIRAL TREATMENT

Antiretrovirals are alien to the body and therefore can cause harm. Patients on ARVs are to be monitored using laboratory tests to assess their well-being and if there is any occurrence of an adverse drug reaction (ADR) (Mehta *et al.*, 2007: 403). Host genetics and diagnostic delays due to insufficient laboratory monitoring may be the cause of disparities in the severity of adverse effects (Subbaraman *et al.*, 2007: 1093). Patient monitoring generally includes

investigations to determine efficacy, toxicity and therapy compliance (Glencross *et al.*, 2003: 263). Some laboratory tests are expensive and this will compromise patient safety especially in developing countries. The annual health budget in developing countries could be affected by total cost of disease monitoring with reference to laboratory monitoring in HIV/AIDS which may constitute a significant challenge (Glencross *et al.*, 2003: 262).

Laboratory monitoring should go together with clinical assessments. Patient body mass loss in HIV-positive patients predicts either a progression of disease, opportunistic infection or death. It is used as a warning sign to prescribers to start investigations and treatment (National Department of Health South Africa, 2010: 28). Nutritional status and HIV infection are factors which add to immune system dysfunction leading to the emergency of opportunistic infections (Lategan *et al.*, 2010: 197). The antiretroviral regimen to be initiated is determined with the assistance of baseline laboratory tests. Before starting ART, baseline information should be provided on CD4 cell count, full blood count especially for AZT, ALT and creatinine clearance for TDF and pregnancy test for women if EFV is considered (World Health Organisation, 2010: 65).

2.7.1 Different laboratory tests conducted in monitoring of patients

Different laboratory tests are conducted depending on the type of regimen the patient is taking. The schedule of different laboratory tests for different drug regimens is shown in table 2.7 below. Nonetheless, viral load monitoring is relatively very expensive and requires a high technical complexity therefore it is not deemed important for patient management in a public-health approach (Gilks *et al.*, 2006: 506).

Table 2.7: Laboratory monitoring schedule for patients on antiretroviral therapy in Lesotho

ARV regimen	Before ARVs are started (baseline)	Day of initiation	Wk 2	Mo1	Mo 2	Mo 3	Mo 6	Mo 9	Mo 12	Every 6 Mo thereafter
All regimens	Rule out active TB (AFB and CXR if coughing)									
	Treatment assistant	X					X	If adherence problems		
	Ask about symptoms of possible side effects		X	X	X	X	X	X	X	X
	Clinical exam (including body mass)	X	X	X	X	X	X	X	X	X
TDF/3TC/EFV	CD4, ALT, FBC, creatinine						CD4, creatinine		CD4, creatinine	CD4, creatinine
TDF/3TC/NVP	CD4, ALT, FBC, Creatinine		ALT	ALT	ALT	ALT	CD4, ALT, creatinine		CD4, ALT, creatinine	CD4, ALT, creatinine
AZT/3TC/EFV	CD4, ALT, FBC			Hb	Hb	Hb, CD4	Hb, CD4	Hb, CD4	Hb, CD4	Hb, CD4
AZT/3TC/NVP	CD4, ALT, FBC		ALT	Hb, ALT	Hb, ALT	Hb, ALT, CD4	Hb, ALT, CD4	Hb, ALT, CD4	Hb, ALT, CD4	Hb, ALT, CD4
D4T/3TC/EFV	CD4, ALT, FBC			Hb		CD4	CD4	CD4	CD4	CD4
D4T/3TC/NVP	CD4, ALT, FBC		ALT	ALT, Hb	ALT	CD4, ALT	CD4, ALT	CD4, ALT	CD4, ALT	CD4, ALT

Mo- month, Wk- week

Adopted from Ministry of Health and Social Welfare (2010: 63) & World Health Organisation (2010: 65)

2.7.1.1 Creatinine

In Lesotho, laboratory monitoring for creatinine is carried out for all patients on TDF-based regimens after which health professionals use the results obtained to manually calculate the creatinine clearance with the aid of the CockcroftGault equation (Ministry of Health and Social Welfare, 2010: 64). To screen for chronic kidney disease by being able to estimate the glomerular filtration rate (GFR), the CockcroftGault equation for creatinine clearance (CL_{cr}) is used. Clinical laboratories should estimate the GFR using an equation designed to estimate or predict the GFR based on available patient data, such as age, sex, body mass, and serum creatinine, whenever reporting a serum creatinine measurement (Spruill *et al.*, 2007: 652). Paw and Park (2007: 243) defined creatinine clearance as follows:

For females: Creatinine clearance (ml/min) = $\frac{(140 - \text{age}) \times \text{body mass (kg)} \times 1.23\ (0.85)}{\text{Creatinine (µmol/L)}}$

For males: Creatinine clearance (ml/min) = $\frac{(140 - \text{age}) \times \text{body mass (kg)} \times 1.23}{\text{Creatinine (µmol/L)}}$

Creatinine clearance monitoring is to be performed for all patients on TDF-based regimens including those with renal diseases risk factors such as diabetes, hypertension, older age groups, and with low body mass (World Health Organisation, 2010: 65).

2.7.1.2 Haemoglobin profile (Hb)

Anaemia is one of the ADRs experienced by patients on AZT-based regimens as a result of AZT (Moyle *et al.*, 2004: 92). Anaemia occurs mostly in AZT thus requiring a baseline Hb measurement before initiation on AZT-based regimens. The Hb baseline measurement is also required when signs and symptoms of anaemia are noticed. Routine Hb monitoring for patients on AZT-based regimens with low body mass and/or low CD4 cell counts should be carried out every month after therapy initiation and every three months afterwards as these patients are at higher risks of anaemia (World Health Organisation, 2010: 65).

2.7.1.3 Neutrophils

Neutrophils are white blood cells that form the body's defence against bacterial infections. When their amount decreases abnormally in the body, the condition is known as neutropenia. In verification of the impairment of the body's ability to fight infections, neutrophil count is

used (Teeter & Franciscus, 2010: 3). Neutropenia can arise from HIV/AIDS, other infections or as a side effect caused by medication and zidovudine is one of the medications that can cause neutropenia (Marfatia & Makrandi, 2005: 45).

2.7.1.4 CD4 cell count

Immunological screening of HIV-positive patients is assessed using CD4 cell count. Observation of CD4 cell count is important in early diagnosis and when to start ART (World Health Organisation, 2012a: 9). Fluctuations in absolute CD4 cell counts may be observed in individuals and with intercurrent ill health. In chief clinical decisions of HIV-positive patients on and/or not on ART, CD4 testing should be done more than once as a single value could be unreliable. CD4 cell count measurements carried out repetitively reflect trends over time thus rendering them more informative than single values (World Health Organisation, 2010: 30). Viral load is essential for early detection of virological failure due to treatment failure thus enabling necessary interventions to be applied (World Health Organisation, 2010: 30). Treatment failure exists in two firms namely lack of virologic response at six months to 12 months (viral load above 1, 000 copies/ml), and viral rebound above 1, 000 copies/ml after previous viral load below 400 copies/ml (Alcorn, 2008).

2.7.1.5 Alanine aminotransferase (ALT)

Liver enzymes laboratory monitoring determined by symptom appearance is recommended for patients on NNRTI-containing regimens (nevirapine and efavirenz) (World Health Organisation, 2010: 65). Alanine aminotransferase is one of the liver enzymes used to monitor hepatotoxicity which is one of the adverse effects caused by NNRTIs (Teeter & Franciscus, 2010: 2). Signs and symptoms of hepatic toxicity encompass systemic symptoms, jaundice, coagulopathy, and markedly elevated alanine aminotransferase (ALT) (Dieterich *et al.*, 2004: S81). Minor ART-related hepatotoxicity is normally reversible. It manifests as abnormal serum ALT and/or aspartate aminotransferase (AST) levels with or without clinical symptoms of liver injury.

2.8 PHARMACOVIGILANCE: IMPORTANCE OF ADVERSE DRUG REACTIONS REPORTING OF ANTIRETROVIRAL DRUGS

The World Health Organisation (2002a) defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse

effects or any other medicine-related problem. The specific aims of pharmacovigilance according to the World Health Organisation (2004) include:

- improvement of patient care and safety in relation to the use of medicines and all medical and paramedical interventions,
- improvement of public health and safety in relation to the use of medicines,
- contribution to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and
- promotion of understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

The scope of pharmacovigilance includes issues related to herbal, traditional and complementary medicines; blood products, biological, medical devices and vaccines; substandard and counterfeit medicines; medication errors and irrational used of medicines; and antimicrobial resistance (World Health Organisation, 2002a: 7). The Programme for International Drug Monitoring was established by the World Health Organisation as a result of the thalidomide tragedy in 1960 (World Health Organisation, 2002a). Thalidomide was widely used in the late 1950s and early1960s for the treatment of nausea in pregnant women and it became apparent in the 1960s that thalidomide treatment resulted in severe birth defects in thousands of children (Kim & Scialli, 2011). Pharmacovigilance activities come within the scope of the criteria of quality, safety and efficacy, as new information is accumulated on the medicinal product under normal conditions of use in the marketing situation (European Commission, 2004a: 13).

Adverse drug reactions experienced by patients are very important to record and report in order to improve patient safety. It is important for a country to have a national pharmacovigilance centre to help in planning and implementing pharmacovigilance activities. The national centres play a critical part in public awareness of drug safety. Drug safety is very vital in public health and clinical practice as a result there is a great need for pharmacovigilance centres in different countries (Word Health Organisation, 2002a: 5). Medicines cause different side effects which are sometimes not seen during clinical trials and it could be because the medicines are tested in a controlled scientific environment with a limited number of participants (World Health Organisation, 2006c: 14). After approval, the medicines are released into the public market. Consequently, assessment and monitoring of new and medically still evolving medicines on safety and effectiveness in an uncontrolled

environment is very crucial (World Health Organisation, 2004: 1). Pharmacovigilance plays a great role in national drug policy development and includes medicines cost, forecasting and budgeting (United Nations Industrial Development Organisation, 2010: 11). This helps in the development of the essential medicines lists and the standard treatment guidelines. National administration is accountable for the availability of good quality, safe and effective medicines and for their proper use. As a result, the presence of a functional well-equipped national regulatory agency and a pharmacovigilance centre are fundamental to the accomplishment of these functions (World Health Organisation, 2004: 2-3).

2.8.1 Pharmacovigilance of ART

Antiretrovirals are very toxic and need regular monitoring therefore; reporting of ADRs will help enhance clinical management of HIV-positive patients (World Health Organisation, 2006d: 11). Some of the duties to be carried out by a pharmacovigilance centre comprise of information dissemination to practitioners, patients and the public on benefit, harm, effectiveness and risk of medicines (World Health Organisation, 2002a: 11). Adverse drug reactions (ADRs) attributable to antiretroviral medicines constitute 17 per cent of Individual Case Safety Reports (ICSR) received by the Nigerian National Pharmacovigilance Centre, through spontaneous reporting system across the country in September 2009 (National Agency for Food and Drug Administration and Control, 2009b: 1).

There is limited information on toxicity profile of ARVs in the developing countries. This is due to the presence of specific factors and conditions which are different from those in the developed countries. These factors include the existence of comorbid conditions such as tuberculosis (TB), malaria and other infections; malnutrition; heavy reliance on traditional and/or alternative therapies; insufficient numbers of trained doctors and pharmacists; abuse of prescription-only medicines; and likelihood of medicine interactions (World Health Organisation, 2007b: 1). Additionally, the local systems for the delivery of health care rely on people who may not have the necessary training, knowledge or expertise, and the medicine regulatory systems are either non-existent or are not adequately equipped to deal with medicine safety issues. The monitoring of ARVs in these countries is of utmost importance.

ARV medicines are associated with significant safety concerns including serious ADRs, with both short-term and long-term effects. The outcome of the long-term adverse effects is unknown. The major events linked to the use of antiretroviral medicines include altered body

fat distribution (lipodystrophy), anaemia and neutropenia, hypersensitivity reactions, hepatic disorders, acute pancreatitis, altered bone structure (osteopenia and osteoporosis), muscle damage (myopathy) of the new-born and lactic acidosis (World Health Organisation, 2009: 3). This may negatively affect a national ARV programme and patient adherence. When confidence in medicine safety is lost, patients may stop taking their ART medicines leading to failure of therapy and possible development of drug-resistant viral strains thus reduced medicine efficacy.

2.8.2 Proper documentation of ADRs

For proper assessment and monitoring of ADRs, the following should be recorded: all new events even if minor; change in a pre-existing condition; abnormal changes in laboratory tests; accidents; all deaths with date and cause; and possible interactions (pharmaceutical or traditional medicines; oral contraceptives, tobacco, alcohol or other commonly ingested products which the patient may not realise are "medicines") (World Health Organisation, 2007b: 6). It is important that non-serious adverse events are recorded, particularly if they are likely to affect adherence. In addition, if only known adverse reactions are reported, unexpected adverse reactions will not be identified. Previously unrecognised adverse reactions are always found when using new medicines. It is important to identify them, understand their importance, determine their incidence and identify the risk factors as quickly as possible (World Health Organisation, 2007b: 6). The main pharmacovigilance methods proposed include spontaneous reporting, cohort event monitoring and targeted spontaneous reporting (World Health Organisation, 2011c).

In spontaneous reporting, the health professionals and pharmaceutical manufacturers voluntarily submit suspected adverse drug reactions to the national regulatory authority. This type of reporting depends on clinicians and other health professionals being encouraged to report details of suspected ADRs in patients on ARV treatment. A challenge with this method is under-reporting. Spontaneous reports have a major role in the identification of safety signals once a medicine is marketed. They can also provide important information on at-risk groups, risk factors, and clinical features of known serious ADRs. This requires fewer human and financial resources than in cohort event monitoring or targeted spontaneous reporting (Joined United Nations Programme on HIV/AIDS & World Health Organisation, 2011: 1). The needs of the countries differ so it is important for the countries to adopt their own reporting form for spontaneous reports. The completed reports can be mailed individually or

in bulk, faxed, sent electronically (if forms are available on the Internet or by email) or reports can be made by telephone (World Health Organisation, 2007b: 10).

In the cohort event monitoring, all adverse events occurring to a person taking antiretroviral drugs are collected regardless of the causality or relationship with the antiretroviral drugs (Joined United Nations Programme on HIV/AIDS & World Health Organisation, 2011: 1). The advantages of the cohort event monitoring over the spontaneous reporting include the ability to produce rates, rapid results, early detection of signals, fewer missing data and less reporting bias. However, the cohort event monitoring requires more resources than spontaneous reporting.

The targeted spontaneous reporting is a method that builds on the principles of both spontaneous reporting and cohort event monitoring. It advances pharmacovigilance within a treatment cohort as a best practice that improves the quality of care (Joined United Nations Programme on HIV/AIDS & World Health Organisation, 2011: 1). Targeted spontaneous reporting enables focus on a specific drug of interest (such as tenofovir or zidovudine), a specific population of interest (such as women receiving extended antiretroviral prophylaxis or treatment for preventing the mother-to-child transmission of HIV or people switching from stavudine to tenofovir) or a specific adverse drug reaction (such as anaemia) (Pal *et al.*, 2013: 77). For this method to be effective there has to be voluntary reporting of suspected adverse reactions by health professionals. As with the cohort event monitoring, everyone within a treatment cohort is monitored, but only data covering the area of interest are collected, unlike the cohort event monitoring, which actively follows up people to collect data on all events (Joined United Nations Programme on HIV/AIDS & World Health Organisation, 2011: 1). Lastly, the targeted spontaneous reporting provides a monitoring method that is affordable, feasible and sustainable in the context of lifelong antiretroviral therapy in settings with limited financial and human resources.

2.8.3 Recording and reporting of ADRs by health professionals

Monitoring of drug safety is a basic component in the context of effective medicines utilisation and high quality medical care. Identification and reporting of ADRs is mostly done by health professionals confident of their aptitude to detect, manage and prevent these reactions. Major role in ADR monitoring and reporting is played by health training

organisations and national pharmacovigilance centres by including principles and methods of pharmacovigilance as a course in schools of pharmacy, medicine and nursing (World Health Organisation, 2002a: 24). When an unknown ADR occurs due to medication, it is easy for the public health sector to notice and take appropriate action which may include withdrawal of that particular drug from the market (David *et al.*, 2010: 2). Occurrence of adverse effects (known or unknown), drug interactions (with foods or other medicines) and other risk factors are observed during the years of post-medicine release into the public (World Health Organisation, 2004: 1).

Healthcare worker/professionals may record and report ADRs. They may work in the public or private health sectors. The following people are potential reporters of ADRs: physicians, pharmacists, pharmacy technician, nurses, public health programmes, pharmaceutical companies, and patients or patient representatives (World Health Organisation, 2009: 3). Additionally, the community health workers should be encouraged to detect and report, preferably to the clinician who prescribed the treatment, or directly to the pharmacovigilance centre.

2.8.4 Pharmacovigilance in Africa

The European Union (EU) pharmacovigilance system is one of the most advanced and comprehensive systems in the world and it ensures a high level of public health protection throughout the Union (European Commission, 2013). The medicinal products in the EU are subjected to strict testing and assessment for quality, efficacy and safety before authorization for use by the public. In public use, the medicinal products are continually monitored to assure that any aspect which could impact the safety profile of the medicine is detected, assessed and necessary measures taken. According to the European Commission (2013), the legal framework of pharmacovigilance for medicines marketed within the EU is provided for in Regulation (EC) No 726/2004 (2004b) with respect to centrally authorised medicinal products and in the Directive 2001/83/EC (2001) with respect to the nationally authorised medicinal products (including those authorised through the mutual recognition and decentralised systems). The Commission Implementing Regulation (EU) No 520/2012 (2012) stipulates operational details in relation to certain aspects of pharmacovigilance to be respected by marketing authorisation holders, national competent authorities and European Medicines Agency (EMA). The EMA has also released good pharmacovigilance practice

guidelines in order to facilitate the performance of pharmacovigilance activities (European Medicines Agency, 2013).

In the United States, the Food and Drug Administration (FDA) has been conducting pharmacovigilance activities. Post-market drug adverse event surveillance is a core Food and Drug Administration (FDA)/ Centre of Drug Evaluation and Research (CDER) pharmacovigilance function supporting the agency's efforts to ensure the safety of drugs and therapeutic biologics (Food and Drug Administration, 2011: 4). The CDER's pharmacovigilance programme uses several processes, methodologies and data sources to detect, characterise and prioritise serious adverse events due to drugs and therapeutic biologics (Food and Drug Administration, 2011: 4). The FDA has developed several guidance documents related to safety of drug and biological products. The U.S. legislation has been significantly enhanced by the Title IX of the Food and Drug Administration Amendments Act (2007). As a result, the FDA conducts a bi-weekly screening of the Adverse Event Reporting System database and posts a quarterly report, available on internet, of any new safety information or potential signal of a serious risk. Secondly, the FDA is empowered to require the company to submit a Risk Evaluation and Mitigation Strategy (REMS), when it is not sure that the benefits of its product outweigh the risks. Thirdly, it is entitled to require post-approval studies or trials to assess a known risk or signals of serious risk and to identify unexpected serious risk emerging from available data, if the existing information is not sufficient to fulfill this assessment. Lastly, the FDA has authority to sanction with civil penalties and the misbranding of the drug all applicants who violate duties related to REMS requirements or post-approval studies/trials (Montanari-Vergallo, 2013: 1000e105).

About seven per cent of the 46 sub-Saharan African countries have a moderately developed medicine regulatory capacity and of the remaining, about 63 per cent have minimal capacities whereas 30 per cent do not have a National Medicines Regulatory Authority (NMRA) in place (World Health Organisation, 2009b). According to the Strengthening Pharmaceutical Systems (2011), of the 46 sub-Saharan Africa countries, 87 per cent do not have a functional pharmacovigilance system, 59 per cent do not have a national policy related to medicine safety, 70 per cent lack legislation to monitor adverse events, 26 per cent do not have a national pharmacovigilance centre, and 61 per cent lack a medicine safety advisory committee. Signal generation and data management by pharmacovigilance systems in sub-

Saharan Africa countries if limited. As stated by the Strengthening Pharmaceutical Systems (2011: 16), "Although 74 per cent have spontaneous reporting systems, less than 50 per cent monitor product quality, medication errors, and treatment failures through existing systems." Risk assessment and evaluation is limited in sub-Saharan Africa countries due to lack of active approaches to identify and evaluate medicine-related risks. Since only two of the 46 surveyed countries collected more than 100 reports per million population in 2010, and most countries generated less than 20 reports per million population per year, the reporting rate is minimal in most sub-Saharan countries (Strengthening Pharmaceutical Services, 2011: 17).

A consortium of partners has been formed through the African Medicines Regulatory Harmonisation (AMRH) Programme to accelerate African regulatory harmonisation building on existing regional effort, political mandates, and initiatives (World Health Organisation, 2009a). The aim is to form five to seven regional medical regulatory authorities out of Africa's 54 independent national medical regulatory authorities (Systems for Improved Access to Pharmaceuticals and Services, 2012: 3). They will possess stronger institutionalised regulatory capacity based on the Economic Community of West Africa States, the East African Community, and the South African Development Community. The regulatory harmonisation initiatives in Africa include quality and safety of medicines being provided to the public. Due to lack of resources, absence of legislation and regulatory capacity; the growth of the pharmaceutical industry is hindered. As a result, a pharmaceutical manufacturing plan of Africa was developed in 2005 (Systems for Improved Access to Pharmaceuticals and Services, 2012: 3).

Poor product quality, adverse drug reaction, and medication/prescription errors have a negative impact on healthcare, particularly the patients' health. Limited numbers of the developing countries have the structures, systems, or resources in place to design and implement a functional medicine safety system, and countries often lack unbiased, evidence-based information to help guide regulatory and patient safety decisions (World Health Organisation, 2009b). There is a big pharmaceutical market in sub-Saharan countries with limited regulatory activity for health products. As a result, little or no attention is paid to medicine safety. Membership of the sub-Saharan countries to the World Health Organisation programme on international drug monitoring does not always indicate that these countries have efficient pharmacovigilance systems (Systems for Improved Access to Pharmaceuticals and Services, 2012: 3).

The national reporting systems in the sub-Saharan countries are not useful as the health professionals do not adhere to the system. These countries have a narrow capacity to assess, evaluate and make decisions based on signals received from reports due to under reporting by the health professionals. This leads to insufficient data being available. There is also a limited involvement of the sub-Saharan pharmaceutical industry in monitoring of medicine safety. Post-marketing surveillance by the pharmaceutical industry is either minimal or absent apart from that conducted by South Africa as it has good systems and structures in place (Systems for Improved Access to Pharmaceuticals and Services, 2012: 3).

The World Health organisation pharmacovigilance toolkit consists of pharmacovigilance tools, resources, and guideline which were generated to support pharmacovigilance systems implementation in the resource-limited countries (World Health Organisation, 2012d). It will assist the countries with quantification of resources needed for establishing a functional pharmacovigilance system and support proposal writing for funding from donors with pharmacovigilance requirements. This toolkit also consists of toolkits specifically for malaria and HIV/AIDS.

There are 23 official members and 10 associate members of the World Health Organisation international drug monitoring program in sub-Saharan Africa, and most of them became members after 2000, excluding South Africa which became a member in 1992, Tanzania in 1993, and Zimbabwe in 1998 (Strengthening Pharmaceutical Services, 2011: 37). Relevant policy and regulations are non-existent. This is one of the limitations for enforcing medicine safety monitoring. The absence of the legal framework for pharmacovigilance in Burkina Faso, Ghana, and Uganda minimised the capability of the regulatory authorities to enforce the responsibilities of the marketing authorisation holder for product stewardship (Strengthening Pharmaceutical Services, 2011: 38). These countries have substantial pharmaceutical industries in Africa and almost none of the pharmaceutical companies were committed to post-marketing surveillance.

In Kenya, a pharmacovigilance system was launched in 2009 with the mandate of improving patient safety and monitoring of product quality and the country is a member of the World Health Organisation International Drug Monitoring Program (Pharmacy and Poisons Board, 2010: 1). The department of Pharmacovigilance at the Pharmacy and Poisons Board has been

actively involved in designing tools and guidelines for detection and reporting of ADRs. In December 2007, the Guidelines for the National Pharmacovigilance System in Kenya were developed followed by sensitisation of healthcare workers through a national sensitisation workshop in Nairobi and through ad hoc meetings as opportunity arose (Ministry of Medical Services, 2009: 4). The guidelines were established to help health workers to participate in the process of continuous surveillance of safety and efficacy of the pharmaceutical products used in clinical practice. Additionally, they assist in achieving the ultimate goal of providing safe and effective treatment to the public. According to the Ministry of Medical Services (2009: 13), all healthcare professionals including clinicians, pharmacists, dentists, nurses, traditional medicine practitioners and the public are encouraged to report ADRs.

Kenya is one of the resource-limited countries. Pharmacovigilance is a challenge but there are also opportunities. The opportunity to set up pharmacovigilance systems emerged due to increasing international donor funding for vertical programmes, and the introduction of new molecules for the management of HIV/AIDS, TB and malaria (Ministry of Medical Services, 2009: 7). The pharmacovigilance system in Kenya is strong due to the presence of the legal framework, availability of various pharmacovigilance tools (yellow and pink forms), strong collaboration with the public health programmes, extensive implementation of post-marketing surveillance activities, and communication systems for sharing information (Systems for Improved Access to Pharmaceuticals and Services, 2012: 3). Challenges faced by the Kenyan pharmacovigilance system include the absence of a national pharmacovigilance policy; limited risk assessment, evaluation and management activities; and limited capacity for data management and pharmacovigilance information communication and dissemination (Systems for Improved Access to Pharmaceuticals and Services, 2012: 3). There is a committee of Expert Safety Review Panel in Kenya which addresses issues in a sporadic manner. This panel met twice in 2010 and discussed issues related to clinical trials (Strengthening Pharmaceutical Services, 2011: 40).

The Democratic Republic of the Congo (DRC) has implemented a spontaneous reporting system in 2009 that builds on the existing health system (Centre National de Pharmacovigilance, 2013: 1). The National Centre for Pharmacovigilance (CNPV), established in 2009 by the Ministry of Health, is affiliated with Faculty of Pharmaceutical Sciences and Faculty of Medicine in the University of Kinshasa (Strengthening Pharmaceutical Services, 2011: 93). The attention of this system minimally covers the local

communities thus limiting the coverage of the pharmacovigilance system. The Government of the Democratic Republic of the Congo is dedicated to supporting pharmacovigilance through the National Pharmacy Policy of 2005 (Systems for Improved Access to Pharmaceuticals and Services, 2012). Several trainings were carried out by CNVP to sensitise the health centres and the hospitals. The reporting forms addressing ADRs and treatment failure have been distributed to hospitals, yet the reporting rate is very low 2.4 per million in 2010 (Strengthening Pharmaceutical Services, 2011: 93). The capacity to process the data, evaluate the risks, and communicate the information is developing.

Pharmacovigilance activities in the public health programme and the health facilities in the DRC are not implemented. Collaboration between CNPV and Public Health Programmes (PHPs) has not been started. Although, there is a focal person in the TB and immunisation programmes and some healthcare workers in the HIV/AIDS programme trained on documenting and reporting adverse events (Strengthening Pharmaceutical Services, 2011: 93). The pharmacovigilance system strengths include the presence of a functional National Pharmacovigilance Centre with a clear mandate, and availability of various pharmacovigilance tools (reporting forms, training tools, data collection tools, analysis tools, awareness campaign tools, and communication tools) (Systems for Improved Access to Pharmaceuticals and Services, 2012). The major challenge is the non-functional pharmacovigilance National Advisory Committee as it limits decision making regarding pharmacovigilance data and information. There is also absence of national guidelines on good pharmacovigilance practice, low reporting by the health professionals, and absence of funding and collaboration with the pharmaceutical companies (Systems for Improved Access to Pharmaceuticals and Services, 2012).

The first attempt to establish a medicine monitoring programme in Senegal was started in 1998 by the Ministry of Health, although the programme became active in 2009 with a reinforced policy to implement a national pharmacovigilance system under the responsibility of Direction de la Pharmacie et des Laboratoires (DPL) (Ministere de la Sante et de la Prevention, 2009). Function of DPL is to monitor and coordinate all activities related to medicine safety issues at the national level. The national pharmacovigilance guidelines provide standards and directions on definitions; both passive and active approaches; scope of pharmacovigilance including medication errors, product quality, and treatment inefficacy; roles and responsibilities of stakeholders; and processes for coordinating the activities in

Senegal (Direction de la Pharmacie et des Laboratories, 2010). The health facilities including hospitals, regional medical centres, and health centres are not active in monitoring and reporting adverse events. The organisational structure, the legal framework for pharmacovigilance, and collaboration with the in-country and international stakeholders exists to support pharmacovigilance activities in Senegal, but functions of the national pharmacovigilance system to collect, analyse, and use medicine safety and quality information need to be strengthened (Strengthening Pharmaceutical Services, 2011: 105).

The Medicines Control Council (MCC), under the Medicines and Related Substances Control Act (101 of 1965) oversees South Africa's regulation of medicines, including pharmacovigilance, and ensures ethical standards in advertisement and promotion of medicines (Strengthening Pharmaceutical Services, 2011: 106). The MCC established a National Adverse Drug Event Monitoring Centre (NADEMC) in collaboration with the University of Cape Town in 1987 to monitor safety of medicines by voluntary reporting of suspected adverse events by the industry and the health professionals (Strengthening Pharmaceutical Services, 2011: 106). Pharmacovigilance system in South Africa is very effective as it has a strong policy, legal, and regulatory framework as well as established systems and structures for pharmacovigilance. In South Africa, pharmacovigilance is in two parts, namely: (a) regulatory pharmacovigilance covering quality and efficacy of all medicines, and (b) programmatic pharmacovigilance covering medicines used in public health programmes (Systems for Improved Access to Pharmaceuticals and Services, 2012). They mainly use spontaneous reporting which also covers poor quality medicine and medication errors. Fifty per cent of all ADR reports from Africa are from South Africa even though there is a wide variation in reporting between different regions or provinces (World Health Organisation, 2012d).

The South African pharmacovigilance system is strengthened by the presence of a National Medicines Policy and a National Policy related to pharmacovigilance and a medicine safety, legal mandate to monitor medicine-related ADRs, and legal provision for MAH to report all serious ADRs to the NMRA (Systems for Improved Access to Pharmaceuticals and Services, 2012). They are challenged by lack of significant acknowledgement of the importance of pharmacovigilance by the Government of South Africa, lack of proper collaboration with the pharmaceutical industry, poor coordination and collaboration in data management, and lack

of capacity for pharmacovigilance by the Ministry of Health and the NMRA (Systems for Improved Access to Pharmaceuticals and Services, 2012).

Nigeria has a sturdy policy, law, and regulatory framework for pharmacovigilance. The national mandate for pharmacovigilance and the National Agency for Food and Drug Administration and Control (NAFDAC) were established in 1993, requiring NAFDAC to ensure the quality, safety, and efficacy of regulated medicine products (National Agency for Food and Drug Administration and Control, 2009a). This country has had its fair share of ADRs where patients lost lives. According to Akunyili (2005), 14 children were reported dead after being administered chloroquine phosphate injections in 1989; and 109 children died after taking paracetamol syrup produced with the toxic ethylene glycol solvent in 1990. The pharmacovigilance system in Nigeria is strengthened by the presence of various pharmacovigilance tools (guidelines for detecting and reporting ADRs, and individual case safety report forms), efficient communication of safety information, and pharmacovigilance is strong within public health programmes.

There is the Direction Générale de la Pharmacie, du Médicament et des Laboratoires (DGPML) in Burkina Faso. The DGPML is the National Medicines Regulatory Authority (NMRA) at the Ministry of Health responsible for drug registration, development, and enforcement of policy and regulations; regulation of pharmacies, wholesalers or distributors, and hospital pharmacies; control of medicines promotion and advertisement; coordination of the procurements in the public sector; quality assurance; control of clinical trials; and safety monitoring of medicines (Ministere de la Sante, 2010). The Ministry of Health's NMRA established a pharmacovigilance unit which coordinates activities related to medicines safety and quality at the national level and adopted an operational plan for the implementation of a national safety monitoring system in 2008 (Strengthening Pharmaceutical Services, 2011: 91).

The institutional capacity for medicine safety monitoring in Burkina Faso is frail. There is the absence of a safety advisory committee or a national pharmacovigilance guideline, lack of training and skills for staff members to conduct pharmacovigilance activities (Strengthening Pharmaceutical Services, 2011: 92). The pharmacovigilance unit also lacks the means of communication, such as newsletters or bulletins, to widely disseminate safety information to stakeholders and the public. Pharmacovigilance is not well integrated into the health system

of Burkina Faso as none of HIV/AIDS, TB, and malaria programmes have structure, guidelines, or policy framework to implement pharmacovigilance activities (Strengthening Pharmaceutical Services, 2011: 92).

The pharmacovigilance system in Tanzania was established in 1989 as a drug information centre and was called Tanzania Drug and Toxicity Information Services (TADATIS) (Management Science for Health, 2006: 2). The TADATIS functions include promoting, reporting and analysing ADRs, with reports submitted to the World Health Organisation. Additionally, it provided pharmaceutical information and education for the public and the healthcare professionals or workers on rational use and prescribing by means of radio, television, bulletins, and newspapers (Management Science for Health, 2006: 2). The medicines safety advisory committee in Tanzania solely focuses on issues related to medicine safety, clinical pharmacology, and regulatory affairs. The aforementioned activities were handled by the Drug Registration Committee previously (Strengthening Pharmaceutical Services, 2011: 40). The downside is that this committee was established recently in October 2010, as a result, there is lack of formal activity (Strengthening Pharmaceutical Services, 2011: 41).

The sources of information in Tanzanian pharmacovigilance database were conducted by the use of spontaneous reports, and adverse events following immunization (AEFI) reports. Additionally, data from active surveillances, PHPs, clinical trials, and pharmaceutical industry was not found in the database (Strengthening Pharmaceutical Services, 2011: 44). The pharmacovigilance system faces challenges due to lack of awareness on ADRs by the healthcare professionals and reporting by the pharmaceutical industry which is not mandatory, technical and financial resources (Management Science for Health, 2006: 3). In addition, there is weak organisational structure leading to uneven distribution and collection of standardised ADR reporting forms (yellow card) from health facilities.

Ghana's Food and Drug Board (FDB) is the national regulatory body under the Ministry of Health, established by the Food and Drug Act (1992), and the Safety Monitoring Unit in the FDB. It is the national pharmacovigilance coordinating centre. The responsibility of FDB is to regulate the manufacture, importation, exportation, distribution, and the ethical standards in the use and advertisement of medicines, food, cosmetics, medical devices, and household chemicals (Strengthening Pharmaceutical Services, 2011: 95). The University of Ghana

Medical School began practicing pharmacovigilance activity in 1992 at the Centre for Tropical Clinical Pharmacology and Therapeutics. Ghana has developed basic structures for conducting pharmacovigilance activities including a national pharmacovigilance unit with a mandate and structure, designated staff members, functional information and technology infrastructure, and collaboration with the World Health Organisation/Uppsala Monitoring Centre since 2001 (Strengthening Pharmaceutical Services, 2011: 95). Some of the challenges affecting the implementation of pharmacovigilance activities are the lack of a dedicated pharmacovigilance budget, a safety bulletin, pharmacovigilance training for the healthcare professionals/workers, a mechanism to coordinate activities, and the pharmacovigilance guidelines.

The Therapeutics Information and Pharmacovigilance centre (TIPC) in Namibia was established in 2007 to provide both therapeutic information and monitoring safety of medicines that are already on the market (Ministry of Health and Social Services, 2011: 14). The patients, families and the community health workers are encouraged to immediately report any adverse event possibly associated with the use of medicines to their health care provider or directly to the TIPC using a simplified reporting form. The healthcare workers, after conducting investigations, are required to immediately report any suspected ADRs, medicine interactions, and unusual effects to the TIPC by fax, email, or post on the safety yellow form.

The Uganda National Pharmacovigilance Centre (NPC) was established in 2005 and became a member of the World Health Organisation Programme for International Drug Monitoring in 2007 (Strengthening Pharmaceutical Services, 2011: 111). It is situated in the Drug Information Department of the National Drug Authority. A national drug policy (2002) contains a basic framework for pharmacovigilance, but there is no legislation or regulation to provide a legal mandate (Strengthening Pharmaceutical Services, 2011: 111). The NPC is well equipped with manuals and standard operating procedures for handling spontaneous reports, providing acknowledgment to reporters, conducting causality assessment for each case report, and providing feedback to the reporter on the assessment outcome (Strengthening Pharmaceutical Services, 2011: 111).

Pharmacovigilance system in Uganda has been decentralised by forming pharmacovigilance centres in regional referral hospitals. There are 14 regional centres established throughout the

country, which are managed by a regional coordinator (Strengthening Pharmaceutical Services, 2011: 111). The regional centres' activities include increasing awareness of monitoring adverse events among the district health workers and the hospital staff, distributing reporting forms, and collecting the forms. Information dissemination by the NPC is done through publishing pharmacovigilance newsletters containing important regulatory decisions, summaries of serious ADR reports received, and safety and efficacy issues identified from external sources (Strengthening Pharmaceutical Services, 2011: 113). Additionally, the press releases and safety alerts are also used for dissemination of important risks. Effective communication to the healthcare workers and the consumers is a challenge.

2.9 CHAPTER SUMMARY

This chapter has discussed the prevalence of HIV/AIDS in Lesotho, the health care system in Lesotho, antiretroviral drug supply in Lesotho, classification of antiretroviral drugs, the importance of adverse drug reactions reporting, the relationship between laboratory monitoring of patients on ART, antiretroviral treatment guidelines of Lesotho and World Health Organisation 2010 and other related guidelines.

CHAPTER 3: EMPIRICAL INVESTIGATION

3.1 INTRODUCTION

An in-depth discussion on research objectives, empirical research methodology, data sources and analysis, reliability and validity of the data collection tools and ethical aspects will be focused on in this chapter.

3.2 GENERAL RESEARCH OBJECTIVE

To assess the prevalence and documentation of ADR in the private and public antiretroviral clinics in Maseru district, with special reference to zidovudine (AZT)-based regimens (AZT/3TC/NVP and AZT/3TC/EFV) and tenofovir (TDF)-based regimens (TDF/3TC/NVP and TDF/3TC/EFV).

3.3 SPECIFIC RESEARCH OBJECTIVES

The study consists of literature review and empirical investigation. The research objectives of the two phases above included the following:

3.3.1 Literature review

The specific research objectives of the literature review included:

- To outline the treatment protocols as stated by the Lesotho 2010 and World Health Organisation 2010 antiretroviral treatment guidelines and other related treatment guidelines.
- To describe ARV drugs according to different classification systems and possible side effects.
- To emphasise the importance of adverse drug reactions reporting on antiretroviral drugs.
- To determine from the literature how proper documentation of ADR can be carried out and maintained to improve patient safety.
- To evaluate the role of health professionals in recording and reporting of adverse drug reactions.

3.3.2 Empirical investigation

The specific research objectives of the empirical investigation were:

- To assess the frequency at which adverse drug reactions (ADRs) occur in patients taking either tenofovir or zidovudine based regimens.
- To evaluate the laboratory tests (e.g. CD4 cell count, blood urea nitrogen (BUN), haemoglobin profile, neutrophil count, alanine aminotransferase (ALT) and creatinine clearance) results for any reflection of the presence of adverse drug reactions. The normal ranges for the laboratory tests are as follows: creatinine measured in millilitres/minute (ml/min) in males 97 to 137 and in females 88 to 128 (Landry & Bazari, 2011), Hb in blood includes 13.8 to 17.2 grams per decilitre (gm/dL) in male and 12.1 to 15.1 gm/dL in female (Bunn, 2011), neutrophils in the body is 40 to 60 per cent (Dinauer & Coates, 2008), ALT found in the liver at 10 to 40 international units per litre (IU/L) (Pratt, 2010), and blood urea nitrogen at 2.1 to 7.1 mmol/L (Landry & Bazari, 2011).
- To evaluate how documentation of adverse drug reactions is being carried out by health professionals.
- To assess health professionals understanding of adverse drug reactions recording or reporting.
- To determine how health professionals manage adverse drug reactions.

3.4 RESEARCH METHOD

3.4.1 Study design

The research was divided into two phases. The first phase was a cross-sectional quantitative retrospective drug utilisation review study which focused on the occurrence of adverse drug reactions in patients taking zidovudine (AZT) and tenofovir (TDF). Cross sectional studies are studies of total populations or population groups in which information is collected about the present and past characteristics, behaviours, or experiences of individuals (Bonita *et al.*, 2006: 44). This study was retrospective because data to be used in the study was collected and recorded previously in the patients' medical files. Drug utilisation is defined by World Health Organisation in 1977 as "the marketing, distribution, prescription, and use of drugs in society, with special emphasis on the resulting medical consequences" (World Health Organisation, 2003: 8).

Patients' medical records were used to capture demographic data, medical history, laboratory results and adverse drug effects. The records were hard copies of clinical and medical assessment of patients from when they tested positive. They are kept in a filing cabinet at the clinics in the Maseru health district. In the second phase, a survey in a form of questionnaires involving health professionals was conducted.

3.4.2 Study sites

The study was conducted in the Maseru district. Sankatana Antiretroviral treatment clinic was the study site for phase one where patient medical records were used to gather data. The private and public antiretroviral clinics situated in Maseru district Lesotho were used as study sites in the second phase of the research. A list of these clinics is provided in table 3.1 below. The questionnaires were distributed to medical doctors, nurses, pharmacists and pharmacy technicians in all these clinics.

Table 3.1: Names of private and public ART sites for the second phase of the study.

Antiretroviral site	Name of the site	ART site manager
Hospitals		
Public	St. Joseph's Hospital	Medical officer
Clinics		
Private	Khanya medical centre	Medical officer
	Healthy lifestyle and diabetes centre	Medical officer
Public	Sankatana ART centre	Medical officer
	Baylor college of medicine	Medical officer

3.4.3 Study population

Phase one

The preliminary total population of HIV-positive adult patients in Sankatana Antiretroviral clinic was estimated to be 1 423 by the clinic statistician. Data was collected retrospectively from the medical files of patients on both AZT- and TDF- based regimens. All patient files on the mentioned regimens were used for data collection by the researcher. The total number of patients on AZT- and TDF- based regimen was 300 out of the total population of 1423 patients on antiretroviral treatment. The following inclusion and exclusion criteria were used in study sample selection:

Inclusion criteria

Tenofovir- or zidovudine- based regimens are the first line regimens used in Lesotho (Ministry of Health and Social Welfare, 2010: 48). Adverse drug reactions due to antiretroviral therapy occur within the first few months after treatment commencement; some are immediate reactions while others come after some time. Adverse drug reactions occur within the first year of treatment initiation and are the common reasons for treatment discontinuation among HIV-positive patients (Borras-Blasco *et al.*, 2008: 879). The inclusion criterion was as follows:

- Medical records for patients who have been on ART for more than six months and getting their services at Sankatana Antiretroviral clinic.
- Patients who are on either TDF- or AZT- based regimens and are both male and female falling in an age range of 18 years and above.

Exclusion criteria

These included:

- HIV-positive patients who had not started ART.
- All HIV/AIDS patients who were transferred out of the clinic.
- HIV/AIDS patients who died during the study period.
- Patients who are not on either TDF- or AZT- based regimens.
- Patients younger than 18 years.

Phase two

Questionnaires were distributed to health professionals working directly with the patients as prescribers and dispensers of ART medicines in the clinics in the Maseru district. The study sample respondents are shown in the table 3.2 below.

Table 3.2: Number of health workers involved per site

Site name	Medical doctors	Nurses	Pharmacists	Pharmacy technicians
Sankatana ART centre	3	5	2	4
Khanya medical centre	1	3	0	1
Healthy lifestyle and diabetes centre	2	4	0	1
Baylor college of medicine	15	8	3	5
St. Joseph's Hospital	*consults	4	2	3
Total (65)	**21**	**24**	**7**	**13**

*Consults- consultant doctors from Baylor College of medicine

3.5 DATA SOURCE FOR THE EMPIRICAL INVESTIGATION

3.5.1 Survey forms

Survey forms were used as data collection tools and each phase had its own survey form. They were used as follows:

In phase one, data was captured by the researcher from the patient medical records using a drug utilisation data collection form *(refer to appendix C)*. For the second phase of the study, a structure questionnaire was used to interview health professionals. The health professional's questionnaire was a structured questionnaire with questions divided into four sections. The sections included questions on demographic information, knowledge-related questions, health professional's opinion and questions about the influence of the professional environment respectively *(refer to appendix E)*.

A structured questionnaire was used because many participants can be questioned in a short time interval, it can be repeated easily, and respondents may be more willing to reveal personal information than in an interview. Close-ended questions were used, where participants were provided with possible answers and participants asked to select an appropriate answer. Open-ended questions were included to obtain free responses from participants. The major part of the questionnaire consisted primarily of close-ended questions as they are easier to answer, answers provided are easier to analyse, compare and interpret.

The participating health professionals included doctors, pharmacists, nurses and pharmacy technicians. These health workers were involved directly with ART through dispensing (pharmacists and pharmacy technicians), prescribing (doctors), and both prescribing and dispensing (nurses). They were all expected to fill in the ADR form, if their patients experience one or more ADRs.

3.5.2 Time period

Phase one

The data collected from the patients' medical files was data recorded in the medical files from 1st January 2010 to 31st December 2011 time period.

Phase two

Questionnaires were distributed to the health professionals.

3.5.3 Field work and data capturing

Phase one

The researcher collected data from the patients' medical records using a data collection sheet. The type of information gathered included patient demographic data, medical history, adverse effects and laboratory data which included CD4 cell count, viral load, haemoglobin profile, creatinine clearance, neutrophil count and alanine aminotransferase (ALT) *(refer to appendix C)*.

Phase two

The health professionals' questionnaires were distributed to different health workers by the researcher and collected after a week to give them time to answer all questions.

3.6 DATA ANALYSIS

Patient body mass and laboratory tests (creatinine clearance, urea, haemoglobin profile, CD4-cell count and ALT) are the measurements which were used to assess the clinical well-being of patients and ADRs that may be experienced. Antiretroviral drugs are foreign to the body and can cause harm if the patient is not monitored using body mass and laboratory tests. Patient monitoring assist in determining the efficacy, toxicity and therapy compliance. Patient on ARVs are to be monitored using laboratory tests to assess their well-being and if there is any occurrence of an adverse drug reaction (ADR) (Mehta *et al.*, 2007: 403). Laboratory

monitoring should go together with clinical assessments. Body mass loss in HIV-positive patients predicts either a progression of disease, opportunistic infection or death. It is used as a warning sign to prescribers to start investigations and treatment (National Department of Health South Africa, 2010: 28). The laboratory tests and body mass were explained in detail in chapter two.

3.6.1 Variables

The variables used in statistical analysis included age, sex, patient body mass, adverse drug reactions codes, initial ART regimens, and current ART regimens. Normal distribution was assumed and the 25^{th} percentile was used to come up with different age and body mass groups. Age groups used were those of patients less than 35 years, greater than 35 and less than 55 years, and greater than 55 years of age. Body mass groups included patients weighing less than 49 kg, greater than 49 kg and less than 56 kg, greater than 56 kg and less than 64 kg, and greater than 64 kg.

The adverse drug reactions codes used were as follows: patients without adverse effects (no condition), those with anaemia, peripheral neuropathy, hepatotoxicity, skin rash, renal impairment, Fanconi syndrome, nausea/vomiting, and diarrhoea. Numbers were assigned to the codes ranging from 0 to 8 respectively. The initial and current antiretroviral regimens were adopted form the Lesotho antiretroviral guidelines 2010 (*refer to section 2.6.2*). The regimens included D4T/3TC/NVP, D4T/3TC/EFV, AZT/3TC/NVP, AZT/3TC/EFV, TDF/3TC/NVP, and TDF/3TC/EFV. Codes were also assigned to each regimen ranging from 1 to 6 respectively. Laboratory findings used in the study were the CD4 cell count, haemoglobin, neutrophil, ALT, creatinine and urea (*refer to sections 2.7.1.1 to 2.7.1.5 and 3.3.2*).

3.6.2 Statistics

Captured data were entered on an excel spread sheet. Statistical Analysis System®, (SAS 9.1®) programme was used for analysis. Statistical analysis system (SAS) is a software programme used for data analysis. SAS is designed to handle large data sets from disparate sources therefore enabling the usage of all data that is available for analysis. This software provides reliable results.

For the statistical analysis, the following descriptive tools were used:

3.6.2.1 Frequency

Data may be described pictorially by means of frequency tables. A frequency distribution consists of a series of predetermined values or intervals and the frequency with which these values occur. Therefore, a frequency table is a tabular presentation of the frequency distribution of a set of data (Knapp, 2000: 35).

3.6.2.2 Mean (arithmetic mean)

The mean is an average that uses the exact value of each entry. To compute the mean, the sum of all values making up the set of observations, is divided by the total number of observations in the set. According to Jones (2010: 137), the formula for calculating the arithmetic mean is as follows:

$$\hat{Y} = \sum Y_i / n$$

Where: $\hat{Y}$ = the average or arithmetic mean, n = the number of terms (e.g. the number of items or numbers being averaged), and Y_i = the value of each individual item in the list of numbers being averaged.

An inference based on sample data was made using the following:

3.6.2.3 Standard deviation

Standard deviation is a measurement that indicates how the data entries differ from the mean. According to Rosner (2010: 18), the standard deviation is defined as follows:

$$s = \sqrt{[\sum (Y_i - \hat{Y})^2 / (N - 1)]}$$

Where: s = standard deviation, Y_i = any value in the data set, $\hat{Y}$ = arithmetic mean (average), and N = number of values

3.6.2.4 Confidence intervals

A confidence interval gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of data. Moore defines the confidence intervals (2009: 365) as follows:

$$\hat{Y} \pm z\ (s/\sqrt{n})$$

Where: $\hat{Y}$ = the mean of the sample, z = the constant described above (For 95 per cent confidence levels, Z = 1.96), and s is the standard deviation of the sample.

The ± (plus and minus) part means that one can subtract this value from the mean to get the lower confidence limit and one can add it to the mean to get the upper confidence limit. Between those limits is the confidence interval.

3.6.2.5 T test procedure

The t test procedure performs t tests for one sample, two samples, and paired observations (SAS Institute Inc., 1986: 3569). In this study, Proc t test was used for analysis of one sample, paired comparisons and group comparisons tests. The Proc t test computed the sample mean of the variables and compared them with a given number in a one sample test. In paired comparisons, the one sample process was used to determine the difference between observations. It was made between many pairs of variables. In group comparisons, Proc t-test was used to compute the sample means for each of the two groups of observations in the data analysis. Moreover, it tested the hypothesis that the population means differed by a certain amount. The underlying assumption of the t test in all three cases was that the observations were random samples drawn from normally distributed populations. Proc t test computed the group comparison t statistic based on the assumption that the variances of the two groups were equal. The degrees of freedom (DF) and probability level were given for each.

For each variable in the analysis, the t test procedure displayed the following summary statistics for each group:

- the name of the dependent variable
- the levels of the classification variable
- N, the number of non-missing values
- Lower CL Mean, the lower confidence bound for the mean
- the Mean or average
- Upper CL Mean, the upper confidence bound for the mean
- Lower CL Std Dev, the lower confidence bound for the standard deviation
- Std Dev, the standard deviation
- Upper CL Std Dev, the upper confidence bound for the standard deviation
- Std Err, the standard error of the mean
- the Minimum value, if the line size allows
- the Maximum value, if the line size allows

For one-sample and paired observations t tests, the t test procedure displayed:

- t Value, the t statistic for testing the null hypothesis that the mean of the group is zero
- DF, the degrees of freedom
- Pr > |t|, the probability of a greater absolute value of t under the null hypothesis. This is the two-tailed significance probability.

3.6.3 Mixed linear model

In this study, data were analysed using hierarchical linear models - SAS Proc Mixed (SAS Mixed Procedure). A mixed linear model is a generalisation of the standard linear model used in the General Linear Models (GLM) procedure. The generalisation being that the data are permitted to exhibit correlation and non-constant variability (SAS Institute Inc., 2008: 3886). Hence the mixed linear model possesses flexibility of modelling for the means of data, their variances and covariances. Proc Mixed computes several different statistics suitable for generating hypothesis tests and confidence intervals and several other statistical parameters. The MIXED procedure fit a variety of mixed linear models to data and enables the use of these fitted models to make statistical inferences about the data (SAS Institute Inc., 2008: 3886). The validity of these statistics depends upon the mean and variance-covariance model selected by the right ordering of the data and picking the right estimate difference, so it is important to choose the right model (Dickey, 2008: 1).

There are primary assumptions underlying the analysis performed using Proc Mixed. It should be assumed that data are normally distributed (Gaussian), and the means (expected values) of the data are linear in terms of a certain set of parameters. Additionally, it should be assumed that the variances and covariances of the data are related to a different set of parameters, and they exhibit a structure matching one of those available in Proc Mixed (SAS Institute Inc., 2008: 3886). Gaussian data can be modelled completely in terms of their means and variance/covariances. As a result, the complete probability distribution of the data is indicated by these sets of parameters.

The fixed-effects parameters are linked with known explanatory variables, as in the standard linear model which can be either qualitative (as in the traditional analysis of variance) or quantitative (as in the standard linear regression). Conversely, the covariance parameters differentiate the mixed linear model from the standard linear model (SAS Institute Inc., 2008:

3886). The covariance parameters are frequently used in application of the following typical scenarios: (a) the experimental units on which the data are measured can be grouped into clusters (groups of patients), and (b) repeated measurements are taken on the same experimental unit, and these repeated measurements are correlated or exhibit variability that changes (SAS Institute Inc., 2008: 3886).

3.7 VALIDITY AND RELIABILITY OF DATA COLLECTION TOOLS

Reliability and validity of the structured questionnaire was done as follows: 1) extensive literature review to select questions relevant to the assessment of adverse drug reactions reporting; and 2) expert discussion panel with academic institutions, medical doctor and the statistics department at the North West University for selection of questions.

Reliability is the extent to which an instrument is repeatable and consistent (Cohen *et al.*, 2007: 148). Reliability of an instrument refers to when the same instrument is used at different times or administered to different subjects from the same population and the findings are the same (Wood & Ross-Kerr, 2011: 209). Validity is the extent to which an instrument measures what it is supposed to measure (Cohen *et al.*, 2007: 134). Face validity which refers to an extent to which an instrument appears valid was used. This type of validity cannot be quantified or tested, but any instrument should be scrutinised by experts in the field to ensure a high degree of face validity (Wood & Ross-Kerr, 2011: 203). A team of experts used to scrutinise the questionnaire included medical doctors, academicians and statisticians.

3.8 ETHICAL ASPECTS

Patient numbers were used instead of patient names so as not to breech patient confidentiality in phase 1. The consent letters were given to health professionals participating in the study before handing out questionnaires in phase 2.

The protocol, informed consent, data collection form and health professionals' questionnaire were first submitted for approval to the Ministry of Health and Social Welfare in Lesotho. Once this local approval was obtained, the letter of approval was sent to Sankatana ART clinic. All the documents sent to the Lesotho Ministry of Health and Social Welfare together with the letter of approval was submitted to the North West University ethics committee. Ethical approval was granted by North West University ethics committee and the ethics number is NWU-00134-12-A5.

3.9 LIMITATIONS OF THE STUDY

The limitations experienced in the study were as follows:

- Incomplete information in the medical records of patients. Laboratory findings were not properly documented leading to insufficient information on which laboratory tests were carried out routinely according to the Lesotho 2010 antiretroviral guidelines.
- The patient's medical records were paper based therefore some of the information was missing. This was a result of miss-filling.
- As this was a retrospective study, the medical records reflect what has occurred during clinical visits of the patients from the diagnosis to the point of data collection. Patients were not interviewed and there was no patient follow-up.
- Some of the health professionals did not submit their questionnaires.
- Other health facilities decided not to participate in the study.
- Some of the questions in the health professional's questionnaire were not answered.

3.10 CHAPTER SUMMARY

In this chapter the research methodology was discussed, which included the general and specific objectives of the study, the different phases of the research project, the research design/method, the data source, the data analysis and statistical analysis of the data. The analysis, together with the results of the empirical study will be reported in Chapter 4.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 INTRODUCTION

In this chapter, the results of the empirical investigation of phases one and two are discussed. Phase one was the drug utilisation review study which focused on the occurrence of adverse drug reactions in patients taking AZT- and TDF- based-regimens. The data collected from the patients' medical files was data recorded in the medical files from 1st January 2010 to 31st December 2011. These dates explain that the information documented within the aforementioned time period in the patients' medical files was used for data analysis. In the second phase, a survey in a form of questionnaires involving health professionals was conducted.

4.2 RESULTS

4.2.1 Phase one: Drug utilisation review

This part of the study focused on the occurrence of adverse drug reactions in patients taking AZT- and TDF- based-regimens. Patients' medical records were used to capture demographic data, medical history, laboratory results (e.g. CD4 cell count, urea, haemoglobin profile, neutrophil count, alanine aminotransferase (ALT) and creatinine clearance), and adverse drug effects. The records were hard copies of clinical and medical assessment of patients from when they tested positive.

4.2.1.1 Demographics of patients on the initial antiretroviral therapy regimens

As a result of inclusion and exclusion criteria (*refer to section 3.4.3*), 300 patients on either TDF- or AZT- based regimens were used as the study sample. Out of the 300 patients, there were 57.33 per cent (n = 172) females and 42.67 per cent (n = 128) males. Thus the majority of the study population consisted of female patients.

Table 4.1: Patients on initial ART regimen according to age group

Age group (years)	Frequency	per cent
Less than 35	120	40
Greater than 35 & less than 55	154	51.33
Greater than 55	26	8.67
Number of observations	300	100

Table 4.1 shows that the majority of patients were in age group of greater than 35 and less than 55 years (51.33 per cent, n = 154) followed by age group of less than 35 years (40 per cent, n = 120). In the age group of greater than 55 years there were 8.67 per cent (n = 26) of patients on initial ART regimen. The study population consisted of mostly adult patients.

Table 4.2: Number of patients on initial ARV regimens

INITIAL ARV REGIMEN		
Initial regimen	**Frequency**	**per cent**
D4T/3TC/EFV	1	0.33
AZT/3TC/NVP	22	7.33
AZT/3TC/EFV	20	6.67
TDF/3TC/NVP	20	6.67
TDF/3TC/EFV	237	79.00
Number of observations	300	100

Table 4.2 illustrates that most of the patients were on TDF/3TC/EFV (79 per cent, n = 237) followed by those on AZT/3TC/NVP (7.33 per cent, n = 22), AZT/3TC/EFV (6.67 per cent, n = 20), and TDF/3TC/NVP (6.67 per cent, n = 20) respectively. There was only one patient on D4T/3TC/EFV (0.33 per cent, n = 1). As a result, the majority of patients were initiated on TDF/3TC/EFV. This could be as a result of the health professionals following the Lesotho 2010 ART guidelines (Ministry of Health and Social Welfare, 2010: 48-59).

Table 4.3: Patients on initial ARV regimens according to age group

Initial Regimens	**Age groups, n = 300**		
	Less than 35 years (per cent)	Greater than 35 & less than 55 years (per cent)	Greater than 55 years (per cent)
D4T/3TC/EFV	0	0.33, n = 1	0
AZT/3TC/NVP	4.67, n = 14	2.33, n = 7	0.33, n = 1
AZT/3TC/EFV	2.00, n = 6	4.00, n = 12	0.67, n = 2
TDF/3TC/NVP	4.67, n = 14	1.67, n = 5	0.33, n = 1
TDF/3TC/EFV	28.66, n = 86	43.00, n = 129	7.33, n = 22

n = number of observations

Table 4.3 shows that the percentages of patients whose initial regimen was TDF/3TC/EFV were high. As a result, most patients were initiated on TDF/3TC/EFV. These patients were in age group ranges of less than 35 years (28.66 per cent, n = 86), greater than 35 and less than 55 years (43 per cent, n = 129), and greater than 55 years (7.33 per cent, n = 22). Also, the greater number of patients on TDF/3TC/EFV was in age group of greater than 35 and less

than 55. The least number of patients were those who were initiated on D4T/3TC/EFV, followed by AZT/3TC/EFV, TDF/3TC/NVP, and AZT/3TC/NVP respectively.

Table 4.4: Patients on initial ARV regimens according to sex

Initial Regimens	Sex , n = 300	
	Female (per cent)	Male (per cent)
D4T/3TC/EFV	0	0.33, n = 1
AZT/3TC/NVP	6.67, n = 20	0.67, n = 2
AZT/3TC/EFV	3.33, n = 10	3.33, n = 10
TDF/3TC/NVP	4.67, n = 14	2.00, n = 6
TDF/3TC/EFV	42.67, n = 128	36.33, n = 109

n = number of observations

Table 4.4 demonstrates that patients on regimens TDF/3TC/EFV (42.67 per cent, n = 128), AZT/3TC/NVP (6.67 per cent, n = 20) and TDF/3TC/NVP (4.67 per cent, n = 14) were females. An equal number of male and female patients were on AZT/3TC/EFV (3.33 per cent, n = 10). As a result, patients in all the regimens shown in the table consisted mainly of female patients.

Table 4.5: Average body mass of patients on initial regimens

INITIAL REGIMEN	N Obs	N	Mean	Std Dev	Minimum	Maximum	Median	Std Error	Lower 95 per cent CL for Mean	Upper 95 per cent CL for Mean
D4T/3TC /EFV	1	1	59.0000000	.	59.0000000	59.0000000	59.0000000	.	.	.
AZT/3TC /NVP	22	22	59.5454545	13.1320302	37.0000000	90.0000000	60.5000000	2.7997582	53.7230385	65.3678705
AZT/3TC /EFV	20	20	58.9500000	13.3000791	42.0000000	89.0000000	55.0000000	2.9739881	52.7253714	65.1746286
TDF/3TC /NVP	20	20	56.7500000	12.2769574	39.0000000	85.0000000	54.5000000	2.7452111	51.0042070	62.4957930
TDF/3TC /EFV	237	237	57.2151899	11.5947689	30.0000000	104.0000000	56.0000000	0.7531612	55.7314120	58.6989677

N & N Obs = number of observations, Std Dev = Standard deviation, Std Error = standard error, CL = Confidence level

Table 4.5 depicts that the baseline average body mass means of patients on the initial regimens were as follows: AZT/3TC/NVP 59.5 ± 13.1 kg (n = 22), D4T/3TC/EFV 59.0 kg (n = 1), AZT/3TC/EFV 59.0 ± 13.3 kg (n = 20), TDF/3TC/EFV 57.2 ± 11.6 kg (n = 237), and

TDF/3TC/NVP 56.8 ± 12.3 kg (n = 20). The average body mass means of patients in all the initial regimens were close to each other.

4.2.1.2 Age, sex and body mass of patients who experienced adverse drug reactions

Of the patients who experienced ADRs, 72.73 per cent (n = 32) of these patients were female and 27.27 per cent (n = 12) were male. Overall, the patients who developed ADRs were female.

Table 4.6: Patients who experienced ADRs according to age group

Age group (years)	Frequency	per cent
Less than 35	24	54.55
Greater than 35 & less than 55	16	36.36
Greater than 55	4	9.09

As shown in table 4.6, most patients who experienced ADRs were patients in the age group less than 35 years (54.55 per cent, n = 24) and those in the age group of years greater than 35 and less than 55 (36.36 per cent, n = 16). Patients greater than 55 year of age experienced less ADRs as a result of the ART regimen they were taking. The younger adults experienced more ADRs than older adults.

Table 4.7: Patients who experienced ADRs according to age group and type of adverse drug reaction

Age group (years)	Type of ADR					
Frequency per cent Row per cent Column per cent	Peripheral neuropathy	Skin rash	Fanconi syndrome	Nausea/vomiting	Diarrhoea	Total
Less than 35	0	16	0	7	1	24
	0.00	36.36	0.00	15.91	2.27	54.55
	0.00	66.67	0.00	29.17	4.17	
	0.00	59.26	0.00	53.85	50.00	
Greater than 35 & less than 55	1	10	1	3	1	16
	2.27	22.73	2.27	6.82	2.27	36.36
	6.25	62.50	6.25	18.75	6.25	
	100.00	37.04	100.00	23.08	50.00	
Greater than 55	0	1	0	3	0	4
	0.00	2.27	0.00	6.82	0.00	9.09
	0.00	25.00	0.00	75.00	0.00	
	0.00	3.70	0.00	23.08	0.00	
Total	1	27	1	13	2	44
	2.27	61.36	2.27	29.55	4.55	100.00

Table 4.7 displays that, most patients in age groups of less than 35, and greater than 35 and less than 55 had a higher number of patients who experienced ADRs respectively. In the age group of patients less than 35 years, 36.36 per cent developed skin rash, 15.91 per cent nausea/vomiting, and 2.27 per cent had diarrhoea. In patients greater than 35 and less than 55 years of age, 22.73 per cent had skin rash, 2.27 per cent Fanconi syndrome, 6.82 per cent nausea/vomiting, and 2.27 per cent presented with diarrhoea.

Table 4.8: Patients who experienced ADRs according to gender and type of adverse drug reaction

Sex	Type of ADR					
Frequency per cent Row per cent Col per cent	Peripheral neuropathy	Skin rash	Fanconi syndrome	Nausea/vomiting	Diarrhoea	Total
Female	0	19	0	12	1	32
	0.00	43.18	0.00	27.27	2.27	72.73
	0.00	59.38	0.00	37.50	3.13	
	0.00	70.37	0.00	92.31	50.00	
Male	1	8	1	1	1	12
	2.27	18.18	2.27	2.27	2.27	27.27
	8.33	66.67	8.33	8.33	8.33	
	100.00	29.63	100.00	7.69	50.00	
Total	1	27	1	13	2	44
	2.27	61.36	2.27	29.55	4.55	100.00

A greater number of patients who experienced ADRs were females with 43.18 per cent presenting with skin rash, 27.27 per cent with nausea/vomiting, and 2.27 per cent with diarrhoea. In male patients, 2.27 per cent had peripheral neuropathy, 18.18 per cent skin rash, 2.27 per cent Fanconi syndrome, 2.27 per cent nausea/vomiting, and 2.27 per cent diarrhoea. Male patients experienced all the types of adverse drug reactions in table 4.8 as opposed to female patients. The majority of female patients experienced skin rash. This could be because females are more prone to developing cutaneous drug reactions than males. Self-determining risk factors which may lead to the development of cutaneous reactions include female sex, CD4 cell counts less than 100 cells/mm^3 and age greater than 40 years (Shibuyama *et al.*, 2006: 1081).

Table 4.9: Average body mass of patients who experienced ADRs according to sex

Sex	N	Mean	Std Dev	Std Err	Minimum	Maximum
Female	32	50.98	10.40	1.84	32.00	71.00
Male	12	51.33	7.15	2.06	37.00	62.00
Diff (1-2)		-0.35	9.66	3.27		

N = number of observations, Std Dev = Standard deviation, Std Error = standard error

As shown in table 4.9, the average body mass of both female and male patients is similar. Comparing the initial average body mass of patients on initial regimen (*refer to section 4.2.1.1, table 4.5*) with average body mass of patients who experienced ADRs (*table 4.9*); there was average body mass loss in these patients. As a result, body mass loss in HIV-

positive patients predicts either a progression of disease, opportunistic infection, adverse drug reactions or death. It is used as a warning sign to prescribers to start investigations and treatment (National Department of Health South Africa, 2010: 28).

Table 4.10: Average body mass of patients who experienced ADRs according to sex

Source	DF	Type I SS	Mean Square	F Value	Pr > F
Sex	2	101.08	50.54	0.54	0.59

DF = Degrees of freedom

According to table 4.10, the practical significance is lacking, as a result, adverse drug reactions experienced by patients are independent of sex.

4.2.1.3 Age, sex and body mass of patients who did not experience adverse drug reactions

Table 4.11: Average body mass of patients who did not experience ADRs according to sex

Sex	N	Mean	Std Dev	Std Err	Minimum	Maximum
Female	172	57.37	13.01	0.10	30.00	104.00
Male	128	57.62	10.04	0.89	35.00	90.00
Diff (1-2)		-0.25	11.83	1.38		

N = number of observations, Std Dev = Standard deviation, Std Error = standard error

As shown in table 4.11, the average body mass of both female 57.37 ± 13.01 kg (n = 172) and male 57.62 ± 10.04 kg (n = 128) patients is similar. Comparing the average body mass of patients on initial ART regimen (*refer to section 4.2.1.1, table 4.5*) with average body mass of patients who did not experience any ADRs (*table 4.11*); the body mass loss in patients was minimal.

Table 4.12: Average body mass of patients who did not experience ADRs according to age group

Analysis Variable : BODY MASS (kg)										
Age group (years)	**N Obs**	**N**	**Mean**	**Std Dev**	**Minimum**	**Maximum**	**Median**	**Std Error**	**Lower 95 per cent CL for Mean**	**Upper 95 per cent CL for Mean**
Less than 35	120	120	55.36	10.49	30.00	85.00	54.00	0.96	53.46	57.25
Greater than 35 & less than 55	154	154	58.91	11.91	37.00	104.00	58.00	0.96	57.01	60.81
Greater than 55	26	26	58.77	15.56	42.00	103.00	55.50	3.05	52.49	65.05

N & N Obs = number of observations, Std Dev = Standard deviation, Std Error = standard error, CL = Confidence level

According to table 4.12, the average body mass of patients in the age group greater than 35 and less than 55 years (58.91 ± 11.91, n = 154), and greater than 55 years (58.77 ± 15.56 kg, n = 26) is higher than for patients in the age group of less than 35 years of age (55.36 ± 10.49 kg, n = 120). Comparing the average body mass of patients on initial ART regimen (*refer to section 4.2.1.1, table 4.5*) with average body mass of patients who did not experience any ADRs (*table 4.12*); the average body mass is similar in patients in age groups of greater than 35 and less than 55, and greater than 55 years of age. A significant difference is seen with patient in age group less than 35 years.

4.2.1.4 Age, sex and body mass of patients whose ART regimen changed due to ADR

60 per cent (n = 3) of the patients whose ART regimen changed due to ADRs were females and 40 per cent (n = 2) were males. Mainly female patients' ART regimen changed as a result of ADRs.

Table 4.13: Patients whose ART regimen changed due to ADR according to age group

Age group (years)	**Frequency**	**per cent**
Less than 35	2	40.00
Greater than 35 & less than 55	2	40.00
Greater than 55	1	20.00

Table 4.13 displays that an equal number of patients in the age groups of less than 35 years of age, and greater than 35 and less than 55 years had the highest patients who changed

treatment (40 per cent, n = 2). Only 20 per cent (n = 1) of patients in the age group of greater than 55 years changed regimen.

Table 4.14: Average body mass of patients whose ART regimen changed due to ADR

Average body mass (kg)								
N	Mean	Std Dev	Minimum	Maximum	Median	Std Error	Lower 95 per cent CL for Mean	Upper 95 per cent CL for Mean
5	57.60	9.32	44.00	70.00	58.00	4.17	46.03	69.17

N = number of observations, Std Dev = Standard deviation, Std Error = standard error, CL = Confidence level

According to table 4.14, there was body mass loss in patients whose regimen changed due to ADRs they were experiencing, but the number of observations was too small to make any conclusions.

4.2.1.5 Results of the average clinical determinants at baseline and last consultations

The covariance parameter estimates showed a 1.02 residual which proves the practical significance of the determinants.

Table 4.15: Average of clinical determinants at baseline and last consultation

	Baseline (n = 1959)			Last consultation (n = 1969)		
Label	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
CD4 cell count (cell/mm³)	298	175.75	114.47	297	428.87	159.96
HB (g/dL)	286	11.90	2.26	182	12.92	1.91
Creatinine (µmol/L)	274	86.92	23.80	299	62.62	13.77
Body mass (kg)	300	57.48	11.82	300	62.19	11.11
Urea (mmol/L)	268	3.87	1.52	236	3.32	0.83
ALT (IU/L)	275	30.25	26.21	299	28.28	15.31
Neutrophil (per cent)	256	52.98	13.84	57	52.60	13.11

N = number of observations, Std Dev = Standard deviation

Table 4.15 shows that there was an increase from baseline to last consultation in CD4 cell count of 253.12 cell/mm³, Hb profile of 1.02 g/dL, and body mass (4.71 kg). A decline was

seen with creatinine (24.3 µmol/L), urea (0.55 mmol/L), ALT (1.97 IU/L) and neutrophil count (0.38 per cent).

Table 4.16: Average of clinical determinants at baseline and last consultation according to sex

female		Label	CD4 cell count (cell/mm^3)	Hb (g/dL)	Creatinine (µmol/L)	Body mass (kg)	Urea (mmol/L)	ALT (IU/L)	Neutrophil (per cent)
	B, n = 1125	N	172	166	157	172	152	158	146
		Mean	192.79	11.30	81.98	57.37	3.58	25.37	50.95
		Std Dev	120.00	2.10	21.93	13.01	1.35	19.63	13.53
	LC, n = 1118	N	171	101	171	172	135	171	25
		Mean	447.73	12.17	59.04	61.90	3.23	24.36	49.78
		Std Dev	158.10	1.91	13.18	12.28	0.83	10.79	11.18
Male	B, n = 834	N	126	120	117	128	116	117	110
		Mean	152.49	12.72	93.56	57.62	4.26	36.83	55.66
		Std Dev	102.41	2.24	24.67	10.04	1.65	32.03	13.86
	LC, n = 851	N	126	81	128	128	101	128	32
		Mean	403.27	13.86	67.36	62.59	3.43	33.52	54.81
		Std Dev	159.52	1.44	13.15	9.34	0.83	18.50	14.23

B = Baseline, LC = last consultation, n = total number of observations, N = number of observations, Std Dev = Standard deviation

According to table 4.16, in female patients, there was a rise in CD4 cell count (254.97 cell/mm³), Hb profile (0.87 g/dL), and body mass (4.53 kg) from baseline to last consultation. A fall was seen with creatinine (22.94 µmol/L), urea (0.35 mmol/L), ALT (1.01 IU/L), and neutrophil count (1.17 per cent). In male patients, there was a rise from baseline to last consultation in CD4 cell count of 250.78 cell/mm³, Hb profile (1.14 g/dL), and body mass (4.97 kg). Also a decline occurred with creatinine of 26.2 µmol/L, urea (0.83 mmol/L), ALT (3.31 IU/L), and Neutrophil count (0.85 per cent).

Table 4.17: Average of clinical determinants at baseline and last consultation according to age group

Less than 35 years		Label	CD4 cell count (cell/mm^3)	Hb (g/dL)	Creatinine (µmol/L)	Body mass (kg)	Urea (mmol/L)	ALT (IU/L)	Neutrophil (per cent)
	B, n = 651	N	119	114	105	120	101	106	104
		Mean	184.27	11.65	84.88	55.36	3.66	28.57	54.42
		Std Dev	112.84	2.32	24.05	10.49	1.36	29.02	14.02
	LC, n = 802	N	119	81	120	120	94	120	28
		Mean	444.42	12.76	60.11	61.27	3.08	27.20	51.65
		Std Dev	171.37	1.95	12.71	9.89	0.72	15.26	9.96
Greater than 35 and less than 55 years	B, n = 1014	N	153	147	143	154	142	143	131
		Mean	164.33	12.10	88.43	58.91	3.97	31.92	52.67
		Std Dev	118.09	2.23	23.36	11.91	1.49	25.73	14.07
	LC, n = 1001	N	152	90	153	154	121	153	25
		Mean	407.13	13.12	63.68	63.04	3.45	29.16	52.39
		Std Dev	153.60	1.81	12.85	11.88	0.82	15.85	15.70
Greater than 55 years	B, n = 175	N	26	25	26	26	25	26	21
		Mean	203.96	11.86	86.88	58.77	4.13	27.88	47.71
		Std Dev	93.91	2.51	25.50	15.56	2.18	14.08	10.15
	LC, n = 166	N	26	11	26	26	21	26	4
		Mean	484.77	12.51	67.92	61.46	3.65	28.15	60.55
		Std Dev	120.63	2.35	20.51	11.75	1.08	12.12	15.82

B = Baseline, LC = last consultation, n = total number of observations, N = number of observations, Std Dev = Standard deviation

For patients in the age group of less than 35 years of age, table 4.17 shows that there was a rise from baseline to last consultation in CD4 cell count (260.15 cell/mm³), Hb profile (1.11 g/dL), and body mass (5.91 kg). Also a decline occurred with creatinine of 24.77 µmol/L, urea (0.58 mmol/L), ALT (1.37 IU/L), and Neutrophil count (2.77 per cent). For patients in the age group of years greater than 35 and less than 55 years of age, there was a rise from baseline to last consultation in CD4 cell count (242.8 cell/mm³), Hb profile (1.02 g/dL), and body mass (4.13 kg). Also a decline occurred with creatinine of 24.75 µmol/L, urea (0.52 mmol/L), ALT (2.76 IU/L), and Neutrophil count (0.28 per cent). For patients in age group of

years greater than 55, there was a rise from baseline to last consultation in CD4 cell count (280.81 cell/mm³), Hb profile (0.65 g/dL), body mass (2.69 kg), ALT (0.27 IU/L), and Neutrophil count (12.84 per cent). Also a decline occurred with creatinine of 18.96 µmol/L, and urea (0.48 mmol/L).

Table 4.18: Average of clinical determinants at baseline and last consultation according to initial ARV regimen

D4T/3TC/EFV		Label	CD4 cell count (cell/mm^3)	Hb (g/dL)	Creatinine (µmol/L)	Body mass (kg)	Urea (mmol/L)	ALT (IU/L)	Neutrophil (per cent)
	B, n = 7	N	1	1	1	1	1	1	1
		Mean	100.0	13.60	94.0	59.0	2.60	16.0	22.40
		Std Dev	-	-	-	-	-	-	-
	LC, n = 8	N	1	1	1	1	1	1	1
		Mean	301.0	13.20	65.0	60.0	2.80	23.0	44.50
		Std Dev	-	-	-	-	-	-	-
AZT/3TC/NVP	B, n = 134	N	22	19	19	22	18	19	14
		Mean	257.36	12.22	76.89	59.55	3.21	21.32	55.42
		Std Dev	78.98	1.63	14.19	13.13	0.76	13.53	14.77
	LC, n = 154	N	22	19	21	22	17	21	10
		Mean	514.23	13.28	63.48	62.09	3.31	26.14	47.46
		Std Dev	128.26	1.32	19.37	12.21	1.05	18.23	13.75
AZT/3TC/EFV	B, n = 132	N	20	20	19	20	17	19	17
		Mean	216.95	12.97	93.58	58.95	4.28	31.26	49.72
		Std Dev	104.25	1.87	31.17	13.30	1.78	18.91	13.07
	LC, n = 140	N	20	15	20	20	19	20	6
		Mean	472.50	13.36	60.60	65.55	3.17	24.60	49.13
		Std Dev	121.70	1.59	11.60	10.62	0.54	11.54	19.56
TDF/3TC/NVP	B, n = 136	N	20	19	20	20	20	20	17
		Mean	171.75	11.87	81.75	56.75	3.42	26.75	53.42
		Std Dev	125.32	1.53	17.57	12.28	1.09	17.96	12.73
	LC, n =	N	19	12	19	19	15	19	2
		Mean	412.74	12.26	57.68	61.32	3.33	25.11	51.70

	124	Std Dev	199.96	2.55	12.37	12.41	0.67	8.87	29.27
TDF/3TC/EFV	B, n = 1550	N	235	227	215	237	212	216	207
		Mean	165.27	11.77	87.67	57.22	3.94	31.33	53.19
		Std Dev	114.04	2.37	24.09	11.59	1.57	28.13	13.84
	LC, n = 1543	N	235	135	238	238	184	238	38
		Mean	419.01	12.88	63.08	62.00	3.34	29.06	54.76
		Std Dev	159.92	1.95	13.48	10.99	0.85	15.71	11.12

B = Baseline, LC = last consultation, n = total number of observations, N = number of observations, Std Dev = Standard deviation

Table 4.18 shows that in patients on D4T/3TC/EFV, there was an increase from baseline to last consultation in CD4 cell count of 201 cell/mm³, body mass (1 kg), urea (0.2 mmol/L), ALT (7 IU/L) and neutrophil count (22.1 per cent). A decline was seen with creatinine (29 µmol/L) and Hb profile of 0.4 g/dL. In patients on AZT/3TC/NVP, there was an increase from baseline to last consultation in CD4 cell count of 256.87 cell/mm³, Hb profile of 1.06 g/dL, body mass (2.54 kg), urea (0.1 mmol/L), and ALT (4.82 IU/L). A decline was seen with creatinine (13.41 µmol/L) and neutrophil count (7.96 per cent). In patients on AZT/3TC/EFV, there was an increase from baseline to last consultation in CD4 cell count of 255.55 cell/mm³, Hb profile of 0.39 g/dL, and body mass (6.6 kg). A decline was seen with creatinine (32.98 µmol/L), urea (1.11 mmol/L), ALT (6.66 IU/L), and neutrophil count (0.59 per cent).

In patients on TDF/3TC/NVP, there was an increase from baseline to last consultation in CD4 cell count of 240.99 cell/mm³, Hb profile of 0.39 g/dL, and body mass (4.57 kg). A decline was seen with creatinine (24.07 µmol/L), urea (0.09 mmol/L), ALT (1.64 IU/L), and neutrophil count (1.72 per cent). In patients on TDF/3TC/EFV, there was an increase from baseline to last consultation in CD4 cell count of an average mean of 253.74 cell/mm³, Hb profile of 1.11 g/dL, body mass (4.78 kg), and neutrophil count (1.57 per cent). A decline was seen with creatinine (24.59 µmol/L), urea (0.6 mmol/L), and ALT (2.27 IU/L).

Table 4.19: Average of clinical determinants at baseline and last consultation according to adverse drug reactions (no condition)

	Baseline (n = 14)			Last consultation (n = 1956)		
Label	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
CD4 (cell/mm³)	2	554.50	410.83	295	430.35	159.47
HB (g/dL)	2	12.90	0.71	181	12.92	1.91
Creatinine (µmol/L)	2	69.00	2.83	297	62.68	13.79
Body mass (kg)	2	51.00	2.83	298	62.19	11.14
Urea (mmol/L)	2	3.35	0.78	234	3.32	0.84
ALT (IU/L)	2	27.50	14.85	297	28.35	15.32
Neutrophil (per cent)	0	-	-	56	52.76	13.17

N = number of observations, Std Dev = Standard deviation

Table 4.19 displays that in patients who did not experience any ADRs; there was an increase from baseline to last consultation in Hb profile of 0.02 g/dL, body mass (11.19 kg), and ALT (0.85 IU/L). A decline was seen with CD4 cell count of 124.15 cell/mm³, creatinine (6.32 µmol/L), and urea (0.03 mmol/L).

4.2.1.6 Clinical determinates parameters

The study sample consisted of 299 patients. Covariance structures: Variance components, spatial power were used to analyse data. It was used because the clinical determinants (e.g. CD4 cell count, urea, haemoglobin profile, neutrophil count, alanine aminotransferase (ALT) and creatinine clearance) test on patients were determined at different time intervals and time periods; as a result the PROC MIXED procedure SAS system was used. The research looked at the trend of change in clinical determinants. The logarithms of the clinical determinants were used to meet the criteria of multivariate normality. To ensure normality of the different clinical variable, the log of each clinical determinates was determined.

4.2.1.6.1 Results of the average CD4 cell counts of patients

The covariance parameter estimates showed a 1.03 residual which proves the practical significance. Table 4.20 shows that at a 5 per cent confidence interval an estimated increase of 0.0025 cell/mm³ in CD4 cell count per day was seen which was statistically significant, but independent from the gender of the patient (p = 0.2013).

Table 4.20: CD4 cell count over the study period according to sex: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Sex**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		-41.9691	2.2306	297	-18.82	<.0001
Sex	Female	0.1391	0.1088	909	1.28	0.2013
Sex	Male	0	.	.	.	.
DAYS		0.002541	0.000120	909	21.20	<.0001

DF = Degrees of freedom

Table 4.21: CD4 cell count over the study period according to sex: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Sex	1	909	1.64	0.2013
DAYS	1	909	449.65	<.0001

DF = Degrees of freedom

Tables 4.21 depicts that the CD4 cell count is independent of sex. As a result there was no statistical significant *(p* = 0.2013) difference in the estimated CD4 cell count increase per day between male and female patients.

Table 4.22: CD4 cell count over the study period according to age group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Age group (years)	2	909	2.23	0.1080
DAYS	1	909	452.98	<.0001

Table 4.22 shows that at 5 per cent confidence level, the increase in CD4 cell count per day was independent of the age group *(p* = 0.1080).

Table 4.23: CD4 cell count over the study period according to body mass group: Solution for fixed effects

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
DAYS	0.002364	0.000120	906	19.76	<.0001

Table 4.23 shows that there was an estimated increase of 0.0024 cell/mm³ in CD4 cell count per day. At 5 per cent confidence level, the increase in CD4 cell count in days is statistical significant ($p < 0.0001$).

Table 4.24: CD4 cell count over the study period according to body mass group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Body mass group	3	906	12.66	<.0001
DAYS	1	906	390.46	<.0001

The CD4 cell count increase is statistically dependent on the body mass group ($p < 0.0001$). As a result there was a difference in CD4 cell count increase per day in the different patient body mass groups *(table 4.24)*.

Table 4.25: CD4 cell count over the study period according to initial ARV regimen: Solution for fixed effects

Solution for Fixed Effects						
Effect	**INITIAL ARV REGIMEN**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		-42.0386	2.2231	295	-18.91	<.0001
Initial regimen	**D4T/3TC /EFV**	0.3583	0.9273	908	0.39	0.6993
Initial regimen	**AZT/3TC /NVP**	0.6614	0.2088	908	3.17	0.0016
Initial regimen	**AZT/3TC /EFV**	0.2908	0.2138	908	1.36	0.1742
Initial regimen	**TDF/3TC /NVP**	-0.2224	0.1944	908	-1.14	0.2531
Initial regimen	**TDF/3TC /EFV**	0	.	.	.	.
DAYS		0.002547	0.000119	908	21.33	<.0001

Table 4.25 demonstrates that there was an increase of 0.0025 cell/mm³ in CD4 cell count per day, which is statistical significant dependent on the type of initial ARV regimen. At 5 per cent confidence level, the increase in CD4 cell count in days is statistical significant ($p < 0.0001$). At 5 per cent confidence level, the difference in the increase in CD4 cell count among the different ART regimens is as follows: AZT/3TC/NVP is statistical significant ($p = 0.0016$), and is not statistical significant in D4T/3TC/EFV ($p = 0.6993$), AZT/3TC/EFV ($p = 0.1742$), and TDF/3TC/NVP ($p = 0.2531$). The increases in CD4 cell counts reveal that patients were adjusting well to their ART. Immunological screening of HIV-positive patients is assessed using CD4 cell count. Antiretroviral treatment guidelines use increases in CD4 cell counts after initiation of therapy as a measure of immunologic response to therapy (The antiretroviral therapy cohort collaboration, 2009: 358).

Table 4.26: CD4 cell count over the study period according to initial ARV regimen: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Initial ARV regimen	4	908	3.37	0.0095
DAYS	1	908	454.92	<.0001

The CD4 cell count increase is dependent on initial ART regimen a patient is taking. As a result there was a difference in CD4 cell count increase per day in the different initial ART regimens. At 5 per cent confidence level of significance, these differences are of practical significance ($p = 0.0095$) (*table 4.26*).

Table 4.27: CD4 cell count over the study period according to adverse drug reactions: Solution for fixed effects

Solution for Fixed Effects						
Effect	**ADR. CODES**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		-29.0031	1.6200	298	-17.90	<.0001
ADR_CODE	No condition	0.1337	0.07356	607	1.82	0.0696
ADR_CODE	Peripheral neuropathy	-0.01155	0.1886	607	-0.06	0.9512
ADR_CODE	Skin rash	0.04168	0.09031	607	0.46	0.6446
ADR_CODE	Fanconi syndrome	0.2099	0.2211	607	0.95	0.3429
ADR_CODE	Nausea/vomiting	0	.	.	.	.
DAYS		0.001852	0.000087	607	21.28	<.0001

Table 4.27 demonstrates that there was an increase of 0.0019 cell/mm^3 in CD4 cell count per day. At 5 per cent confidence level, the increase in CD4 cell count in days is statistical significant ($p < 0.0001$). At 5 per cent confidence level, the difference in the increase in CD4 cell count among the different ART ADRs is as follows: no condition is statistical significant ($p = 0.0696$), and is not statistical significant for peripheral neuropathy ($p = 0.9512$), skin rash ($p = 0.6446$), and Fanconi syndrome ($p = 0.3429$). The CD4 cell count increase is independent of adverse drug reactions a patient is experiencing. This could be because the ADRs weaken the immune system and allow new infections to attack the body. As a result, the opportunistic infections are responsible for the CD4 cell count decrease and not the adverse drug reaction. Occurrence of ADRs weakens the patient's immunological response.

Table 4.28: CD4 cell count over the study period according to adverse drug reactions: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
ADR_CODE	4	607	1.59	0.1749
DAYS	1	607	452.81	<.0001

4.2.1.6.2 Results of the average Hb profile of patients

The covariance parameter estimates showed a 1.0015 residual. Table 4.29 shows that there was an increase of 0.00021 g/dL in Hb profile per day. At 5 per cent level, the increase in Hb profile in days is statistically significant ($p < 0.0001$).

Table 4.29: Hb profile over the study period according to sex: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Sex**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		-1.2327	0.5285	297	-2.33	0.0204
Sex	Female	-0.1304	0.01861	784	-7.00	<.0001
Sex	Male	0	.	.	.	.
DAYS		0.000205	0.000028	784	7.20	<.0001

Table 4.30: Hb profile over the study period according to sex: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Sex	1	784	49.06	<.0001
DAYS	1	784	51.89	<.0001

Tables 4.30 depicts that the Hb profile is dependent on sex. As a result there was a difference in the estimated Hb profile increase per day between male and female patients.

Table 4.31: Hb profile over the study period according to age group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Age group (years)**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		-1.5754	0.5412	296	-2.91	0.0039
Age group	Less than 35 years	-0.02209	0.03746	784	-0.59	0.5555
Age group	greater than 35 and less than 55 years	0.01629	0.03667	784	0.44	0.6571
Age group	Greater than 55 years	0	.	.	.	.
DAYS		0.000220	0.000029	784	7.52	<.0001

Table 4.31 shows that there was a statistical significant ($p < 0.0001$) increase of 0.00022 g/dL in Hb profile per day which were independed of the age group of the patient. As a result there was no difference in Hb profile increase per day in the different patient age groups (*table 4.31*). At 5 per cent confidence level, the difference in the increase in Hb profile among the different age groups is not statistic significant in patients less than 35 years of age ($p = 0.5555$), and those greater than 35 and less than 55 years ($p = 0.6571$).

Table 4.32: Hb profile over the study period according to age group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Age group (years)	2	784	1.67	0.1882
DAYS	1	784	56.61	<.0001

Table 4.33: Hb profile over the study period according to body mass group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Body mass group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		-0.8762	0.5511	298	-1.59	0.1129
Body mass group	Less than 49 kg	-0.08860	0.01988	781	-4.46	<.0001
Body mass group	Greater than 49 and less than 56 kg	-0.04396	0.01734	781	-2.54	0.0114
Body mass group	Greater than 56 and less than 64 kg	-0.02506	0.01549	781	-1.62	0.1062
Body mass group	Greater than 64 kg	0	.	.	.	.
DAYS		0.000184	0.000030	781	6.21	<.0001

Table 4.33 shows that there was a statistical significance ($p < 0.0001$) increase of 0.00018 g/dL in Hb profile per day which is dependent on the body mass group. As a result there was

a difference in the estimated Hb profile increase per day in the different patient body mass groups (*table 4.33*). At 5 per cent confidence level, the difference in the increase in Hb profile among the different age groups is statistic significant in the body mass group of less than 49 kg ($p < 0.0001$), and the body mass group of greater than 49 kg and less than 56 kg ($p = 0.0114$). Additionally, it is not statistic significant in the body mass group greater than 56 kg and less than 64 kg ($p = 0.1062$). The increase of Hb profile according to body mass group was less than an increase according to age group (*table 4.31*), and sex (*refer to table 4.29*).

Table 4.34: Hb profile over the study period according to body mass group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Body mass group	3	781	6.92	0.0001
DAYS	1	781	38.61	<.0001

Table 4.35: Hb profile over the study period according to initial ARV regimen: Solution for fixed effects

Solution for Fixed Effects						
Effect	**INITIAL ARV REGIMEN**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		-1.5268	0.5420	295	-2.82	0.0052
Initial ARV regimen	**D4T/3TC /EFV**	0.1084	0.1741	783	0.62	0.5338
Initial ARV regimen	**AZT/3TC /NVP**	0.03450	0.03876	783	0.89	0.3737
Initial ARV regimen	**AZT/3TC /EFV**	0.03952	0.03976	783	0.99	0.3206
Initial ARV regimen	**TDF/3TC /NVP**	-0.03975	0.03931	783	-1.01	0.3122
Initial ARV regimen	**TDF/3TC /EFV**	0	.	.	.	.
DAYS		0.000217	0.000029	783	7.42	<.0001

Table 4.35 demonstrates that there was an increase of 0.00022 g/dL in Hb profile per day. At 5 per cent level, the increase in Hb profile in days is statistic significant ($p < 0.0001$), but independed of the initial ARV regimen. The difference in Hb profile increase among the different ART regimens is not statistic significant in D4T/3TC/EFV ($p = 0.5338$), AZT/3TC/NVP ($p = 0.3737$), AZT/3TC/EFV ($p = 0.3206$), and TDF/3TC/NVP ($p = 0.3122$). The increases in Hb profile reveal that the patients were adjusting well to their ART. The Hb

profile is measured to assess the occurrence of anaemia. It is done routinely especially for patients on AZT- based regimen. Normal levels of Hb in women are 12.1 to 15.1 g/dL and 13.8 to 17.2 g/dL in males (Marks & Glader, 2008). Anaemia in HIV-infected patients may lead to serious implications which range from functional and quality-of-life decrements to an association with disease progression and decreased survival (Volberding *et al.*, 2004: 1454).

Table 4.36: Hb profile over the study period according to initial ARV regimen: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Initial ARV regimen	4	783	0.83	0.5034
DAYS	1	783	55.12	<.0001

The Hb profile increase is independent of initial ART regimen a patient is taking (p = 0.5034). As a result there was no statistical significance difference in the Hb profile increase per day in the different initial ART regimens.

Table 4.37: Hb profile over the study period according to adverse drug reactions: Solution for fixed effects

Solution for Fixed Effects						
Effect	**ADR. CODES**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		-1.0437	0.5214	296	-2.00	0.0462
ADR_CODE	No condition	-0.1415	0.09732	494	-1.45	0.1466
ADR_CODE	Peripheral neuropathy	-0.1662	0.1338	494	-1.24	0.2147
ADR_CODE	Skin rash	-0.1837	0.09932	494	-1.85	0.0650
ADR_CODE	Fanconi syndrome	-0.1803	0.1219	494	-1.48	0.1398
ADR_CODE	Nausea/vomiting	-0.1598	0.1009	494	-1.58	0.1138
ADR_CODE	Diarrhoea	0	.	.	.	.
DAYS		0.000199	0.000028	494	7.15	<.0001

Table 4.37 demonstrates that there was an increase of 0.00020 g/dL in Hb profile per day, but this was independent of adverse drug reactions a patient was experiencing. At 5 per cent confidence level, the difference in the increase in Hb profile among the different ART ADRs was as follows: skin rash is statistical significant (p = 0.0650), and is not statistical significant for peripheral neuropathy (p = 0.2147), no condition (p = 0.1466), Fanconi syndrome (p = 0.1398), and nausea/vomiting (p = 0.1138). The increase of Hb profile according to ADRs experienced by patients was less than an increase according to initial ART regimen (*refer to table 4.35*), age group (*refer to table 4.31*), sex (*refer to table 4.29*) and body mass group (*refer to table 4..33*).

Table 4.38: Hb profile over the study period according to adverse drug reactions: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
ADR_CODE	5	494	1.46	0.2007
DAYS	1	494	51.17	<.0001

The Hb profile increase is independent of the type of ADR a patient is experiencing (p = 0.2007).

4.2.1.6.3 Results of the average serum creatinine of patients

The covariance parameter estimates showed a 0.075 residual. Table 4.39 shows that there was at a 5 per cent confidence interval an estimated decrease of 0.00038 µmol/L in serum creatinine per day, which was statistically significant, but dependent on the sex of the patient ($p < 0.0001$).

Table 4.39: Serum creatinine over the study period according to sex: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Sex**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		11.3714	0.7185	297	15.83	<.0001
Sex	Female	-0.1364	0.02234	1030	-6.11	<.0001
Sex	Male	0	.	.	.	.
DAYS		-0.00038	0.000039	1030	-9.82	<.0001

Table 4.40: Serum creatinine over the study period according to gender: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Sex	1	1030	37.28	<.0001
DAYS	1	1030	96.39	<.0001

Tables 4.40 depicts that the serum creatinine is dependent on sex. As a result there was a statistical significant ($p < 0.0001$) difference in the estimated serum creatinine decrease per day between male and female patients.

Table 4.41: Serum creatinine over the study period according to age group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Age group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		11.5257	0.7455	296	15.46	<.0001
Age group	Less than 35 years	-0.04959	0.04351	1030	-1.14	0.2547
Age group	Greater than 35 and less than 55 years	-0.00964	0.04253	1030	-0.23	0.8208
Age group	Greater than 55 years	0	.	.	.	.
DAYS		-0.00039	0.000040	1030	-9.73	<.0001

Table 4.41 shows that there was a decrease of 0.00039 µmol/L in serum creatinine per day but this decrease was independent of the age group *(p* = 0.2176) (*table 4.42*).

Table 4.42: Serum creatinine over the study period according to age group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Age group (years)	2	1030	1.53	0.2176
DAYS	1	1030	94.70	<.0001

Table 4.43: Serum creatinine over the study period according to body mass group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Body mass group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		11.6210	0.7488	298	15.52	<.0001
Body mass group	Less than 49 kg	0.008968	0.02650	1027	0.34	0.7351
Body mass group	Greater than 49 and less than 56 kg	-0.00714	0.02330	1027	-0.31	0.7594
Body mass group	Greater than 56 and less than 64 kg	0.009480	0.02070	1027	0.46	0.6471
Body mass group	Greater than 64 kg	0	.	.	.	.
DAYS		-0.00040	0.000040	1027	-9.87	<.0001

Table 4.43 shows that there was an estimated decrease of 0.00040 µmol/L in serum creatinine per day. At 5 per cent confidence level, the decrease in serum creatinine in days is statistical significant ($p < 0.0001$). The decrease in serum creatinine according to body mass group was more than a decrease according to age group (*table 4.41*), and sex (*refer to table 4.39*). At 5 per cent confidence level, the difference in the decrease in serum creatinine among the

different body mass groups is not statistical significant in body mass group of less than 49 kg (p = 0.7351), greater than 49 kg and less than 56 kg (p = 0.7594), and in greater than 56 kg and less than 64 kg (p = 0.6471).

Table 4.44: Serum creatinine over the study period according to body mass group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Body mass group	3	1027	0.39	0.7585
DAYS	1	1027	97.48	<.0001

The serum creatinine decrease is not statistical dependent on the body mass group (p = 0.7585). As a result there was no difference in serum creatinine decrease per day in the different patient body mass groups (*table 4.43*).

Table 4.45: Serum creatinine over the study period according to initial ARV regimen: Solution for fixed effects

Solution for Fixed Effects						
Effect	**INITIAL ARV REGIMEN**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		11.7262	0.7465	295	15.71	<.0001
Initial ARV regimen	**D4T/3TC /EFV**	0.03345	0.2053	1029	0.16	0.8706
Initial ARV regimen	**AZT/3TC /NVP**	-0.1220	0.04625	1029	-2.64	0.0085
Initial ARV regimen	**AZT/3TC /EFV**	-0.01058	0.04710	1029	-0.22	0.8223
Initial ARV regimen	**TDF/3TC /NVP**	-0.03441	0.04556	1029	-0.76	0.4503
Initial ARV regimen	**TDF/3TC /EFV**	0	.	.	.	.
DAYS		-0.00040	0.000040	1029	-10.02	<.0001

Table 4.45 demonstrates that there was a decline of 0.00040 µmol/L in serum creatinine per day, which is statistical significant depended on the type of initial ARV regimen. At 5 per cent confidence level, the decrease in serum creatinine in days is significant (p < 0.0001). The difference in serum creatinine decrease among the different ART regimens is not statistic significant in D4T/3TC/EFV (p = 0.8706), AZT/3TC/EFV (p = 0.8223), and TDF/3TC/NVP (p = 0.4507). It is statistic significant for patients on AZT/3TC/NVP (p = 0.0085). The decrease in serum creatinine according to initial ART regimen was the same as that of body

mass group (*refer to table 4.43*). It was more than a decline according to age group (*refer to table 4.41*), and sex (*refer to table 4.39*).

Table 4.46: Serum creatinine over the study period according to initial ARV regimen: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Initial ARV regimen	4	1029	1.83	0.1206
DAYS	1	1029	100.35	<.0001

The serum creatinine decrease is independent of initial ART regimen a patient is taking. As a result there was no difference in serum creatinine decrease per day in the different initial ART regimens. At 5 per cent confidence level of significance, these differences are of no practical significance (p = 0.1206) (*table 4.46*). The serum creatinine will be dependent on the factors affecting renal function before the patients were put on ART. Problems with kidney function in HIV-positive patients may be due to other medications a patient is consuming or HIV/AIDS itself (Kamga *et al.*, 2010: 30).

Table 4.47: Serum creatinine over the study period according to adverse drug reactions: Solution for fixed effects

Solution for Fixed Effects						
Effect	**ADR. CODES**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		9.4099	0.7540	298	12.48	<.0001
ADR_CODE	No condition	-0.09413	0.04591	752	-2.05	0.0407
ADR_CODE	Peripheral neuropathy	-0.1610	0.1686	752	-0.95	0.3400
ADR_CODE	Skin rash	-0.1007	0.05827	752	-1.73	0.0842
ADR_CODE	Fanconi syndrome	-0.08615	0.1598	752	-0.54	0.5899
ADR_CODE	Nausea/vomiting	0	.	.	.	.
DAYS		-0.00028	0.000040	752	-6.81	<.0001

Table 4.47 demonstrates that there was a decrease of 0.00028 µmol/L in serum creatinine per day. At 5 per cent confidence level, the decrease in serum creatinine in days is statistically significant (p < 0.0001). At 5 per cent confidence level, the differences in the decrease in serum creatinine among the different ART ADRs were statistically significant for patients who had no condition (p = 0.0407), and those who developed skin rash (p = 0.0842). Also the decrease was not statistical significant for peripheral neuropathy (p = 0.3400), and Fanconi syndrome (p = 0.5899). The decrease according to ADRs experienced by patients was less than a decrease according to initial ART regimen (*refer to table 4.45*), age group (*refer to table 4.41*), sex (*refer to table 4.39*) and body mass group (*refer to table 4.43*). This decrease

in serum creatinine could be due to firstly, the renal function deteriorating with age and secondly, due to patients being on TDF- based regimens experiencing ADR of TDF (that is renal impairment). Nephrotoxicity, including renal insufficiency and Fanconi's syndrome, has been reported infrequently but the incidence, risk factors, and time to resolution remain uncertain (Nelson *et al.*, 2007: 1274).

Table 4.48: Serum creatinine over the study period according to adverse drug reactions: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
ADR_CODE	4	752	1.11	0.3518
DAYS	1	752	46.38	<.0001

4.2.1.6.4 Results of the average neutrophil count of patients

The covariance parameter estimates showed a 0.0529 residual. Table 4.49 shows that there was an increase of 0.000062 per cent in neutrophil count per day. At 5 per cent level, the increase in neutrophil count in days is not statistically significant ($p = 0.3294$).

Table 4.49: Neutrophil count over the study period according to sex: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Sex**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		2.7730	1.1735	290	2.36	0.0188
Sex	Female	-0.05168	0.02804	469	-1.84	0.0659
Sex	Male	0	.	.	.	.
DAYS		0.000062	0.000063	469	0.98	0.3294

Table 4.50: Neutrophil count over the study period according to sex: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Sex	1	469	3.40	0.0659
DAYS	1	469	0.95	0.3294

Tables 4.50 depicts that the neutrophil count is independent of sex. As a result there was a no difference in the estimated neutrophil count increase per day between male and female patients.

Table 4.51: Neutrophil count over the study period according to age group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Age group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		2.9834	1.1793	289	2.53	0.0119
Age group	Less than 35 years	0.07931	0.05281	469	1.50	0.1338
Age group	Greater than 35 and less than 55 years	0.02751	0.05179	469	0.53	0.5955
Age group	Greater than 55 years	0	.	.	.	.
DAYS		0.000046	0.000064	469	0.73	0.4674

There was a statistical significant increase of 0.000046 per cent in neutrophil count per day which was independent of the age group of the patient (*table 4.51*). As a result there was no difference in neutrophil count increase per day in the different patient age groups (*table 4.52*). At 5 per cent confidence level, the difference in the increase in neutrophil count among the different age groups is not statistic significant in patients less than 35 years of age (p = 0.1338), those greater than 35 and less than 55 years (p = 0.5955).

Table 4.52: Neutrophil count over the study period according to age group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Age group (years)	2	469	2.07	0.1278
DAYS	1	469	0.53	0.4674

Table 4.53: Neutrophil count over the study period according to body mass group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Body mass group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		2.6178	1.1810	291	2.22	0.0274
Body mass group	Less than 49 kg	0.03560	0.03574	466	1.00	0.3197
Body mass group	Greater than 49 and less than 56 kg	0.02667	0.03297	466	0.81	0.4190
Body mass group	Greater than 56 and less than 64 kg	-0.00537	0.03184	466	-0.17	0.8662
Body mass group	Greater than 64 kg	0	.	.	.	.
DAYS		0.000068	0.000064	466	1.07	0.2872

Table 4.53 shows that there was a statistical significance increase of 0.000068 per cent in neutrophil count per day which is independent of the body mass group. As a result there was no difference in the estimated neutrophil count increase per day in the different patient body mass groups (*table 4.54*). At 5 per cent confidence level, the difference in the increase in neutrophil count among the different age groups is not statistic significant in body mass group of less than 49 kg (p = 0.3197), body mass group of greater than 49 kg and less than 56 kg (p = 0.4190), and body mass group greater than 56 kg and less than 64 kg (p = 0.8662). The increase of neutrophil count according to body mass group was more than an increase according to age group (*table 4.51*), and sex (*refer to table 4.49*).

Table 4.54: Neutrophil count over the study period according to body mass group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Body mass group	3	466	0.68	0.5661
DAYS	1	466	1.14	0.2872

Table 4.55: Neutrophil count over the study period according to initial ARV regimen: Solution for fixed effects

Solution for Fixed Effects						
Effect	**INITIAL ARV REGIMEN**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		2.7415	1.1822	288	2.32	0.0211
Initial ARV regimen	**D4T/3TC /EFV**	-0.2202	0.2287	468	-0.96	0.3360
Initial ARV regimen	**AZT/3TC /NVP**	-0.00999	0.05212	468	-0.19	0.8480
Initial ARV regimen	**AZT/3TC /EFV**	-0.04472	0.05596	468	-0.80	0.4246
Initial ARV regimen	**TDF/3TC /NVP**	0.01113	0.05578	468	0.20	0.8419
Initial ARV regimen	**TDF/3TC /EFV**	0	.	.	.	.
DAYS		0.000062	0.000064	468	0.97	0.3304

Table 4.55 demonstrates that there was an increase of 0.000062 per cent in neutrophil count per day. At 5 per cent level, the increase in neutrophil count in days is not statistic significant (p = 0.3304), and is independed of the initial ARV regimen. The difference in neutrophil count increase among the different ART regimens is not statistic significant in D4T/3TC/EFV

(p = 0.3360), AZT/3TC/NVP (p = 0.8480), AZT/3TC/EFV (p = 0.4246), and TDF/3TC/NVP (p = 0.8419).

Table 4.56: Neutrophil count over the study period according to initial ARV regimen: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Initial ARV regimen	4	468	0.41	0.8028
DAYS	1	468	0.95	0.3304

The neutrophil count increase is independent of initial ART regimen a patient is taking (p = 0.8028). As a result there was no statistical significance difference in the neutrophil count increase per day in the different initial ART regimens.

Table 4.57: Neutrophil count over the study period according to adverse drug reactions: Solution for fixed effects

Solution for Fixed Effects						
Effect	**ADR. CODES**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		0.6289	1.4848	262	0.42	0.6723
ADR_CODE	No condition	0.1457	0.2794	234	0.52	0.6025
ADR_CODE	Peripheral neuropathy	0.4359	0.3805	234	1.15	0.2531
ADR_CODE	Skin rash	0.1985	0.2870	234	0.69	0.4899
ADR_CODE	Fanconi syndrome	0.7207	0.3620	234	1.99	0.0476
ADR_CODE	Nausea/vomiting	0.06725	0.2941	234	0.23	0.8193
ADR_CODE	Diarrhoea	0	.	.	.	.
DAYS		0.000166	0.000079	234	2.10	0.0364

Table 4.57 demonstrates that there was an increase of 0.00017 per cent in neutrophil count per day, but this was independent of adverse drug reactions a patient is experiencing. At 5 per cent confidence level, the difference in the increase in neutrophil count among the different ART ADRs is statistic significant for Fanconi (p = 0.0476). It is not statistical significant for peripheral neuropathy (p = 0.2531), no condition (p = 0.6025), skin rash (p = 0.4899), and nausea/vomiting (p = 0.8193). The increase of neutrophil count according to ADRs experienced by patients was more than an increase according to initial ART regimen (*refer to table 4.55*), age group (*refer to table 4.51*), sex (*refer to table 4.49*) and body mass group (*refer to table 4.53*).

Table 4.58: Neutrophil count over the study period according to adverse drug reactions: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
ADR_CODE	5	234	1.82	0.1095
DAYS	1	234	4.43	0.0364

The Hb profile increase is independent of the type of ADR a patient is experiencing (p = 0.2007).

4.2.1.6.5 Results of the average alanine aminotransferase (ALT) of patients

The covariance parameter estimates showed a 0.158. Table 4.59 shows that there was an increase of 0.000044 IU/L in ALT per day. At 5 per cent level, the increase in ALT in days is not statistically significant (p = 0.5060).

Table 4.59: ALT over the study period according to sex: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Sex**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		2.5925	1.2397	296	2.09	0.0374
Sex	Female	-0.3028	0.04473	1030	-6.77	<.0001
Sex	Male	0	.	.	.	.
DAYS		0.000044	0.000067	1030	0.67	0.5060

Table 4.60: ALT over the study period according to sex: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Sex	1	1030	45.83	<.0001
DAYS	1	1030	0.44	0.5060

Tables 4.60 depicts that ALT is dependent on sex. As a result there was a difference in the estimated ALT increase per day between male and female patients.

Table 4.61: ALT over the study period according to age group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Age group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		2.4298	1.2689	295	1.91	0.0565
Age group	Less than 35 years	-0.02527	0.08855	1030	-0.29	0.7754
Age group	Greater than 35 and less than 55 years	0.06058	0.08664	1030	0.70	0.4846
Age group	Greater than 55 years	0	.	.	.	.
DAYS		0.000043	0.000068	1030	0.63	0.5320

Table 4.61 shows that there was a statistical significant increase of 0.000043 IU/L in ALT per day, and was independent of the age group of the patient. As a result there was no difference in ALT increase per day in the different patient age groups (*table 4.62*). At 5 per cent confidence level, the difference in the increase in ALT among the different age groups is not statistic significant in patients less than 35 years of age (p = 0.7754), those greater than 35 and less than 55 years (p = 0.4846).

Table 4.62: ALT over the study period according to age group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Age group (years)	2	1030	1.51	0.2221
DAYS	1	1030	0.39	0.5320

Table 4.63: ALT over the study period according to body mass group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Body mass group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		2.3757	1.2839	297	1.85	0.0653
Body mass group	Less than 49 kg	0.04546	0.05102	1027	0.89	0.3731
Body mass group	Greater than 49 and less than 56 kg	0.01608	0.04461	1027	0.36	0.7186
Body mass group	Greater than 56 and less than 64 kg	0.007386	0.03911	1027	0.19	0.8503
Body mass group	Greater than 64 kg	0	.	.	.	.
DAYS		0.000046	0.000069	1027	0.67	0.5048

Table 4.63 shows that there was a statistical significance increase of 0.000046 IU/L in ALT per day which is independent of the body mass group. As a result there was no difference in the estimated ALT increase per day in the different patient body mass groups (*table 4.64*). At

5 per cent confidence level, the difference in the increase in ALT among the different age groups is not statistic significant in body mass group of less than 49 kg (p = 0.3731), body mass group of greater than 49 kg and less than 56 kg (p = 0.7186), and body mass group greater than 56 kg and less than 64 kg (p = 0.8503). The increase of ALT according to body mass group was more than an increase according to age group (*table 4.61*), and sex (*refer to table 4.59*).

Table 4.64: ALT over the study period according to body mass group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Body mass group	3	1027	0.31	0.8155
DAYS	1	1027	0.45	0.5048

Table 4.65: ALT over the study period according to initial ARV regimen: Solution for fixed effects

Solution for Fixed Effects						
Effect	**INITIAL ARV REGIMEN**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		2.7410	1.2682	294	2.16	0.0315
Initial ARV regimen	**D4T/3TC /EFV**	-0.1438	0.4125	1029	-0.35	0.7274
Initial ARV regimen	**AZT/3TC /NVP**	-0.2205	0.09501	1029	-2.32	0.0205
Initial ARV regimen	**AZT/3TC /EFV**	-0.07315	0.09536	1029	-0.77	0.4432
Initial ARV regimen	**TDF/3TC /NVP**	-0.02924	0.09327	1029	-0.31	0.7540
Initial ARV regimen	**TDF/3TC /EFV**	0	.	.	.	.
DAYS		0.000028	0.000068	1029	0.41	0.6784

Table 4.66 demonstrates that there was an increase of 0.000028 IU/L in ALT per day. At 5 per cent level, the increase in ALT in days is not statistic significant (p = 0.6784), and is independed of the initial ARV regimen. The difference in ALT increase among the different ART regimens is not statistic significant in D4T/3TC/EFV (p = 0.7274), AZT/3TC/EFV (p = 0.4432), and TDF/3TC/NVP (p = 0.7540). The difference was statistic significant in patients on AZT/3TC/NVP (p = 0.0205). The increase in ALT according to initial ART regimen was less than an increase according to age group (*refer to table 4.61*), sex (*refer to table 4.59*) and

body mass group (*refer to table 4.53*). The levels of ALT could be affected by factors such as liver toxicity, damage or disease which could have been brought about as a result of hepatitis co-infection, adverse drug reactions, alcohol abuse or other medication that can cause elevations in ALT levels. Liver enzymes laboratory monitoring determined by symptom appearance is recommended for patients on NNRTI-containing regimens (nevirapine and efavirenz) (World Health Organisation, 2010: 65).

Table 4.66: ALT over the study period according to initial ARV regimen: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Initial ARV regimen	4	1029	1.46	0.2129
DAYS	1	1029	0.17	0.6784

The ALT increase is independent of initial ART regimen a patient is taking (p = 0.2129). As a result there was no statistical significance difference in the ALT increase per day in the different initial ART regimens.

Table 4.67: ALT over the study period according to adverse drug reactions: Solution for fixed effects

Solution for Fixed Effects						
Effect	**ADR. CODES**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		5.7058	1.3402	297	4.26	<.0001
ADR_CODE	No condition	0.02187	0.07519	751	0.29	0.7712
ADR_CODE	Peripheral neuropathy	-0.1806	0.2756	751	-0.66	0.5125
ADR_CODE	Skin rash	-0.1349	0.09554	751	-1.41	0.1585
ADR_CODE	Fanconi syndrome	0.1522	0.2610	751	0.58	0.5601
ADR_CODE	Nausea/vomiting	0	.	.	.	.
DAYS		-0.00013	0.000072	751	-1.83	0.0670

Table 4.67 demonstrates that there was a decrease of 0.00013 IU/L in ALT count per day, but this was independent of adverse drug reactions a patient is experiencing. At 5 per cent confidence level, the difference in the decrease in ALT among the different ART ADRs was not statistic significant for Fanconi syndrome (p = 0.5601), peripheral neuropathy (p = 0.5125), no condition (p = 0.7712), and skin rash (p = 0.1585).

Table 4.68: ALT over the study period according to adverse drug reactions: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
ADR_CODE	4	751	1.89	0.1110
DAYS	1	751	3.36	0.0670

The ALT decrease is independent of the type of ADR a patient is experiencing ($p = 0.1110$).

4.2.1.6.6 Results of the average urea of patients

The covariance parameter estimates showed a 0.0677. Table 4.69 shows that there was at a 5 per cent confidence interval an estimated decrease of 0.00023 mmol/L in urea per day, which was statistically significant, but dependent on the sex of the patient ($p < 0.0001$).

Table 4.69: Urea over the study period according to sex: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Sex**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		5.5227	0.7960	295	6.94	<.0001
Sex	Female	-0.1007	0.02614	829	-3.85	0.0001
Sex	Male	0	.	.	.	.
DAYS		-0.00023	0.000043	829	-5.33	<.0001

Table 4.70: Urea over the study period according to sex: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Sex	1	829	14.84	0.0001
DAYS	1	829	28.46	<.0001

Table 4.70 depicts that urea is dependent on sex. As a result there was a statistical significant ($p < 0.0001$) difference in the estimated urea decrease per day between male and female patients.

Table 4.71: Urea over the study period according to age group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Age group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		5.3935	0.7987	294	6.75	<.0001
Age group	Less than 35 years	-0.1545	0.04831	829	-3.20	0.0014
Age group	Greater than 35 and less than 55 years	-0.07460	0.04728	829	-1.58	0.1150
Age group	Greater than 55 years	0	.	.	.	.
DAYS		-0.00022	0.000043	829	-5.10	<.0001

Table 4.71 shows that there was a decrease of 0.00022 mmol/L in urea per day and this decrease was dependent on the age group *(p* = 0.0009) (*table 4.72*).

Table 4.72: Urea over the study period according to age group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Age group	2	829	7.09	0.0009
DAYS	1	829	25.98	<.0001

Table 4.73: Urea over the study period according to body mass group: Solution for fixed effects

Solution for Fixed Effects						
Effect	**Body mass group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		5.3971	0.8060	296	6.70	<.0001
Body mass group	Less than 49 kg	0.04094	0.03252	826	1.26	0.2084
Body mass group	Greater than 49 and less than 56 kg	-0.00384	0.02882	826	-0.13	0.8939
Body mass group	Greater than 56 and less than 64 kg	0.002046	0.02666	826	0.08	0.9388
Body mass group	Greater than 64 kg	0	.	.	.	.
DAYS		-0.00023	0.000043	826	-5.20	<.0001

Table 4.73 shows that there was an estimated decrease of 0.00023 mmol/L in urea per day. At 5 per cent confidence level, the decrease in urea in days is statistical significant ($p < 0.0001$). The decrease of urea according to body mass group was more than a decrease according to age group (*table 4.71*), and similar to the decrease according to sex (*refer to table 4.69*). At 5 per cent confidence level, the difference in the decrease in urea among the different body mass groups is not statistical significant in body mass group of less than 49 kg ($p = 0.2084$),

greater than 49 kg and less than 56 kg (p = 0.8939), and in greater than 56 kg and less than 64 kg (p = 0.9388).

Table 4.74: Urea over the study period according to body mass group: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Body mass group	3	826	0.95	0.4156
DAYS	1	826	27.07	<.0001

The urea decrease is not statistical dependent on the body mass group (p = 0.4156). As a result there was no difference in urea decrease per day in the different patient body mass groups *(table 4.73).*

Table 4.75: Urea over the study period according to initial ARV regimen: Solution for fixed effects

Solution for Fixed Effects						
Effect	**INITIAL ARV REGIMEN**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		5.6872	0.8045	293	7.07	<.0001
Initial ARV regimen	**D4T/3TC /EFV**	-0.2628	0.2221	828	-1.18	0.2370
Initial ARV regimen	**AZT/3TC /NVP**	-0.1264	0.05309	828	-2.38	0.0175
Initial ARV regimen	**AZT/3TC /EFV**	-0.01245	0.05228	828	-0.24	0.8119
Initial ARV regimen	**TDF/3TC /NVP**	-0.07638	0.05182	828	-1.47	0.1409
Initial ARV regimen	**TDF/3TC /EFV**	0	.	.	.	.
DAYS		-0.00024	0.000043	828	-5.54	<.0001

Table 4.75 demonstrates that there was a decline of 0.00024 mmol/L in urea per day, which is statistical significant dependent on the type of initial ARV regimen. . At 5 per cent confidence level, the decrease in urea in days is significant (p <0.0001). The difference in urea decrease among the different ART regimens is not statistic significant in D4T/3TC/EFV (p = 0.2370), AZT/3TC/EFV (p = 0.8119), and TDF/3TC/NVP (p = 0.1409). It is statistic significant for AZT/3TC/NVP (p = 0.0175). The decrease in urea in relation to initial ART regimen was more than a decrease according to age group (*refer to table 4.71*), sex (*refer to table 4.69*) and body mass group (*refer to table 4.73*). Several medications used in the

treatment of HIV/AIDS are detrimental to the kidneys. These include antiretroviral medications and some medications used to treat HIV-related health problems. HIV disease can also cause kidney failure due to HIV infection of kidney cells which is known as HIV-Associated Nephropathy (HIVAN) (Okuonghae *et al.*, 2011: 27). Other causes of kidney disease include diabetes and high blood pressure.

Table 4.76: Urea over the study period according to initial ARV regimen: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Initial ARV regimen	4	828	2.15	0.0733
DAYS	1	828	30.66	<.0001

The urea decrease is dependent on initial ART regimen a patient is taking. As a result there was a difference in urea decrease per day in the different initial ART regimens. At 5 per cent confidence level of significance, these differences are of practical significance (p = 0.0733) (*table 4.76*).

Table 4.77: Urea over the study period according to adverse drug reactions: Solution for fixed effects

Solution for Fixed Effects						
Effect	**ADR. CODES**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		4.1007	0.7897	292	5.19	<.0001
ADR_CODE	No condition	-0.1086	0.07306	561	-1.49	0.1377
ADR_CODE	Peripheral neuropathy	-0.3934	0.2551	561	-1.54	0.1236
ADR_CODE	Skin rash	-0.1165	0.09609	561	-1.21	0.2260
ADR_CODE	Fanconi syndrome	-0.09848	0.2479	561	-0.40	0.6914
ADR_CODE	Nausea/vomiting	0	.	.	.	.
DAYS		-0.00015	0.000042	561	-3.54	0.0004

Table 4.77 demonstrates that there was a decrease of 0.00015 mmol/L in urea per day. At 5 per cent confidence level, the decrease in urea in days is statistical significant (p = 0.0004). At 5 per cent confidence level, the difference in the decrease in serum creatinine among the different ART ADRs is not statistic significant for no condition (p = 0.1377), skin rash (p = 0.2260), peripheral neuropathy (p = 0.1236), and Fanconi syndrome (p = 0.6914). The decrease of urea according to ADRs experienced by patients was less than a decrease in relation to initial ART regimen (*refer to table 4.75*), age group (*refer to table 4.71*), sex (*refer to table 4.69*) and body mass group (*refer to table 4.73*).

Table 4.78: Urea over the study period according to adverse drug reactions: Type 3 tests for fixed effects

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
ADR_CODE	4	561	0.90	0.4647
DAYS	1	561	12.52	0.0004

4.2.2 Phase two: Health professional questionnaire

The preliminary number of health professionals was 65. It consisted of 21 medical doctors, 24 nurses, 7 pharmacists and 13 pharmacy technicians. Out of 65 participants, only 49 health professionals responded to the questionnaire, resulting in 75.4 per cent response rate. This response rate was because participants did not want to answer the questionnaires. Their thoughts were that they will be exposing the negative side of ADR reporting/recording in their health facilities and also the weaknesses of the health system of the country.

4.2.2.1 Section A: Demographic information

This section provides demographic data of the health professionals who participated in the study. It shows the professional qualifications, sex, name of the health facility and type of the health centre. In addition, it depicts the work experience in HIV/AIDS management of the different health professionals and the duration of time they took in attending trainings in HIV/AIDS management and pharmacovigilance.

Question 1: Professional qualification

38.78 per cent (n = 19) of health professionals who answered the questionnaire were medical doctors, 34.69 per cent (n = 17) nurses, 10.2 per cent (n = 5) pharmacists and 16.33 per cent (n = 8) pharmacy technicians. The majority of the participants were medical doctors then nurses, pharmacy technicians and pharmacists respectively.

Question 2: What is your sex?

Among the 49 health professionals, 63.21 per cent (n = 31) were females and 36.73 per cent (n = 18) were males.

Question 3: Which health facility do you work for?

Four health facilities were used to source health professionals. All the health facilities (clinic or hospital) were found in Maseru district. Table 4.79 below depicts that Baylor College of Medicine had the highest number of health professionals working in close contact with patients either by prescribing, dispensing or both prescribing and dispensing of medication with 63.27 per cent and Khanya medical centre with 4.08 per cent representing a health facility with the least number of health professionals.

Table 4.79: Number of health professionals found in health facilities

Name of health facility	Number of health professionals (per cent), n = 49
Sankatana ART centre	20.41, n = 10
Khanya medical centre	4.08, n = 2
Baylor college of medicine	63.27, n = 31
St. Joseph's hospital	12.24, n = 6

n = number of observations

Question 4: Is it a clinic or hospital?

87.76 per cent (n = 43) of the health professionals worked in clinics while 12.24 per cent (n = 6) worked in a hospital. The majority of them worked in clinics as a result of decentralisation of ART to clinics for easy access of medication and clinical services for HIV-positive patients.

Question 5: Which sector are you working for?

Those from a private setting were 4.08 per cent (n = 2) and the rest were from a public setting 95.92 per cent (n = 47). Therefore, most of the health professionals worked in public health facilities.

Question 6: Work experience in the health professional's respective professional capacity or qualification

- *Question 6.1: Work experience in the management of HIV/AIDS.*

The different health professionals had working experience in HIV/AIDS management. Table 4.80 below showed that the majority of health professionals had working experience in HIV/AIDS management of less than 5 years.

Table 4.80: Health professionals with work experience in management of HIV/AIDS

Experience (years)	Number of health professionals (per cent), n = 49
Less than 5	61.22, n = 30
5 to 10	18.37, n = 9
10 to 15	8.16, n = 4
15 to 20	8.16, n = 4
Greater than 20	4.08, n = 2

n = number of observations

- *Question 6.2: Did you attend any training in HIV/AIDS management?*

Most health professionals did not attend any training on HIV/AIDS management with a percentage of 61.22 per cent (n = 30), 28.57 per cent (n = 14) went for a 2 days course, 4.08 per cent (n = 2) went for 5 days, and 6.12 per cent (n = 3) for 3 weeks.

- *Question 6.3: Did you attend any training in Pharmacovigilance?*

When the participants were undergraduate students, 8.16 per cent (n = 4) attended lectures on pharmacovigilance while the remaining 91.84 per cent (n = 45) did not have any lessons in this. 2.04 per cent (n = 1) of participants went to an in-service training and 97.96 per cent (n = 48) did not. 97.96 per cent (n = 48) of health professionals did not attend any training on pharmacovigilance specifically for ARVs and 2.04 per cent (n = 1) went for training. The Ministry of Health held a workshop on pharmacovigilance with poor attendance of 6.12 per cent (n = 3) of attendants and 93.88 per cent (n = 46) who did not partake according to the finding of the study.

4.2.2.2 Section B: Knowledge related questions

Question in this section were targeted towards assessing the basic knowledge of the health professional's familiarity with an adverse drug reaction reporting form and how it was used.

Question 7: Do the health care workers in your facility fill the adverse drug reactions form?

Out of 49 health professional, 4.08 per cent (n = 2) responded positively (yes) to the question while 95.92 per cent (n = 47) gave a negative (no) reply. The majority of health professionals showed that they did not fill the adverse drug reaction form in their different facilities.

Table 4.81: Health professionals who filled the ADR reporting form in their health facilities

Categories	Number of health professionals (per cent), n = 49
Yes	4.08, n = 2
No	95.92, n = 47

n = number of observations

Question 8: Who is qualified to fill the form? Please indicate if more than one professional was allowed to fill the ADR form?

The list of professionals to complete an ADR form was as follows: medical doctor, nurse, pharmacist, pharmacy technician and laboratory technician. The health professionals were to choose from the previously mentioned list of professions. As displayed in table 4.82 below, all categories of health professional are qualified to fill the ADR form, medical doctors have the highest number of positive responses of 93.44 per cent, pharmacist 93.88 per cent, nurses 87.76 per cent, pharmacy technicians 77.55 per cent and laboratory technicians 20.41 per cent.

Table 4.82: Different health professionals qualified to fill the adverse drug reactions reporting form

Categories	Number of health professionals (per cent)				
	Medical doctor, n = 49	Nurse, n = 49	Pharmacist, n = 49	Pharmacy, technician, n = 49	Laboratory technician, n = 49
Not answered	4.08, n = 2	4.08, n = 2	2.04, n = 1	4.08, n = 2	40.82, n = 20
Yes	93.88, n = 46	87.76, n = 43	93.88, n = 46	77.55, n = 38	20.41, n = 10
No	2.04, n = 1	8.16, n = 4	4.08, n = 2	18.37, n = 9	38.78, n = 19

n = number of observations

Question 9: To whom should the filled form be submitted? Please indicate if it could be submitted in more than one place.

The following places were selected as the possible places for the completed ADR reporting form to be submitted: director of pharmaceuticals, hospital pharmacotherapeutics committee (HPTC), national pharmacotherapeutics committee (NPTC) and Drug Companies. The health professional who took part in responding to this question had to choose among these places. As shown in table 4.83 below, the majority of health professionals stated that the place for submission of the completed ADR reporting form is director of pharmaceuticals 73.47 per cent followed by NPTC 57.14 per cent, HPTC 55.1 per cent and Drug Companies with 20.41

per cent. The highest number of participants 48.98 per cent showed that the drug companies were not the appropriate place to submit the form.

Table 4.83: Different options of the places where the ADR reporting form could be submitted

Categories	Percentages (per cent)			
	Director of pharmaceuticals, n = 49	Hospital pharmacotherapeutics committee (HPTC), n = 49	National pharmacotherapeutics committee (NPTC), n = 49	Drug companies, n = 49
Not answered	8.16, n = 4	10.2, n = 5	8.16, n = 4	30.61, n = 15
Yes	73.47, n = 36	55.1, n = 27	57.14, n = 28	20.41, n = 10
No	18.37, n = 9	34.69, n = 17	34.69, n = 17	48.98, n = 24

n = number of observations

Question 10: How do you rule out side effects caused by other medication a patient is taking? If more than one please indicate.

There are several ways health professionals use to rule out side effects caused by other medication and not ARVs. The methods from which they had to choose from while attempting this question included: using World Health Organisation (WHO) definition of ADR, Lesotho ART guidelines, consulting Hospital Pharmacotherapeutics Committee (HPTC) or National Pharmacotherapeutics Committee (NPTC), referring to academicians, and referring to text books of medicine and surgery and medical science. The results displayed in table 4.84 below show that most health professionals relied on the Lesotho ART guidelines (97.96 per cent), followed by using WHO definition of ADR (73.47 per cent), and reference to text books of medicine and surgery and medicinal science (69.39 per cent). The health professionals did not consult with HPTC or NPTC (89.8 per cent), or refer to academicians (77.55 per cent).

Table 4.84: Possible methods used by health professionals to rule out side effects caused by other medication a patient is taking and not ARVs

Categories	Number of health professionals (per cent)				
	Using WHO definition of ADR, n = 49	Lesotho ART guidelines, n = 49	Consulting HPTC or NPTC, n = 49	Referring to academicians, n = 49	Referring to text books of medicine and surgery and medicinal science, n = 49
Not answered	6.12, n = 3	0	6.12, n = 3	4.08, n = 2	2.04, n = 1
Yes	73.47, n = 36	97.96, n = 48	4.08, n = 2	18.37, n = 9	69.39, n = 34
No	20.41, n = 10	2.04, n = 1	89.80, n = 44	77.55, n = 38	28.57, n = 14

n = number of observations

Question 11: How important do you think it is to fill the ADR reporting form?

None of the health professional thought the filling of the ADR reporting form was unimportant or only slightly important. 20.41 per cent said it was important, 48.98 per cent very important and 30.61 per cent critical. These conclude that the majority of the health professionals view filling the ADR reporting form as very important.

Table 4.85: The importance of filing the ADR reporting form

Categories	Number of health professionals (per cent), n = 49
Not important	0
Important	20.41, n = 10
Very important	48.98, n = 24
Critical	30.61, n = 15

n = number of observations

4.2.2.3 Section C: Health professional's opinion

Questions in this section of the questionnaire determined the reasons why the health workers might not fill the ADR form by evaluating their views towards the ADR form and the reporting system as a whole.

Question 12: How often do you fill the ADR reporting form?

The majority of health professionals (91.84 per cent) did not fill the adverse drug reactions reporting form in their working environment.

Table 4.86: How often health professionals filled the adverse drug reactions reporting form in their respective facilities

Categories	Number of health professionals (per cent), n = 49
Never	91.84, n = 45
Sometimes	6.12, n = 3
Often	2.04, n = 1
Always	0

n = number of observations

Question 13: How easy is it to fill the ADR reporting form?

The majority of the participants found it easy to fill the ADR reporting form (40.82 per cent), 32.65 per cent found it very easy, 6.12 per cent said it was difficult, and 4.08 per cent found it to be extremely easy to complete. This question was not answer by 16.33 per cent of the health professionals.

Table 4.87: Simplicity of filling the ADR reporting form.

Categories	Number of health professionals (per cent), n = 49
Not answered	16.33, n = 8
Difficult	6.12, n = 3
Easy	40.82, n = 20
Very easy	32.65, n = 16
Extremely easy	4.08, n = 2

n = number of observations

Question 14: How efficient is the current system of reporting ADR?

The efficiency of the current reporting system of ADRs in different health facilities was found to be slightly efficient by 26.53 per cent of the health professionals, 16.33 per cent rated it as moderately efficient while 18.37 per cent said it was very efficient. 38.78 per cent of the health professionals did not find the system efficient. In conclusion, most health professionals found the current reporting system not efficient.

Table 4.88: The efficiency of the current ADR reporting system in the health facilities as assessed by health professionals

Category	Number of health professionals (per cent), n = 49
Not efficient	38.78, n = 19
Slightly efficient	26.53, n = 13
Moderately efficient	16.33, n = 8
Very efficient	18.37, n = 9

n = number of observations

Question 15: How do you think the current ADR reporting system is affected by the following factors: time consuming, lack of training, afraid of taking responsibility, forms not available and/or lack of confidence in discussing the ADR with other colleagues?

In all the categories mentioned in table 4.89 below, the majority of health professionals were neutral in their response. Also a greater number of health professionals stated that lack of training and absence of the ADR reporting forms were the two reasons that mostly affected the current reporting systems in the health facilities.

Table 4.89: Reasons affecting the current adverse drug reactions reporting system in the health facilities

Categories	Number of health professionals (per cent)				
	Time consuming, n = 49	Lack of training, n = 49	Afraid of taking responsibility, n = 49	Forms not available, n = 49	Lack of confidence in discussing the ADR with other colleagues, n = 49
Not answered	2.04, n = 1	4.08, n = 2	8.16, n = 4	2.04, n = 1	6.13, n = 3
Strongly agree	4.08, n = 2	51.02, n = 25	32.65, n = 16	93.88, n = 46	4.08, n = 2
Agree	16.33, n = 8	14.29, n = 7	2.04, n = 1	4.08, n = 2	4.08, n = 2
Neutral	57.14, n = 28	12.24, n = 6	30.61, n = 15	0	42.86, n = 21
Disagree	16.33, n = 8	10.20, n = 5	14.29, n = 7	0	8.16, n = 4
Strongly disagree	4.08, n = 2	8.16, n = 4	12.24, n = 6	0	34.69, n = 17

n = number of observations

4.2.2.4 Section D: Influence of the professional environment

Section D assessed the participation of professionals in ADR reporting activities and how they maintain patient safety in their different work settings.

Question 16: How do you report ADRs?

The health professionals were given different methods used to report ADRs and they were to select among these methods. They included yellow card scheme, individual case safety reports, structured databases, patient bukana, and patient HIV/AIDS ART card. According to table 4.90 below, the yellow card scheme was not used at all by health professionals. They mainly used patient bukana (85.71 per cent) and structures databases (57.14 per cent).

Table 4.90: Different methods used when reporting adverse drug reactions

Categories	Number of health professionals (per cent)				
	Yellow card scheme, n = 49	Individual case safety reports, n = 49	Structured databases, n = 49	Patient bukana, n = 49	Patient HIV/AIDS ART card, n = 49
Not answered	0	0	0	6.12, n = 3	93.88, n = 46
Yes	0	34.69, n = 17	57.14, n= 28	85.71, n = 42	6.12, n = 3
No	100, n = 49	65.31, n = 32	42.86, n = 21	8.16, n = 4	0

n = number of observations

Question 17: How often do you educate patients about adverse drug reactions? Question 18: How often do you teach patients about regimen specific side effects?

6.12 per cent (n = 3) of the health professionals who took part in the study never educated patients about ADR, 28.57 per cent (n = 14) sometimes did, 32.65 per cent (n = 16) often educated patients, and 32.65 per cent (n = 16) always did. 10.2 per cent (n = 5) never taught patients about regimen specific side effects, 24.49 per cent (n = 12) sometimes did, 22.45 per cent (n = 11) often did, and 42.86 per cent (n = 21) of the health professionals always educated patients about regimen specific side effects.

Table 4.91: Patient education on adverse drug reactions and regimen specific side effect

Categories	**Number of health professionals (per cent)**	
	Education on adverse drug reactions, n = 49	Education on regimen specific side effect, n = 49
Never	6.12, n = 3	10.2, n = 5
Sometimes	28.57, n = 14	24.49, n = 12
Often	32.65, n = 16	22.45, n = 11
Always	32.65, n = 16	42.86, n = 21

n = number of observations

Question 19: How do you pick adverse effects? If more than one option exists please indicate.

The health professionals were given the following options to choose from: laboratory results, patient clinical examination, both laboratory results and patient clinical examination, and ask patient questions. Table 4.92 shows that the majority of health professionals use patient clinical examination (97.96 per cent), laboratory results (93.88 per cent), both patient clinical examination and laboratory results (89.8 per cent), and asking patients questions (85.71 per cent). They mostly rely on patient clinical examination to detect ADRs**.**

Table 4.92: Different ways which health professionals utilize to detect adverse drug reactions

Categories	**Number of health professionals (per cent)**			
	Laboratory results, n = 49	Patient clinical examination, n = 49	Both laboratory results and patient clinical examination, n = 49	Ask patient questions, n = 49
Not answered	2.04, n = 1	0	4.08, n = 2	2.04, n = 1
Yes	93.88, n = 46	97.96, n = 48	89.80, n = 44	85.71, n = 42
No	4.08, n = 2	2.04, n = 1	6.12, n = 3	12.24, n = 6

n = number of observations

4.3 DISCUSSION

4.3.1 Drug Utilisation review

Nutritional status and HIV infection are factors which add to immune system dysfunction leading to the emergency of opportunistic infections (Lategan *et al.*, 2010: 197). Body mass loss is used as a warning sign to prescribers to start investigations and treatment (National Department of Health South Africa, 2010: 28). Comparing the average body mass of patients on initial ART regimen (*refer to table 4.5*) with average body mass of patients who did not experience any ADRs (*refer to table 4.12*); the body mass loss in patients was not significant. On the other hand, comparing the initial average body mass of patients on initial regimen (*refer to table 4.5*) with average body mass of patients who experienced ADRs (*table 4.9*); there was an average body mass loss in these patients. Therefore, patient body mass loss in HIV-positive patients predicts either a progression of disease, opportunistic infection or death hence why it is important to monitor HIV-positive patients' body mass.

The average body mass increased by 4.62 kg between the baseline (57.48 ± 11.82 kg, *n* = 300) and last consultation (62.19 ± 11.11 kg, *n* = 300) (*refer to table 4.15*). There was a

general increase in average body mass in female and male patients, in patients with the different age groups, in patients on initial ART regimens, and in patients with no condition of ADR (*refer to tables 4.16, 4.17, 4.18, 4.19*). Generally, body mass gain in patients shows that the majority of patients were responding well to their antiretroviral treatment.

The majority of female patients experienced skin rash as compared to male patients (*refer to table 4.8).* This could have been because females are more prone to developing cutaneous drug reactions than males. According to Shibuyama *et al.* (2006: 1081), self-determining risk factors which may led to the development of cutaneous reactions include female sex, CD4 cell counts less than 100 cells/mm^3 and age greater than 40 years. Additionally, skin rash (*refer to tables 4.7 & 4.8*) experienced by most patients could be due to non-nucleoside reverse transcriptase inhibitors (NVP and EFV) which formed part of their ART regimens. The main side effects induced by NNRTIs are cutaneous problems (rash) and hepatotoxicity (Wit *et al.,* 2008: 933).

Nausea/vomiting is one of the side effects caused by AZT and TDF and some of the patients who developed these adverse drug reactions were on either AZT- or TDF- based regimens. Anaemia which is one of the adverse effects caused by AZT significantly impacts on the quality of life because of its association with nausea, fatigue and weakness (Agarwal *et al.,* 2010: 387). Therefore, nausea/vomiting might have been signs of anaemia in patients who had these side effects. Additionally, patients on tenofovir-based regimens commonly experience mild to moderate gastrointestinal events which may include diarrhoea, nausea, flatulence and vomiting (Kumarasamy *et al.,* 2011: 791). The number of patients whose regimen changed due to ADRs was five. The number of observations was too small to make any conclusions.

Immunological screening of HIV-positive patients is assessed using CD4 cell count. The average CD4 cell count increased by 253.12 cell/mm^3 between the baseline (175.75 ± 114.47 cell/mm^3, n = 298) and last consultation (428.87 ± 159.96 cell/mm^3, n = 297) (*refer to table 4.15*). There was a general increase in CD4 cell count in female and male patients, in patients within the different age groups, and in patients on initial ART regimens (*refer to tables 4.16, 4.17, & 4.18*). The increase in CD4 cell counts in patients revealed that the patients were adjusting well to treatment. Antiretroviral treatment guidelines use increases in CD4 cell

counts after initiation of therapy as a measure of immunologic response to therapy (The antiretroviral therapy cohort collaboration, 2009: 358).

Hb profile is measured to assess the occurrence of anaemia. Anaemia in HIV-infected patients may lead to serious implications which range from functional and quality-of-life decrements to an association with disease progression and decreased survival (Volberding *et al.*, 2004: 1454). It is done routinely especially for patients on AZT- based regimen. Normal levels of Hb in women are 12.1 to 15.1 g/dL and 13.8 to 17.2 g/dL in males (Marks & Glader, 2008). The average Hb profile increased by 1.02 g/dL between the baseline (11.90 ± 2.26 g/dL, n = 286) and last consultation (12.92 ± 1.91 g/dL, n = 182) (*refer to table 4.15*). There was a general increase in Hb profile in female and male patients, in patients from the different age groups, in patients on initial ART regimens, and in patients who had no ADRs (*refer to tables 4.16, 4.17, 4.18, & 4.19*). The increase in Hb indicates that the patients were adjusting very well to their regimens.

Normal ranges of neutrophil count are 40 to 80 per cent (Curry, 2012). The average neutrophil count decreased by 0.38 per cent between the baseline (52.98 ± 13.84 per cent, n = 256) and last consultation (52.60 ± 13.11 per cent, n = 57) (*refer to table 4.15*). There was an increase in neutrophil count in patients in age groups greater than 55 years, those on D4T/3TC/EFV, and those on TDF/3TC/EFV (*refer to table 4.17, 4.18, section 4.2.1.5*). The major decrease in neutrophil count was experienced by patients on AZT- based regimens (*refer to table 4.18*) and this could have been due to patients experiencing AZT adverse reaction (neutropenia). There was a general decrease in neutrophil count in female and male patients, in patients from the different age groups, and in patients on initial ART regimens (*refer to tables 4.16, 4.17, & 4.18*). The decrease could also signify the advancing of the stages of AIDS. Neutropenia is common in advanced stages of AIDS and often caused or exacerbated by concomitant myelosuppressive drugs, in addition, ADRs and their complications can cause neutropenia in patients with HIV/AIDS (Dikshit *et al.*, 2009).

The ALT blood test is used to determine if the liver is damaged or diseased. The normal average levels of ALT in males are 10 to 40 IU/L and in females 7 to 35 IU/L (Health testing centres: 2013). The average ALT decreased by 1.97 IU/L between the baseline (30.25 ± 26.21 IU/L, n = 275) and last consultation (28.28 ± 15.31 IU/L, n = 299) (*refer to table 4.15*). There was a general decrease in ALT in female and male patients, in patients from the

different age groups, and in patients on initial ART regimens (*refer to tables 4.16, 4.17, & 4.18*). There was an increase in ATL in patients in age groups greater than 55 years; those on D4T/3TC/EFV, AZT/3TC/NVP, and those without an ADR condition (*refer to tables 4.17, 4.18, & 4.19*). Regardless of the decreases in the levels of ALT, the levels were within the normal range in the majority of patients. As a result, the test shows the absence of liver toxicity or damage which could have been brought about as a result of adverse drug reactions, alcohol abuse or other medication that can cause elevations in ALT levels.

The normal range of serum creatinine for males is 53 to 106 µmol/L and 70 to 133 µmol/L for females (Walker *et al.*, 1990). According to Nelson *et al.* (2007: 1274), nephrotoxicity, including renal insufficiency and Fanconi's syndrome, has been reported infrequently but the incidence, risk factors, and time to resolution remain uncertain. The average serum creatinine decreased by 24.3 µmol/L between the baseline (86.92 ± 23.80 µmol/L, n = 274) and last consultation (62.62 ± 13.77 µmol/L, n = 299) (*refer to table 4.15*). There was a general decrease in serum creatinine in female and male patients, in patients from the different age groups, in patients on initial ART regimens, and in patients with no ADR condition (*refer to tables 4.16, 4.17, 4.18, & 4.19*). This decrease in serum creatinine could be due to the renal function deteriorating with age or due to patients being on TDF- based regimens experiencing ADR of TDF (that is renal impairment).

Several medications used in the treatment of HIV/AIDS are detrimental to the kidneys. This includes antiretroviral medications and some medications used to treat HIV-related health problems. Normal range of blood urea nitrogen (BUN) is 2.5 to 8.0 mmol/L (Food and Drug Administration news, 2012). The HIV disease can also cause kidney failure due to HIV infection of kidney cells which is known as HIV-Associated Nephropathy (HIVAN) (Okuonghae *et al.*, 2011: 27). Other causes of kidney disease include diabetes and high blood pressure. Generally, a high blood urea nitrogen level means that the kidneys are not performing well. The average urea decreased by 0.55 mmol/L between the baseline (3.87 ± 1.52 mmol/L, n = 268) and last consultation (3.32 ± 0.83 mmol/L, n = 236) (*refer to table 4.15*). There was a general decrease in urea in female and male patients, in patients for the different age groups, in patients on initial ART regimens, and in patients with no ADR condition (*refer to tables 4.16, 4.17, 4.18, & 4.19*). Therefore, the patients are doing well on treatment.

4.3.2 Health professional's questionnaire

As illustrated in *table 4.90,* the highest number of health professionals used the patient bukana as opposed to structured databases, individual case safety reports, and patient HIV/AIDS ART card. As a result, the most popular or used method of recording ADRs in the health facilities is the patient bukana. The patient bukana is kept by the patient. The patients might either loss or misplace the bukana with the ADR information and use a new one without the ADR information. This is dangerous to the patient as they might be re-challenged with the drug they experienced ADRs when taking it.

Table 4.86 shows that the majority of the health professionals never completed the ADR reporting form in their health facilities even though they found the form very straightforward to complete with few and/no problems (*refer to table 4.87*). As a result, information on ADRs was lacking. This leads to lack of improvement in patient management and health care system. This could be due to some of the reasons which affected the current reporting systems in their health facilities. These reasons being forms not being made available for them to complete, lack of training, and being afraid of taking responsibility, respectively *(also refer to table 4.89)*. The health professionals stated that it was very important to fill the ADR reporting form (*refer to table 4.85*).

Table 4.8 shows that most health professionals consider medical doctors and pharmacists as the main professionals to fill in the adverse drug reactions reporting form followed by nurses and lastly pharmacy technicians. This concludes that medical doctors, pharmacists, nurses and pharmacy technicians are considered by the health professionals to be the qualified professionals to complete the ADR reporting form while laboratory technicians are not. The health professionals who took part in the study viewed the director of pharmaceuticals as the main place where the ADR reporting form should be submitted after being filled (*refer to table 4.83*). As displayed in *table 4.84*, the highest numbers of health professionals used the Lesotho ART guidelines followed by those who used the World Health Organisation definition of ADR, referring to text books of medicine and surgery and medicinal science, and referring to academicians respectively.

The patients are being taught about adverse drug reactions and regimen specific side effects depending on the type of regimen they are taking (*refer to table 4.91*). This will keep the patient informed and involved in their treatment plan. Patient confidence is increased in the

health care system and they could be able to identify ADRs and get help immediately. A very small number of health professionals do not educate patients at all on adverse drug reactions and regimen specific side effects.

Most health professionals used patient clinical examinations to detect adverse effects, followed by the utilisation of laboratory results, both laboratory results and patient clinical examination, and asking the patients questions respectively (*refer to table 4.92*). As a result health professionals do have knowledge of how to detect adverse effects. These methods when used in combination increases the chances of the health professional detecting ADRs and thus taking appropriate action.

4.4 CHAPTER SUMMARY

In this chapter the results of the empirical investigation were outlined. The focus mainly fell on the occurrence of adverse drug reactions in HIV-positive patients on TDF- or AZT- based ART regimens for the study period 1 January 2010 to 31 December 2011. In addition, the opinion of health professionals on adverse drug reactions recording and reporting was looked at. In chapter five, the conclusion, limitations and recommendations of the study will be discussed.

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

The conclusions of the study are based on the results of the literature review and the empirical investigation. Recommendations derived from this study regarding assessment of adverse drug reactions and the recording and reporting of adverse drug reactions caused by ARV medicine will be discussed. Limitations encountered during the study were discussed in chapter 3.

5.2 CONCLUSIONS

5.2.1 The following conclusions can be formulated with regard to the literature review:

*The **first research objective** was to outline the treatment protocols as stated by the Lesotho 2010 and World Health Organisation 2010 antiretroviral treatment guidelines and other related treatment guidelines.*

This was done by evaluating treatment protocols for HIV-positive patients with and/or without co-morbid diseases as stated by the World Health organisation 2010 and 2013 ART treatment guidelines for HIV-positive adolescents and adults, Lesotho 2010 ART guidelines, and tuberculosis treatment guidelines (*refers to section 2.6*).

Table 2.6.1, section 2.6.1 indicates recommendations for initiating antiretroviral treatment in adults and adolescents with documented HIV infection according to the World Health Organisation (World Health Organisation, 2013: E1). *Section 2.6.1* also states the first-line and second-line regimens proposed by the World Health Organisation (World Health Organisation, 2010: 20). Recommended antiretroviral treatment regimens in Lesotho comprise of zidovudine, abacavir, tenofovir, lamivudine, nevirapine and efavirenz as first-line drugs, lopinavir/ritonavir and atazanavir/ritonavir as second-line drugs, and darunavir, ritonavir as a pharmacokinetic booster; raltegravir and etravirine as third-line drugs (Ministry of Health and Social Welfare, 2010: 48-59) *(refer to section 2.6.2 last paragraph). Section 2.6.3.1* indicates how HIV-positive adolescents and adult patients with and/or without concomitant TB must be treated (World Health Organisation, 2011b: 5-6 & World Health Organisation, 2010: 22). Cotrimoxazole prophylaxis guidelines for HIV-infected individuals, including those on ART, particularly from Pneumocystis jiroveci (formerly Pneumocystis carinii) (World Health Organisation, 2008:13) were discussed *(section 2.6.3.2)*. Lastly, *section 2.6.3.3* points out the management of HIV-positive patients on ART with co-morbid

diseases which may include diabetes, hypertension and hepatitis B virus may be treated (WHO, 2010: 20 & 33).

*The **second research objective** was to describe ARV drugs according to different classification systems and possible side effects.*

The focus was on different classes of antiretroviral drugs and their examples. Also class side effects, specific drug side effects and highly active antiretroviral therapy (HAART) regimens were addressed (*refer to section 2.5*).

Table 2.5.1.1, section 2.5 depicts different classes of antiretroviral drugs and examples for each classification (Hartmann & Enk (2007: A1099), Kumarasamy *et al.* (2011: 789) & Orrell (2011: 235). According to Shibuyama *et al.* (2006: 1075), antiretrovirals are categorised according to their mechanism of action. The different drug classes include nucleoside and nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors, and fusion inhibitors (De Clercq, 2010: 507) *(section 2.5.1.1).*

The possibility of specific side effects differs from drug to drug, from drug class to drug class, and from patient to patient (Montessori *et al.*, 2004: 229). Class specific side effects were elaborated on in *sections 2.5.1.1.1 to 2.5.1.1.4*. *Table 2.5.3, section 2.5.3* illustrates specific drug side effects (Hartmann & Enk (2007); Kumarasamy *et al.* (2011: 791), Ministry of Health and Social Welfare (2010: 53), Orrell (2011: 235) & World Health Organisation (2010:66)). Drug side effects, regimens complexity, co-morbidities, life-long pill consumption and the quality of life of patients on HAART may limit the outcome of ART (AIDS support and technical assistance resources, 2010: 6). Categories and examples of HAART regimens are shown in *table 2.5.2, section 2.5.2* (Maniar *et al.* (2007: 34) & World Health Organisation (2010: 34)). Highly Active Antiretroviral Therapy combines at least three antiretroviral (ARV) (Rajesh *et al.*, 2010: 84).

*The **third and fourth research objectives** were to emphasise the importance of adverse drug reactions reporting on antiretroviral drugs; and to determine from the literature how proper documentation of ADR can be done and maintained to improve patient safety respectively.*

These research objectives were clearly elaborated on in *section 2.8.1 & 2.8.2*. Antiretrovirals are very toxic and need regular monitoring; therefore reporting of ADRs will help enhance clinical management of HIV-positive patients (World Health Organisation, 2006d: 11). Adverse drug reactions experienced by patients are very important to record and report in

order to improve patient safety. As a result, the concept of pharmacovigilance was focused on. Drug safety is very vital in public health and clinical practice as a result there is a great need for pharmacovigilance centres in different countries (World Health Organisation, 2002a: 5). A national pharmacovigilance centre is responsible for creating a standardised ADR reporting documentation to be used in a country. Some of the duties to be carried out by a pharmacovigilance centre comprise information dissemination to practitioners, patients and the public on benefit, harm, effectiveness and risk of medicines (World Health Organisation, 2002a: 11).

The clinicians and other prescribers should be advised to record any clinical event recorded in the patient medical record also in the adverse event questionnaire or form. For proper assessment and monitoring of ADRs, the following should be recorded: all new events even if minor; change in a pre-existing condition; abnormal changes in laboratory tests; accidents; all deaths with date and cause; and possible interactions (pharmaceutical or traditional medicines; oral contraceptives, tobacco, alcohol or other commonly ingested products which the patient may not realize are "medicines") (World Health Organisation, 2007b: 6).

The main pharmacovigilance methods proposed include spontaneous reporting, cohort event monitoring and targeted spontaneous reporting (World Health Organisation, 2011c). In spontaneous reporting, the health professionals and pharmaceutical manufacturers voluntarily submit suspected adverse drug reactions to the national regulatory authority. In cohort event monitoring, all adverse events occurring to a person taking antiretroviral drugs are collected regardless of the causality or relationship with the antiretroviral drugs (Joint United Nations Programme on HIV/AIDS & World Health Organisation, 2011: 1). Targeted spontaneous reporting enables focus on a specific drug of interest (such as tenofovir or zidovudine), a specific population of interest (such as women receiving extended antiretroviral prophylaxis or treatment for preventing the mother-to-child transmission of HIV or people switching from stavudine to tenofovir) or a specific adverse drug reaction (such as anaemia) (Pal *et al.*, 2013: 77) (*refer to section 2.8.2*).

*The **fifth research objective** was to evaluate the role of health professionals in identification, recording and reporting of adverse drug reactions.*

Laboratory monitoring using different laboratory techniques depending on the type of regimen the patient is taking is used to detect different adverse reactions resulting from antiretroviral drugs. Patients on ARVs are to be monitored using laboratory tests to assess

their well-being and if there is any occurrence of an adverse drug reactions (ADRs) (Mehta *et al.*, 2007: 403) *(refer to section 2.7)*. Health professionals in direct contact with patients either through prescribing, dispensing or both are expected to record and report adverse drug reactions. Identification and reporting of ADRs is mostly done by confident health professionals in their aptitude to detect, manage and prevent these reactions. A major role in ADR monitoring and reporting is played by health training organisations and national pharmacovigilance centres by including principles and methods of pharmacovigilance as a course in schools of pharmacy, medicine and nursing (World Health Organisation, 2002a: 24) *(section 2.8.3, chapter 2)*.

*Table 2.7.1, section 2.*7 demonstrated different laboratory tests conducted depending on the type of regimen the patient is taking used in Lesotho (Ministry of Health and Social Welfare (2010: 63) & World Health Organisation (2010: 65)). Individual tests conducted include creatinine, haemoglobin profile, neutrophils, CD4 cell count, and alanine aminotransferase which were discussed in detail in *sections 2.7.1.1 to 2.7.1.5*. When an unknown ADR occurs due to medication, it is easy for the public health sector to notice and take appropriate action which may include withdrawal of that particular drug from the market (David *et al.*, 2010: 2). Occurrence of adverse effects (known or unknown), drug interactions (with foods or other medicines) and other risk factors are observed during the years of post-medicine release into the public (World Health Organisation, 2004: 1) *(section 2.8.3)*.

5.2.2 The following conclusions can be formulated with regard to the empirical investigation:

5.2.2.1 Drug utilisation review

*The **first research objective** was to assess the frequency at which adverse drug reactions (ADRs) occurred in patients taking either tenofovir or zidovudine based regimens.*

The average body mass of both female 57.37 ± 13.01 kg (n = 172) and male 57.62 ± 10.04 kg (n = 128) patients is similar. Comparing the average body mass of patients on initial ART regimen (*refer to section 4.2.1.1, table 4.5*) with average body mass of patients who did not experience any ADRs (*refer to table 4.12, section 4.2.1.3*); the body mass loss in patients was not significant. *Table 4.12, section 4.2.1.3* displayed that the average body mass of patients in age group greater than 35 and less than 55 years (58.91 ± 11.91, n = 154), and greater than 55 years (58.77 ± 15.56 kg, n = 26) was higher than for patients in age group of less than 35 years of age (55.36 ± 10.49 kg, n = 120). Comparing the average body mass of patients on

initial ART regimen (*refer to table 4.5, section 4.2.1.1*) with average body mass of patients who did not experience any ADRs (*refer to table 4.12, section 4.2.1.3*); the average body mass was similar in patients in age groups of greater than 35 and less than 55, and greater than 55 years of age. A significant difference was seen with patient in age group less than 35 years.

Patients who experienced ADRs were 44. Of the patients who experience ADRs, 72.73 per cent (n = 32) of these patients were female and 27.27 per cent (n = 12) were male. The majority of patients who developed ADRs were female. Most patients who experienced ADRs were patients in age group less than 35 years (54.55 per cent, n = 24) and those in age group of years greater than 35 and less than 55 (36.36 per cent, n = 16). Patients greater than 55 year of age experienced less ADRs as a result of the ART regimen they were taking. The younger adults experienced more ADRs than older adults (*refer to table 4.6, section 4.2.1.2*).

The majority of patients in age groups of less than 35, and greater than 35 and less than 55 experienced ADRs. In age group of patients less than 35 years, 36.36 per cent (n = 16) developed skin rash, 15.91 per cent (n = 7) nausea/vomiting, and 2.27 per cent (n = 1) had diarrhoea. In patients greater than 35 and less than 55 years of age, 22.73 per cent (n = 10) had skin rash, 2.27 per cent (n = 1) Fanconi syndrome, 6.82 per cent (n = 3) nausea/vomiting, and 2.27 per cent (n = 1) presented with diarrhoea (*refer to table 4.7, section 4.2.1.2*).

A greater number of patients who experienced ADRs were females with 43.18 per cent (n = 19) presenting with skin rash, 27.27 per cent (n = 12) with nausea/vomiting, and 2.27 per cent (n = 1) with diarrhoea. In male patients, 2.27 per cent (n = 1) had peripheral neuropathy, 18.18 per cent (n = 8) skin rash, 2.27 per cent (n = 1) Fanconi syndrome, 2.27 per cent (n = 1) nausea/vomiting, and 2.27 per cent (n = 1) diarrhoea. Male patients experienced all the types of adverse drug reactions (*refer to table 4.8, section 4.2.1.2*) as opposed to female patients. The majority of female patients experienced skin rash. This could be because females are more prone to developing cutaneous drug reactions than males. Self-determining risk factors which may led to the development of cutaneous reactions include female sex, CD4 cell counts less than 100 cells/mm^3 and age greater than 40 years (Shibuyama *et al.*, 2006: 1081).

As shown in *table 4.9, section 4.2.1.2*, the average body mass of both female and male patients is similar. Comparing the initial average body mass of patients on initial regimen (*refer to section 4.2.1.1, table 4.5*) with average body mass of patients who experienced ADRs (*table 4.9, section 4.2.1.2*); there was average body mass loss in these patients. As a result, body mass loss in HIV-positive patients predicts either a progression of disease, opportunistic infection, adverse drug reactions or death. It is used as a warning sign to

prescribers to start investigations and treatment (National Department of Health South Africa, 2010: 28). According to *table 4.10, section 4.2.1.2*, the practical significance is lacking, as a result, adverse drug reactions experienced by patients are independent of sex.

Patients whose ART regimen changed due to ADRs were five. 60 per cent (n = 3) of the patients were females and 40 per cent (n = 2) were males. Mainly female patients' ART regimen changed as a result of ADRs. *Table 4.13, section 4.2.1.4* displays that, an equal number of patients in age groups of less than 35 years of age, and greater than 35 and less than 55 years had the highest patients who changed treatment (40 per cent, n = 2). Only 20 per cent (n = 1) of patients in age group of greater than 55 years changed regimen.

*The **second research objective** was to evaluate the laboratory tests (e.g. CD4 cell count, haemoglobin profile, neutrophil count, alanine aminotransferase (ALT), serum creatinine, and urea) results for any reflection of the presence of adverse drug reactions.*

Body mass: The average body mass increased by 4.62 kg between the baseline (57.48 ± 11.82 kg, *n* = 300) and last consultation (62.19 ± 11.11 kg, *n* = 300) (*refer to table 4.15, section 4.2.1.5*). There was a general increase in average body mass in female and male patients, in patients with the different age groups, in patients on initial ART regimens, and in patients with no condition of ADR (*refer to tables 4.16, 4.17, 4.18, 4.19; section 4.2.1.5*. Generally body mass gain in patients shows that the majority of patients were responding well to their antiretroviral treatment.

CD4 cell count: The average CD4 cell count increased by 253.12 cell/mm³ between the baseline (175.75 ± 114.47 cell/mm³, *n* = 298) and last consultation (428.87 ± 159.96 cell/mm³, *n* = 297) (*refer to table 4.15, section 4.2.1.5*). There was a general increase in CD4 cell count in female and male patients, in patients with the different age groups, and in patients on initial ART regimens (*refer to tables 4.16, 4.17, 4.18; section 4.2.1.5*). The increase in CD4 cell counts in patients revealed that the patients were adjusting well to their ART. Immunological screening of HIV-positive patients is assessed using CD4 cell count. Antiretroviral treatment guidelines use increases in CD4 cell counts after initiation of therapy as a measure of immunologic response to therapy (The antiretroviral therapy cohort collaboration, 2009: 358). There was a decline in CD4 cell counts in patients who developed no ADRs of 124.15 cell/mm³ between the baseline (554.50 ± 410.83 cell/mm³, *n* = 2) and last consultation (430.35 ± 159.47 cell/mm³, *n* = 2) (*refer to table 4.19, section 4.2.1.5*).

Table 4.20, section 4.2.1.6.1 shows that there was an estimated increase of 0.0025 cell/mm³ in CD4 cell count per day according to sex which was statistically significant at 5 per cent

level. *Tables 4.21, section 4.2.1.6.1* depicts that the CD4 cell count is independent of sex. The CD4 cell count increase is independent of age group (*refer to table 4.18, section 4.2.1.6.1*). *Table 4.18, section 4.2.1.6.1* shows that there was an estimated increase of 0.0024 cell/mm³ in CD4 cell count per day which was significant at 5 per cent level of significance. The CD4 cell count increase is dependent on body mass group (*refer to table 4.24, section 4.2.1.6.1*). *Table 4.25, section 4.2.1.6.1* demonstrates that there was an estimated increase of 0.0025 cell/mm³ in CD4 cell count per day, and at 5 per cent level, the increase in CD4 cell count in days was significant. The CD4 cell count increase is dependent on the initial ART regimen a patient is consuming (*refer to table 4.26, section 4.2.1.6.1*). *Table 4.27, section 4.2.1.6.1* demonstrates that there was an estimated increase of 0.0019 cell/mm³ in CD4 cell count per day, and at 5 per cent level, the increase in CD4 cell count in days is significant. The CD4 cell count increase is independent of adverse drug reactions a patient is experiencing (*refer to table 4.28, section 4.2.1.6.1*).

Haemoglobin profile: The average Hb profile increased by 1.02 g/dL between the baseline (11.90 ± 2.26 g/dL, *n* = 286) and last consultation (12.92 ± 1.91 g/dL, *n* = 182) (*refer to table 4.15, section 4.2.1.5*). There was a general increase in Hb profile in female and male patients, in patients from the different age groups, in patients on initial ART regimens, and in patients who had no ADRs (*refer to tables 4.16, 4.17, 4.18, 4.19; section 4.2.1.5*). Hb profile is measured to assess the occurrence of anaemia. It is done routinely especially for patients on AZT- based regimen. Normal levels of Hb in women are 12.1 to 15.1 g/dL and 13.8 to 17.2 g/dL in males (Marks & Glader, 2008). The increase in Hb indicates that the patients are adjusting very well to their regimen. Anaemia in HIV-infected patients may lead to serious implications which range from functional and quality-of-life decrements to an association with disease progression and decreased survival (Volberding *et al.*, 2004: 1454). There was a decline in Hb profile in patients on D4T/3TC/EFV of 0.4 g/dL between the baseline (13.60 g/dL, *n* = 1) and last consultation (13.20 g/dL, *n* = 1) (*refer to table 4.18, section 4.2.1.5*). *Table 4.29, section 4.2.1.6.1* shows that there was an estimated increase of 0.00021 g/dL in Hb profile per day according to sex which was statistically significant at 5 per cent level. *Tables 4.30, section 4.2.1.6.1* depicts that the Hb profile is dependent on sex. There was an estimated increase of 0.00022 g/dL in Hb profile per day according to age group, and at 5 per cent level, the increase in Hb profile in days was significant (*refer to table 4.31, section 4.2.1.6.1*). The Hb profile increase is independent of age group (*refer to table 4.32, section 4.2.1.6.1*).

Table 4.33, section 4.2.1.6.1 shows that there was an estimated increase of 0.00018 g/dL per day which was significant at 5 per cent level of significance. Hb profile increase is dependent on body mass group (*refer to table 4.34, section 4.2.1.6.1*). *Table 4.35, section 4.2.1.6.1* demonstrates that there was an estimated increase of 0.00022 g/dL per day, and at 5 per cent level, the increase in days was significant. The Hb profile increase is independent of the initial ART regimen a patient is consuming (*refer to table 4.36, section 4.2.1.6.1*). *Table 4.37, section 4.2.1.6.1* demonstrates that there was an estimated increase of 0.00020 g/dL per day, and at 5 per cent level, the increase in Hb profile in days is significant. The increase in Hb profile is independent of adverse drug reactions a patient is experiencing (*refer to table 4.38, section 4.2.1.6.1*).

Neutrophil count: The average neutrophil count decreased by 0.38 per cent between the baseline (52.98 ± 13.84 per cent, n = 256) and last consultation (52.60 ± 13.11 per cent, n = 57) (*refer to table 4.15, section 4.2.1.5*). There was a general decrease in neutrophil count in female and male patients, in patients from the different age groups, and in patients on initial ART regimens (*refer to tables 4.16, 4.17, 4.18; section 4.2.1.5*). There was an increase in neutrophil count in patients in age groups greater than 55 years, those on D4T/3TC/EFV, and those on TDF/3TC/EFV (*refer to table 4.17, 4.18, section 4.2.1.5*). Normal ranges of neutrophil count are 40 to 80 per cent (Curry, 2012). The major decrease in neutrophil count was experienced by patients on AZT- based regimens and this could be a result of patients experiencing AZT adverse reaction (neutropenia). Also, the decrease in other patients could signify the advancing of the stages of AIDS. Neutropenia is common in advanced stages of AIDS and often caused or exacerbated by concomitant myelosuppressive drugs, in addition, ADRs and their complications can cause neutropenia in patients with HIV/AIDS (Dikshit *et al.*, 2009).

Table 4.49, section 4.2.1.6.1 shows that there was an estimated increase of 0.000062 per cent in neutrophil count per day according to sex which was not statistically significant at 5 per cent level. *Tables 4.50, section 4.2.1.6.1* depicts that the neutrophil count is not dependent on sex. There was an estimated increase of 0.000046 per cent in neutrophil count per day according to age group, and at 5 per cent level, the increase in neutrophil count in days was insignificant (*refer to table 4.51, section 4.2.1.6.1*). The neutrophil count increase is independent of age group (*refer to table 4.52, section 4.2.1.6.1*).

Table 4.53, section 4.2.1.6.1 shows that there was an estimated increase of 0.000068 per cent in neutrophil count per day which was not significant at 5 per cent level of significance. The neutrophil count increase is not dependent on body mass group (*refer to table 4.54, section*

4.2.1.6.1). *Table 4.55, section 4.2.1.6.1* demonstrates that there was an estimated increase of 0.000062 per cent in neutrophil count per day, and at 5 per cent level, the increase in neutrophil count in days was insignificant. The neutrophil count increase is not dependent on the initial ART regimen a patient is consuming (*refer to table 4.56, section 4.2.1.6.1*). *Table 4.57, section 4.2.1.6.1* demonstrates that there was an estimated increase of 0.00017 per cent in neutrophil count per day, and at 5 per cent level, the increase in neutrophil count in days is insignificant. The neutrophil count increase is independent of the adverse drug reactions a patient is experiencing (*refer to table 4.58, section 4.2.1.6.1*).

Alanine aminotransferase (ALT): The average ALT decreased by 1.97 IU/L between the baseline (30.25 ± 26.21 IU/L, n = 275) and last consultation (28.28 ± 15.31 IU/L, n = 299) (*refer to table 4.15, section 4.2.1.5*). There was a general decrease in ALT in female and male patients, in patients from the different age groups, and in patients on initial ART regimens (*refer to tables 4.16, 4.17, 4.18; section 4.2.1.5*). There was an increase in ATL in patients in age groups greater than 55 years; those on D4T/3TC/EFV, AZT/3TC/NVP, and those without an ADR condition (*refer to tables 4.17, 4.18, 4.19, section 4.2.1.5*). The ALT blood test is used to determine if the liver is damaged or diseased. The normal average levels of ALT in males are 10 to 40 IU/L and in females 7 to 35 IU/L (Health testing centres: 2013). The levels of ALT are within the normal range in the majority of patients. As a result, the test shows the absence of liver toxicity, damage or disease which could have been brought about as a result of hepatitis co-infection, adverse drug reactions, alcohol abuse or other medication that can cause elevations in ALT levels. Liver enzymes laboratory monitoring determined by symptom appearance is recommended for patients on NNRTI-containing regimens (nevirapine and efavirenz) (World Health Organisation, 2010: 65).

Table 4.59, section 4.2.1.6.1 shows that there was an estimated increase of 0.000044 IU/L in ALT per day according to sex which was not statistically significant at 5 per cent level. *Tables 4.60, section 4.2.1.6.1* depicts that ALT is dependent on sex. There was an estimated increase of 0.000043 IU/L in ALT per day according to age group, and at 5 per cent level, the increase in ALT in days was insignificant (*refer to table 4.61, section 4.2.1.6.1*). The ALT increase is independent of age group (*refer to table 4.62, section 4.2.1.6.1*).

Table 4.63, section 4.2.1.6.1 shows that there was an estimated increase of 0.000046 IU/L in ALT per day which was not significant at 5 per cent level of significance. The ALT increase is not dependent on body mass group (*refer to table 4.64, section 4.2.1.6.1*). *Table 4.65, section 4.2.1.6.1* demonstrates that there was an estimated increase of 0.000028 IU/L in ALT per day, and at 5 per cent level, the increase in ALT in days was insignificant. The ALT

increase is not dependent on the initial ART regimen a patient is consuming (*refer to table 4.66, section 4.2.1.6.1*). *Table 4.67, section 4.2.1.6.1* demonstrates that there was an estimated decrease of 0.000013 IU/L in ALT per day, and at 5 per cent level, the decrease in ALT in days is slightly significant. ALT decrease is independent of the adverse drug reactions a patient is experiencing (*refer to table 4.68, section 4.2.1.6.1*).

Serum creatinine: The average serum creatinine decreased by 24.3 µmol/L between the baseline (86.92 ± 23.80 µmol/L, *n* = 274) and last consultation (62.62 ± 13.77 µmol/L, *n* = 299) (*refer to table 4.15, section 4.2.1.5*). There was a general decrease in serum creatinine in female and male patients, in patients from the different age groups, in patients on initial ART regimens, and in patients with no ADR condition (*refer to tables 4.16, 4.17, 4.18, 4.19; section 4.2.1.5*). The normal range of serum creatinine for males is 53 to 106 µmol/L and 70 to 133 µmol/L for females (Walker *et al.*, 1990). This decrease in serum creatinine could be due to firstly, the renal function deteriorating with age and secondly, due to patients being on TDF- based regimens experiencing ADR of TDF (that is renal impairment). Nephrotoxicity, including renal insufficiency and Fanconi's syndrome, has been reported infrequently but the incidence, risk factors, and time to resolution remain uncertain (Nelson *et al.*, 2007: 1274).

Table 4.39, section 4.2.1.6.1 shows that there was an estimated decrease of 0.00038 µmol/L in serum creatinine per day according to sex which was statistically significant at 5 per cent level. *Tables 4.40, section 4.2.1.6.1* depicts that the serum creatinine is dependent on sex. There was an estimated decrease of 0.00039 µmol/L in serum creatinine per day according to age group, and at 5 per cent level, the decrease in serum creatinine in days was significant (*refer to table 4.41, section 4.2.1.6.1*). The serum creatinine decrease is independent of age group (*refer to table 4.42, section 4.2.1.6.1*).

Table 4.43, section 4.2.1.6.1 shows that there was an estimated decrease of 0.00040 µmol/L per day which was significant at 5 per cent level of significance. The serum creatinine decrease is independent of body mass group (*refer to table 4.44, section 4.2.1.6.1*). *Table 4.45, section 4.2.1.6.1* demonstrates that there was an estimated decrease of 0.00040 µmol/L per day, and at 5 per cent level, the decrease in days was significant. The serum creatinine decrease is independent of the initial ART regimen a patient is consuming (*refer to table 4.46, section 4.2.1.6.1*). *Table 4.47, section 4.2.1.6.1* demonstrates that there was an estimated decrease of 0.00028 µmol/L in serum creatinine per day, and at 5 per cent level, the decrease in serum creatinine in days is significant. The decrease in serum creatinine is independent of the adverse drug reactions a patient is experiencing (*refer to table 4.48, section 4.2.1.6.1*).

Urea: The average urea decreased by 0.55 mmol/L between the baseline (3.87 ± 1.52 mmol/L, *n* = 268) and last consultation (3.32 ± 0.83 mmol/L, *n* = 236) (*refer to table 4.15, section 4.2.1.5*). There was a general decrease in urea in female and male patients, in patients for the different age groups, in patients on initial ART regimens, and in patients with no ADR condition (*refer to tables 4.16, 4.17, 4.18, 4.19; section 4.2.1.5*). Several medications used in the treatment of HIV/AIDS are detrimental to the kidneys. This includes antiretroviral medications and some medications used to treat HIV-related health problems. HIV disease can also cause kidney failure due to HIV infection of kidney cells which is known as HIV-Associated Nephropathy or HIVAN (Okuonghae *et al.*, 2011: 27). Other causes of kidney disease include diabetes and high blood pressure. Normal range of blood urea nitrogen (BUN) is 2.5 to 8.0 mmol/L (Food and Drug Administration news, 2012). Generally, a high blood urea nitrogen level means that the kidneys are not performing well.

There was an increase in urea in patients on D4T/3TC/EFV of 0.2 mmol/L between the baseline (2.60 mmol/L, *n* = 1) and last consultation (2.80 mmol/L, *n* = 1) (*refer to table 4.18, section 4.2.1.5*). There was another increase in urea in patients on AZT/3TC/NVP of 0.1 mmol/L between the baseline (3.21 ± 0.76 mmol/L, *n* = 18) and last consultation (3.31 ± 1.05 mmol/L, *n* = 17) (*refer to table 4.18, section 4.2.1.5*).

Table 4.69, section 4.2.1.6.1 shows that there was an estimated decline of 0.00023 mmol/L in urea per day according to sex which was statistically significant at 5 per cent level. *Tables 4.70, section 4.2.1.6.1* depicts that urea is dependent on sex. There was an estimated decrease of 0.00022 mmol/L in urea per day according to age group, and at 5 per cent level, the decrease in days was significant (*refer to table 4.71, section 4.2.1.6.1*). The decline in urea is dependent on age group (*refer to table 4.72, section 4.2.1.6.1*).

Table 4.73, section 4.2.1.6.1 shows that there was an estimated decrease of 0.00023 mmol/L per day which was significant at 5 per cent level of significance. The decrease in urea is independent of body mass group (*refer to table 4.74, section 4.2.1.6.1*). *Table 4.75, section 4.2.1.6.1* demonstrates that there was an estimated decrease of 0.00024 mmol/L per day, and at 5 per cent level, the decrease in days was significant. Urea decrease is slightly dependent of the initial ART regimen a patient is consuming (*refer to table 4.76, section 4.2.1.6.1*). *Table 4.77, section 4.2.1.6.1* demonstrates that there was an estimated decrease of 0.00015 mmol/L in urea per day, and at 5 per cent level, the decrease in urea in days is significant. The decrease in urea is independent of the adverse drug reactions a patient is experiencing (*refer to table 4.78, section 4.2.1.6.1*).

5.2.2.2 Health professional's questionnaire

*The **third research objective** was to evaluate how documentation of adverse drug reactions is being done by health professionals.*

As illustrated in *table 4.90, section 4.2.2.4, question 16,* none of the health professionals used the yellow card scheme method of reporting ADRs. The highest number of them used the patient bukana and the proportion decreased with structured databases, individual case safety reports, and patient HIV/AIDS ART card respectively. As a result, the most popular or used method of recording ADRs in the health facilities is the patient bukana. Also a very small number of health professionals used patient HIV/AIDS ART card for reporting ADRs and the majority chose not to respond to this method.

Table 4.86, section 4.2.2.3, question 12 showed that the majority of the health professionals never completed the ADR reporting form in their health facilities. The trend decreases from never, sometimes, often and always respectively. *Table 4.87, section 4.2.2.3, question 13* illustrated that the health professionals found the form very straightforward to complete with few and/no problems. The highest number of health professionals found the current ADR reporting system used in their different health facilities not efficient. Though the numbers show that the majority of people say the system is not efficient, there is a significant number of people in the categories of slightly, moderately and very efficient. As a result, there is a slight efficiency in the reporting systems of the health facilities. *(Refer table 4.88, section 4.2.2.3, question 14)*

Table 4.89, section 4.2.2.3, question 15 illustrated that the majority of health professionals strongly agreed that the most possible reasons affecting the current reporting systems were as follows: forms not being available, lack of training, and being afraid of taking responsibility, respectively. As a result, the majority of health professionals who never filled the ADR reporting form could be due to any of the previously mentioned reasons with strong emphasis on the reason of forms not being available for them to fill *(refer to table 4.86, section 4.2.2.3, question 12).* As for the other reasons (time consuming, and lack of confidence in discussing the ADR with other colleagues), the majority of the people were neutral.

*The **fourth research objective** was to assess health professionals understanding of adverse drug reactions recording/reporting.*

Table 4.81, section 4.2.2.2, question 7 depicted that the majority of health professionals did not fill the ADR reporting form in their health facilities. This could be due to some of the reasons which affected the current reporting systems in their health facilities. These reasons

being forms not being made available for them to complete, lack of training, and being afraid of taking responsibility, respectively *(also refer to table 4.89, section 4.2.2.3, question 15).*

Table 4.82, section 4.2.2.2, question 8) showed that most health professionals consider medical doctors and pharmacists as the main professionals to fill the adverse drug reactions reporting form, followed by nurses and lastly pharmacy technicians. A higher number of participants said that laboratory technicians should not fill the ADR reporting form. This concludes that medical doctors, pharmacists, nurses and pharmacy technicians are considered by the health professionals to be the qualified professionals to complete the ADR reporting form while laboratory technicians are not.

The health professionals who took part in the study viewed the director of pharmaceuticals as the main place where the ADR reporting form should be submitted after being filled. Secondly, a smaller number of health professionals selected the national pharmacotherapeutics committee and hospital pharmacotherapeutics committee as other places where the completed form could be submitted. Although a high number of health professionals did not answer the option of Drug Companies, a significant number of people said the completed form should not be submitted to the drug company. *(Refer to table 4.83, section 4.2.2.2, question 9)*

As displayed in *table 4.84, section 4.2.2.2, question 10*, the highest numbers of health professionals use the Lesotho ART guidelines followed by those who use the WHO definition of ADR, referring to text books of medicine and surgery and medicinal science, and referring to academicians respectively. The lowest numbers of the health professionals consult HPTC or NPTC.

Table 4.85, section 4.2.2.2, question 11 showed that the health professionals stated that it was very important to fill the ADR reporting form decreasing to critical and important categories respectively. None of them said it was unimportant and/or slightly important.

*The **fifth research objective** was to determine how health professionals manage adverse drug reactions.*

Table 4.91, section 4.2.2.4, questions 17 and 18 demonstrated that patients are being taught about adverse drug reactions and regimen specific side effects depending on the type of regimen they are taking. A very small number of health professionals do not educate patients at all on adverse drug reactions and regimen specific side effects.

Table 4.92, section 4.2.2.4, question 19 revealed that most health professionals used patient clinical examinations to detect adverse effects, followed by the utilization of laboratory

results, both laboratory results and patient clinical examination, and asking the patients questions respectively. As a result health professionals do have knowledge of how to detect adverse effects.

5.3 RECOMMENDATIONS

The following recommendations can be made after the completion of this study:

Part 1: Drug utilisation review

- An electronic system to record all patient medical information should be established to enable easy access of patient information.
- Health professionals should be motivated to fill in complete patient information in the medical files.
- Patient clinical visits and laboratory monitoring should be scheduled at three month or six months intervals to assist with effective patient monitoring for ADRs.
- Patients should be encouraged to keep clinical appointments as this will help to effectively monitor and detect ADRs before they do more harm to the patient.

Part 2: Health professional's questionnaire

- A pharmacovigilance system should be established at the central level in the Ministry of Health
- There should be a national form available for ADR reporting to make the reporting system the same throughout the country.
- There should be frequent training, mentoring and supervision for health professionals on the reporting/recording system of ADRs caused by antiretroviral therapy.
- Health professionals and health education institutions should educate health professionals and students about pharmacovigilance.
- Patients should always be taught about regimen specific adverse drug reactions by health professionals and which measures to take when experiencing them.

5.4 CHAPTER SUMMARY

In this chapter, the conclusions of this study were drawn and discussed. The recommendations that were derived in completion of the study have been discussed.

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APPENDICES

Appendix A: Letter of approval from Ministry of Health Lesotho

Ministry of Health
and Social Welfare
PO Box 514
Maseru 100

11 April 2012

Lineo Maja
Department of Pharmacy
NUL

Dear M . Lineo ,

Re: Assessment of Adverse Drug Reactions in HIV and AIDS patients caused by HAART at private and public ART clinics in Lesotho

Thank you for resubmitting the above mentioned protocol. The Ministry of Health and Social Welfare Research and Ethics Committee having reviewed your protocol hereby authorizes you to conduct this study among the specified population. However, we would like to suggest you to add "Maseru District" in front of "Lesotho" in your title, because the study will be conducted in one district only. The study is authorized with the understanding that the protocol will be followed as stated. Departure from the stipulated protocol will constitute a breach of the permission.

We are looking forward to have a progress report and final report at the end of your study.

Sincerely,

Dr. M. M. Moteetee
Chairperson Research and Ethics Committee
Director General of Health Services

Appendix B: Letter of approval from North West University

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT

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Ethics Committee
Tel +27 18 299 4850
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Email Ethics@nwu.ac.za

22 May 2013

ETHICS APPROVAL OF PROJECT

The North-West University Ethics Committee (NWU-EC) hereby approves your project as indicated below. This implies that the NWU-EC grants its permission that, provided the special conditions specified below are met and pending any other authorisation that may be necessary, the project may be initiated, using the ethics number below.

Project title : Assessment of adverse drug reactions caused by HAART at antiretroviral clinics in Maseru district

Project Leader: **Dr. Rakumakoe**

Ethics number: NWU-00134-12-A5
(Institution – Project Number – Year – Status)

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Approval date: 2013/05/21 **Expiry date:** 2018/05/20

Special conditions of the approval (if any): None

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:

- *The project leader (principle investigator) must report in the prescribed format to the NWU-EC:*
  - *annually (or as otherwise requested) on the progress of the project,*
  - *without any delay in case of any adverse event (or any matter that interrupts sound ethical principles) during the course of the project.*
- *The approval applies strictly to the protocol as stipulated in the application form. Would any changes to the protocol be deemed necessary during the course of the project, the project leader must apply for approval of these changes at the NWU-EC. Would there be deviated from the project protocol without the necessary approval of such changes, the ethics approval is immediately and automatically forfeited.*
- *The date of approval indicates the first date that the project may be started. Would the project have to continue after the expiry date, a new application must be made to the NWU-EC and new approval received before or on the expiry date.*
- *In the interest of ethical responsibility the NWU-EC retains the right to:*
  - *request access to any information or data at any time during the course or after completion of the project;*
  - *withdraw or postpone approval if:*
    - *any unethical principles or practices of the project are revealed or suspected,*
    - *it becomes apparent that any relevant information was withheld from the NWU-EC or that information has been false or misrepresented,*
    - *the required annual report and reporting of adverse events was not done timely and accurately,*
    - *new institutional rules, national legislation or international conventions deem it necessary.*

The Ethics Committee would like to remain at your service as scientist and researcher, and wishes you well with your project. Please do not hesitate to contact the Ethics Committee for any further enquiries or requests for assistance.

Yours sincerely

Prof Amanda Lourens
(chair NWU Ethics Committee)

Appendix C: Data collection form for individual patients in the Sankatana clinic

1. ANTIRETROVIRAL ADVERSE DRUG REACTION SURVEY FORM

Instructions: Complete and tick below.

A. DEMOGRAPHIC INFORMATION

Patient ID: _____ Date of birth: _____

Sex: female: [0] male: [1]

B. MEDICATION INFORMATION

DRUG HISTORY

ART initiation date: ___/___/___

Regimen of initiation:

D4T/3TC/NVP	D4T/3TC/EFV	AZT/3TC/NVP	AZT/3TC/EFV	TDF/3TC/NVP	TDF/3TC/EFV
1	2	3	4	5	6

Current ART regimen

D4T/3TC/NVP	D4T/3TC/EFV	AZT/3TC/NVP	AZT/3TC/EFV	TDF/3TC/NVP	TDF/3TC/EFV
1	2	3	4	5	6

C. CLINICAL ASSESSMENT

Visit	Consultation Date	Body mass (kg)	Visit	Consultation Date	Body mass (kg)
1(baseline)			**7**		
2			**8**		
3			**9**		
4			**10**		
5			**11**		
6			**12**		

D. ADVERSE DRUG EFFECTS

Adverse drug effect, treatment and outcomes:

		Treatment				Treatment outcome			
Adverse drug effect (Tick)		**No treatment**	**Medical Please specify:**	**Non-medical Please specify:**	**Unknown***	**No outcome**	**Resolved**	**Not resolved**	**Unknown**
Scale	**0-8**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
No condition	0								
Anaemia	1								
Peripheral neuropathy	2								
Hepatotoxicity	3								
Skin rash	4								
Renal impairment	5								
Fanconi syndrome	6								
Nausea/vomiting	7								
Diarrhoea	8								

Source: National guidelines for HIV and AIDS care and treatment, 2010: 132-135 and WHO, 2010: 71-72

*** Unknown**: refers to when the treatment given to the patient was not specified in the patient's medical record.

Action taken

- **No action taken: [0]**
- **Change of regimen**: **[1]** If yes, which regimen:

D4T/3TC/NVP	D4T/3TC/EFV	AZT/3TC/NVP	AZT/3TC/EFV	TDF/3TC/NVP	TDF/3TC/EFV
1	2	3	4	5	6

- **Unknown/not specified: [2]**
- **Hospitalisation required: Yes [0] No [1]**

E. LABORATORY FINDINGS

DATES							
Date of consultation	**Date of laboratory test**	**CD4-cell count (cells/mm^3)**	**Haemoglobin profile (Hb) (g/dL)**	**Neutrophil count (per cent)**	**ALT (IU/L)**	**Creatinine (µmol/L)**	**Urea (mg/dL)**
(Baseline :)							

Appendix D: Data summary and analysis for drug utilisation review

1. Demographics

A. Age (column B), gender (column C) and body mass (column F) distribution of patients on initial regimens (column E).

B. Age (column B), gender (column C) and body mass (column F) distribution of patients whose initial regimens (column E) changed due to ADRs (column G).

C. Age (column B), gender (column C) and body mass (column F) distribution of patients who experienced ADRs (column G) and those who did not experience ADRs (column G).

D. Incidence of adverse drug reactions (column G) in patients on initial regimens (TDF-based against AZT-based) (column E) by gender (column C), age (column B) and body mass (column F).

2. Outcome

A. CD4 count (column N) at the beginning of ARV treatment by initial regimen (column E), by gender (column C), age (column B) and body mass (column F).

B. CD4 count in 2010 and 2011 (column N) by current regimen (column K), age (column B), gender (column C) and body mass (column F).

C. Initial body mass (column F) at the beginning of ARV treatment by initial regimen (column E), by gender (column C), age (column B).

D. Initial Hb (column P) at the beginning of ARV treatment by initial regimen (AZT-based) (column E), by gender (column C) and age (column B).

E. Hb in 2010 and 2011 (column P) by current regimen (AZT based) (column K), by gender (column C) and age (column B).

F. Initial creatinine clearance (column Q) at the beginning of ARV treatment by initial regimen (TDF-based) (column E), by gender (column C) and age (column B).

G. Creatinine clearance in 2010 and 2011 (column Q) by current regimen (TDF-based) (column K), by gender (column C) and age (column B).

H. Initial neutrophil (column O) at the beginning of ARV treatment by initial regimen (column E), by gender (column C) and age (column B).

I. Neutrophil count in 2010 and 2011 (column O) by current regimen (column K), by gender (column C) and age (column B).

J. Initial urea (column R) at the beginning of ARV treatment by initial regimen (TDF-based) (column E), by gender (column C) and age (column B).

K. Urea in 2010 and 2011 (column O) by current regimen (TDF-based) (column K), by gender (column C) and age (column B).

L. Initial ALT (column O) at the beginning of ARV treatment by initial regimen (column E), by gender (column C) and age (column B).

M. ALT in 2010 and 2011 (column O) by current regimen (column K), by gender (column C) and age (column B).

N. Treatment of adverse drug reactions (column H) against adverse drug reactions (column G) experienced by patients on initial regiment (E).

O. Treatment outcome (column I) of adverse drug reactions (column H) experienced by patients on initial regimen (column E).

Appendix E: Health professional's questionnaire

Questionnaire number: ____

HEALTH PROFESSIONALS' QUESTIONNAIRE:

Title: Assessment of adverse drug reactions caused by HAART at antiretroviral clinics in Maseru district, Lesotho.

I am a student at the North West University conducting a research on assessment of adverse drug reactions in HIV/AIDS patients caused by HAART at private and public clinics in Lesotho. Information provided will be kept confidential. No incentives will be offered. I would greatly appreciate your participation in this research.

The questions are subdivided into demographic information, knowledge-related, attitude-related questions and questions about the influence of the professional environment.

SECTION A: DEMOGRAPHIC INFORMATION

1. **Professional qualification**

Profession	Medical doctor	Nurse	Pharmacist	Pharmacy technician
Tick	1	2	3	4

2. **What is your sex? Female [0] Male [1]**

3. **Which health facility do you work for? _____**

Health facility	Sankatana ART centre	Khanya medical centre	Healthy lifestyle and diabetes centre	Baylor college of medicine	St. Joseph's hospital
Tick	1	2	3	4	5

4. **Is it a clinic [0] or hospital [1]?**

5. **Sector you are working: Private [0] Public [1]**

6. **Work experience in the health professional's respective professional capacity/qualification.**

6.1 Work experience in the management of HIV/AIDS

Work experience (in years)	0 – 5	5 – 10	10 – 15	15 – 20	≥ 20
Please tick where appropriate	1	2	3	4	5

6.2 Did you attend any training in HIV/AIDS management

Scale	None	1 day course	2 day course	3 weeks course	other
Please tick	1	2	3	4	

If other explain/specify:

_____

6.3 Did you attend any training in Pharmacovigilance?

Code	Type	Yes (1)	No (2)
6.3.1	Undergraduate (as a student)	1	2
6.3.2	In service training-general training	1	2
6.3.3	Specifically for ARV	1	2
6.3.4	Ministry of Health workshop on pharmacovigilance		
6.3.5	Other	1	2

If other explain/specify:

_____

SECTION B: KNOWLEDGE RELATED QUESTIONS

These questions are targeted towards assessing the basic knowledge of the health professional's familiarity with an ADR report form, reporting and its use.

7. Do the health care workers in your facility fill the adverse drug reactions form?

Yes ___ [1] No ___ [2]

8. Who is qualified to fill the form? Please indicate if more than one professional is allowed to fill the ADR form.

	Profession	Yes (1)	No (2)
8.1	Medical doctor	1	2
8.2	Nurse	1	2
8.3	Pharmacist	1	2
8.4	Pharmacy technician	1	2
8.5	Others: Specify.....	1	2

9. To whom should the filled form be submitted? Please indicate if it can be submitted in more than one place.

	Place of submission	Yes (1)	No (2)
9.1	Director of Pharmaceutical Services	1	2
9.2	Hospital Pharmacotherapeutics Committee (HPTC)	1	2
9.3	National Pharmacotherapeutics Committee (NPTC)	1	2
9.4	Others: Specify.....	1	2

10. How do you rule out side effects caused by other medication a patient is taking? If more than one please indicate.

		Yes (1)	No (1)
10.1	Using WHO definition of ADR	1	2
10.2	Lesotho ART guidelines	1	2
10.3	Consulting HPTC or NPTC	1	2
10.4	Referring to academicians	1	2
10.5	Referring to text books of medicine and surgery and medicinal science	1	2
10.6	Other, Specify.....	1	2

11. How important do you think it is to fill the ADR reporting form?

Scale	Unimportant	Slightly important	Important	Very important	Critical
Please tick	**1**	**2**	**3**	**4**	**5**

SECTION C: HEALTH PROFESSIONAL'S OPINION

This section determines the reasons why the health workers might not fill the ADR form by evaluating their view towards the ADR form and the system as a whole.

12. How often do you fill the form?

Scale	Never	Sometimes	Often	Always
Please tick	1	2	3	4

13. How easy is it to fill the ADR reporting form?

Scale	Difficult	Easy	Very easy	Extremely easy
Please tick	1	2	3	4

14. How efficient is the current system of reporting ADR?

Scale	Not efficient	Slightly efficient	Moderately efficient	Very efficient
Please tick	1	2	3	4

15. How do you think the current ADR reporting system is affected by the following reasons?

		Strongly agree	Agree	Neutral	Disagree	Strongly disagree
15.1	Time consuming	1	2	3	4	5
15.2	Lack of training	1	2	3	4	5
15.3	Afraid of taking responsibility	1	2	3	4	5
15.4	Forms not available	1	2	3	4	5
15.5	Lack of confidence in discussing the ADR with other colleagues	1	2	3	4	5

SECTION D: INFLUENCE OF THE PROFESSIONAL ENVIRONMENT

This section assesses the participation of professionals in ADR activities and how they maintain patient safety in their different work settings.

16. How do you report ADRs?

	Yes (1)	No (2)
Yellow card scheme		
Individual case safety reports		
Structured databases		
Other Specify:.....		

17. How often do you educate patients about adverse drug reactions?

	Never	Sometimes	Often	Always
Please tick	1	2	3	4

18. How often do you teach patients about regimen specific side effects?

Scale	Never	Sometimes	Often	Always
Please tick	1	2	3	4

19. How do you pick adverse effects? If more than one option exists please indicate.

Options	Yes (1)	No (2)
Laboratory results		
Patient clinical examination		
Both the above		
Ask patient questions		

Thank you very much for your participation.

Appendix F: Data summary and analysis for health professional's questionnaire

1. Section A

Demographic information

A. Frequency distribution of professional qualification (column A), gender (column B), name of health facility (column C), type of health facility (column D), private or public sector (column E) and work experience in management of HIV/AIDS (column F).

B. Frequency distribution of professional qualification (column A), name of health facility (column C), type of health facility (column D), private or public sector (column E), training on HIV/AIDS management (column G) and training on pharmacovigilance (columns H, I, J, K)

2. Section B

A. Distribution of professional qualification (column A), name of health facility (column C), healthcare workers filling ADR form (column L), and people qualified to fill the ADR form (column M, N, O, P, Q)

B. Distribution of professional qualification (column A), name of health facility (column C), and place where filled ADR form should be submitted (column R, S, T, U)

C. Distribution of professional qualification (column A), name of health facility (column C), the importance of filling ADR form (column AA), and methods used to rule out side effects caused by medication a patient is taking (column V, W, X, Y, Z).

3. Section C

A. Distribution of professional qualification (column A), name of health facility (column C), frequency of filling the form (column AB), how easy it is to fill the ADR form (column AC), and the efficiency of the current ADR reporting system (column AD)

B. Distribution of professional qualification (column A), name of health facility (column C), and factors affecting the current ADR reporting system (column AE, AF, AG, AH, AI)

4. **Section D**
    A. Distribution of professional qualification (column A), name of health facility (column C), and methods used to report ADRs (column AJ, AK, AL, AM)
    B. Distribution of professional qualification (column A), name of health facility (column C), how often are patients educated about ADRs (column AN), and how often are patients taught about regimen specific side effects (column AO).
    C. Distribution of professional qualification (column A), name of health facility (column C), and methods used to pick adverse effects (column AP, AQ, AR, AS)

Appendix G: Health professional's consent form

NORTH WEST UNIVERSITY

Title: Assessment of adverse drug reactions caused by HAART at antiretroviral clinics in Maseru District, Lesotho.

This letter is an invitation to consider participating in a study I, Lineo Maja, is conducting as part of my Master's degree in the School of Pharmacy at the North West University. The purpose of the study is to assess the management of antiretroviral adverse drug reactions at private and public clinics in the Maseru district, Lesotho, if proper documentation is being done in the patient medical files and which measures were taken when the patient experienced side effects.

You were selected as a possible participant in this study because of your direct involvement with clinical assessment and treatment monitoring of HIV/AIDS patients. This questionnaire is voluntary. You have the right to withdraw at any time. I expect that the interview will take about 15 minutes. There will be no compensation for this interview. This project will be completed by December 2013.

You have the right to ask questions related to the research during participation.

Feel free to contact me at: Cell number: (+266) 58404323/63833008

E-mail address: majalineo@gmail.com

Physical address: National University of Lesotho
Pharmacy department
Office SCH 2212

Health professional's name (in full) …….

Health professional's signature …… Date……