



UNIVERSITY OF THE WESTERN CAPE
SCHOOL OF PHARMACY: DISCIPLINE OF PHARMACOLOGY

**ADVERSE EFFECTS EXPERIENCED BY PATIENTS ON FIRST LINE
ANTIRETROVIRAL DRUGS USED AT KEETMANSHOOP HOSPITAL
(NAMIBIA)**



UNIVERSITY of the

A thesis submitted in fulfilment of the requirements for the degree of

Magister Scientiae (MSc) in Pharmaceutical Sciences

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Abstract

Adverse effects are a significant factor that determine how long patients will tolerate a given antiretroviral drug regimen. They also influence treatment options, and play an important role in the much needed adherence to treatment by patients on Highly Active Antiretroviral Therapy (HAART). This study is aimed at understanding adverse effects experienced by patients on the first line antiretroviral therapy at Keetmanshoop Hospital in Namibia. **Methods:** A retrospective quantitative method was used to review records of patients on first line antiretroviral treatment who started treatment between November 1st 2007 and December 1st, 2008 and followed up until they reached 36 – 48 months on treatment. Records of 94 patients were found eligible to be included in the study. Data was analysed using Stata 12 data analysis software. **Results:** The most reported adverse effect was musculoskeletal disorders (25%) whereas headache (16%) was the least reported. Low haemoglobin (78%) was the most common recorded hematologic adverse effect whereas low red cell distribution width and low mean platelet volume were the least recorded adverse effects (0%). A Male patient was more likely to experience a low haemoglobin levels compared to a female patient (adjusted OR: 3.29, 95% CI: 1.3 – 8.3). A male patient was found to be 64% times less likely to experience a higher mean cell haemoglobin compared to a female patient (adjusted OR. 0.31, 95% CI: 0.11 – 0.87). A patient on nevirapine was more likely to experience an elevated creatinine level compared to a patient on efavirenz (adjusted OR; 36.0, 95%CI: 2.02 – 62.5). At baseline, a patient who had prior exposure to ART had an 81 times (adjusted OR: 81.4, 95%CI: 5.3 – 119, p-value=0.00) increased odds of experiencing a high mean cell volume (MCV) compared to a patient with no ART exposure. A patient with a higher CD4 count was also less likely to experience a low hemoglobin compared to a patient with low CD4 count (adjusted OR; 0.31, 95% CI: 0.12 – 0.77). The author **recommends**

further studies with higher sample size to confirm whether higher creatinine levels are more prevalent in patients on nevirapine compared to patients on efavirenz; this will have clinical implications especially in patients with impaired renal system. Antiretroviral treatment increases chances of developing macrocytosis anaemia; clinical implication of this condition may need to be investigated.



DEDICATION

To my mother, for her endless love and support



DECLARATION

I declare that *adverse effects experienced by patients on first line antiretroviral drugs used at Keetmanshoop Hospital (Namibia)* is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full Name: Nicholus Mbangu Mutenda

Date:.....

Signed:



ACKNOWLEDGEMENTS

My utmost gratitude goes to Prof. P. Mugabo, who never gave up on this work when there was a cloud of no progress. I am also grateful to the Namibian Ministry of Health and Social Services and the regional and district management staff of the Karas Region for accepting the study. A sincere gratitude also goes to the staff of the Keetmanshoop Communicable Disease Clinic for availing the required patient records. I am thankful to everyone who enabled this study to continue, the support of friends who believed that the study will be completed is also acknowledged.



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List of abbreviations

3TC = Lamivudine	NRTI = Nucleoside reverse transcriptase inhibitor
ADR = Adverse Drug Reaction	NVP = Nevirapine
AE = Adverse effects	OR = Odds Ratio
AIDS = Acquired Immunodeficiency Syndrome	OIs = Opportunistic infections
ALT = alanine aminotransferase enzymes	RCC = Red Cell Count
ART = Antiretroviral therapy	RDW = Red Cell Distribution
ARVs = Antiretroviral medications	TB = Tuberculosis
AST = Aspartate aminotransferase	TDF = Tenofovir
AUC = Area under the plasma drug concentration-time curve	WCC = White Cell Count
AZT = Zidovudine	WHO = World Health Organisation
C_{max} = Maximum plasma concentration	
CNS = Central Nervous System	
CYP = Cytochrome P450 enzyme	
D4T = Stavudine	
EFV = Efavirenz	
HAART = Highly Active Antiretroviral Therapy	
HB = Haemoglobin	
HCV = Hepatitis C Virus	
HIV = Human Immunodeficiency Virus	
HIVAN = HIV Associated Nephropathy	
HSR = Hypersensitivity Reaction	
IRIS = Immune Reconstitution Syndrome	
MCH = Mean Cell Haemoglobin	
MCV = Mean Cell Volume	
MCHC = Mean Cell Haemoglobin Concentration	
MPV = Mean Platelet Volume	
MCV = Mean Cell Volume	
NIP = Namibia Institute of Pathology	
NNRTI = Non-nucleoside reverse transcriptase inhibitor	

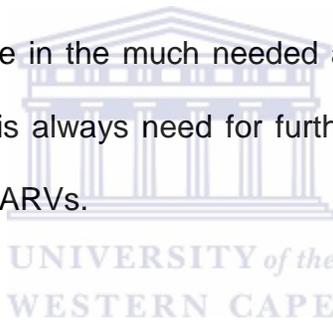


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Chapter 1: Study overview

1.1. Introduction

With the scourge of HIV infections still on the increase, antiretroviral medications (ARVs) have brought relief to many people. Many lives are being saved and many HIV positive people enjoy healthy productive lives. However there are challenges related to this phenomenon, among others, the need to maintain patients on effective ARV regimens. Adverse effects are among others, a significant factor that determine how long a patient will tolerate a given ARV regimen, influence treatment options, and also plays an important role in the much needed adherence to treatment by a patient. For this reason there is always need for further information in the field of adverse effects associated with ARVs.



This document discusses a study done at Keetmanshoop Hospital's ARV clinic. The study is discussed in terms of objectives, literature review, methods used in the study, results, discussion of results, conclusions and recommendations.

1.2. About Keetmanshoop and Namibia

The Keetmanshoop district hospital is one of the main referral public health facilities in the Karas Region with an estimated catchment population of about 38 865. The district has an estimated HIV prevalence rate of about 12.4, (Ministry of Health, 2013). The ARV clinic in the district was opened in 2003, by February 2011, a cumulative number of about 2 640 patients were enrolled into HIV, of which 1413

were on Highly Active Antiretroviral Therapy (HAART). According to hospital based statistics, about 619 patients have been on treatment for a continuous period of four or more years, which made these clients eligible to be included in the criteria set for this study.

The first line ARV regimen in Namibia includes Tenofovir (TDF), Lamivudine (3TC) and Nevirapine (NVP) or Efavirenz (EFV), with first line alternatives of Zidovudine (AZT), 3TC and EFV or NVP (Ministry of Health, 2010).

1.3. Significance of the research

A lot is known about the types and expected adverse effects of different ARV regimens from clinical trials and various experiences in the field. Outside or confounding factors such as nutrition, geographical location, genetic influences and people's habits could easily cause some variation in trends of how adverse effects are experienced. According to the World Health Organisation, (WHO, 2007), some factors that make ARV toxic profiles to be less well known in the developing world include, existence of co-morbidities, malnutrition, reliance on local alternative or traditional medicines, level of training of the human resources managing patients on ARVs, non-existence of medicine safety regulatory systems etc. Given these facts it can be concluded that some adverse effects of medications remains unknown, and therefore it becomes significant to carry out a study of this nature despite the available information.

1.4. Aim of the study

This study is aimed at finding out the prevalence and type of adverse effects (reported, hematologic, hepatic and renal function related adverse effects) experienced by patients on the first line ARVs treatment as ascertained and documented by health care providers at Keetmanshoop Hospital. The study also aimed at assessing the risk factors for development of adverse effects in HIV-positive patients on antiretroviral therapy (ART).

1.5. Study objectives

Specific objectives of this study were:

1. To determine the prevalence of adverse effects (reported, hematologic, hepatic and renal function related adverse effects) related to first line ART.
2. To find out any association between adverse effects and any of the following factors: patient gender, drugs used, treatment duration, patient age and stage of HIV infection.

1.6. Research questions

The study sought to answer the following questions:

- a) What is the prevalence of adverse effects in patients on first line ART?
- b) Is there any association between adverse effects and gender?
- c) Which adverse effects are drug specific?
- d) Is there any association between the duration of treatment and adverse effects?

- e) Is there any association between patient age and adverse effects?
- f) Is there any association between HIV infection stage and adverse effects?

1.7. Hypotheses

The following hypotheses were tested using various statistical tests.

1. (a) Adverse effects experienced by male patients are different from adverse effects experienced by female patients.
(b) There is no difference in the types of adverse effects experienced by male and female patients on first line ART.
2. (a) Patients on nevirapine based treatment are at an increased risk of developing adverse effects compared to patients on efavirenz based treatment of the first line drugs.
(b) There is no difference in adverse effects experienced between nevirapine based and efavirenz based ART treatment.
3. (a) Patients who are longer on ART treatment are at increased risk of experiencing adverse effects compared to patients with shorter treatment durations.
(b) There is no association in the risks of experiencing adverse effects and treatment duration.
4. (a) Older patients on first line ART drugs are more prone to experiencing adverse effects than younger patients.
(b) Older patients on first line ART drugs are not prone to experiencing adverse effects compared to younger patients.

5. (a) Patients with advanced HIV infection are more likely to experience adverse effects compared to patients with less advanced HIV infection.
- (b) There is no difference in the adverse effects experienced by patients with advanced and less advanced HIV disease.



Chapter 2: Literature review

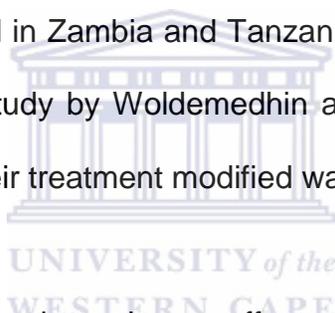
2.1. Overview

Literature review was done to reveal what exists on the topic. Little information was found on the topic from Namibia and none from Keetmanshoop. Many studies from Africa and the international community are available.

2.2. Adverse effects lead to low adherence to antiretroviral medications

A study carried out at Katutura Health Centre in Windhoek, the capital city of Namibia, using questionnaire and interviews by the University of Namibia and the University of Toronto (2007), revealed that factors leading to none adherence and suboptimal adherence has multiple causes. However this qualitative study does not give indication as to which causes were found to be most common or ranked the highest. Factors affecting adherence were categorised as patient factors and healthcare worker factors. Minor side effects were among other factors mentioned as causes that can lead to suboptimal adherence. Similar findings were ascertained in Botswana by Kip *et al.* (2009). A study done on clients taking ARVs in selected towns of Namibia by Ibis Namibia, Lironga Eparu and the Rainbow Project (2005), ascertained that about 57% of clients interviewed had at one point or the other experienced adverse effects. This study also ascertained that 20% of these clients had found adverse effects bad enough leading them to stop taking ARV medicines.

There is increasing evidence that nutrition is one of the common factors affecting adherence to ARV medications. This is evidenced by many studies conducted on adherence mostly in the resource constrained areas of Southern African (Hardon *et al*, 2006; *The Global HIV/AIDS news* 2009). Clients will usually not take ARV medicines if there is inadequate food due to fears of exacerbating adverse effects. Issues leading to suboptimal adherence are consistent in many studies but varied in ranking from place to place. For example, whereas side effects were reported to be less significant in influencing adherence to ART in the Botswana study (Hardon *et al*. 2006; Kgatlwane, 2004), it was reported to be one of the first reasons for suboptimal adherence in studies conducted in Zambia and Tanzania respectively (Hardon *et al*. 2006; Murray *et al*. 2007). A study by Woldemedhin and Wabe (2012), found that 67% of the patients who had their treatment modified was due to adverse effects.



This all point to the significance that adverse effects have on HIV treatment. As pointed out in the above studies there is evidence that depending on other external factors such as nutrition, genetic, geographical differences and type of study, there could be differences in the way adverse effects are experienced from one place to another.

2.3. Pharmacology of 1st line antiretroviral drugs

The following are pharmacological terms used to describe the reactions and effects that can result from the use of various medications, their inclusion here is made for

clarification purposes and to enhance understanding of the context under which they are used in this section.

Adverse drug reaction

Refers to a response related to drug or medicinal product that is harmful or unpleasant, which predicts hazard from future use and warrants prevention or specific treatment, or alteration of the dosage regimen or product withdrawal (Edwards and Aronson, 2000).

Adverse effects

Is a more mild and encompassing term that refers to all unwanted outcomes attributed to some action of the drug (Edwards and Aronson, 2000).

Adverse events

Adverse events on the other hand, are adverse outcomes occurring at the same time a patient is taking the drug, which is not or not necessarily attributable to the drug (Edwards and Aronson, 2000). If an adverse event is attributable to a drug it becomes a suspected adverse drug reaction (Aronson, 2009).

Side effect

Is an expected and known outcome resulting from the use of a drug which happens not to be the intended therapeutic effect of that drug (Edwards and Aronson, 2000). They are predictable and undesired therapeutic effects of a drug occurring at normal therapeutic dose ranges (*S Buys Training and Development Academy 2007*). The Medical dictionary (2012) states that, pharmacological side effects are true drug effects. Side effects may be related or unrelated to the mechanism of the drug being administered and may be dose related or not (Edwards & Aronson, 2000). Side

effects can also be wanted or unwanted effects from medicines (Edwards & Aronson, 2000).

Toxic effects (drug toxicity)

A toxic effect is a response to a drug which is harmful to the health or life of an individual (*Medical dictionary* 2012). Toxic effects are related to the main pharmacologic action of the drug e.g. bleeding with anticoagulant or unrelated e.g. liver damage from Paracetamol (Rang *et al.* 2012). Toxic effects are usually an exaggeration of the expected therapeutic effects that rarely occurs at normal doses (Edwards & Aronson, 2000).

Secondary effects

Are undesired effects produced in addition to the pharmacologic effects of the drug (*Nursing buddy* 2012).

Hypersensitivity reactions

Hypersensitivity reactions are unpredictable and abnormal reactions occurring with the use of medicines. These reactions can be divided into, allergic, paradoxical and genetic anomalies (*S Buys Training and Development Academy* 2007).

Idiosyncratic reaction

Is a reaction that occurs in a small number of persons and does not correlate to dosage or means of therapy (Utrecht and Naisbitt, 2013; *The free dictionary* 2012).

Drug interaction

Refers to the modification of the effect of a drug by another drug or drugs, the modification could be negative or positive and can result from concurrent



administration of drugs, herbs, medications, nutritional supplements or disease (*The free dictionary* 2012).

Drug antagonism

Refers to the drug interaction situation where one drug's effect is reduced, completely cancelled out or enhanced by the presence of another drug (Rang *et al.* 2012).

Chemical antagonism

Refers to a situation where two substances combine in a solution and results in the loss of the effects of one or both drugs (Rang *et al.* 2012).

Pharmacokinetic antagonism

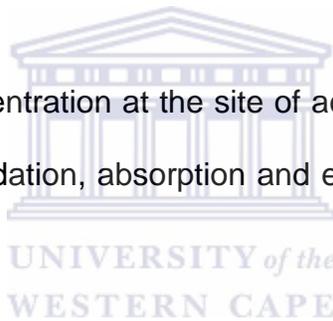
Refers to the reduction in concentration at the site of action of one drug by another, this can be by metabolic degradation, absorption and excretion interferences (Rang *et al.*, 2012).

Competitive antagonism

Refers to a situation where an antagonist and agonist drugs with similar affinity for a receptor, competes for the occupancy of the receptor, however in this situation, raising the level of the agonist can restore its effect (Rang *et al.* 2012).

Non-competitive antagonism (Interruption of receptor – effector linkage)

Refers to a situation where an antagonist binds to a site different from the agonist but influences the effect of the agonist by reducing its binding or effect (Rang *et al.* 2012).

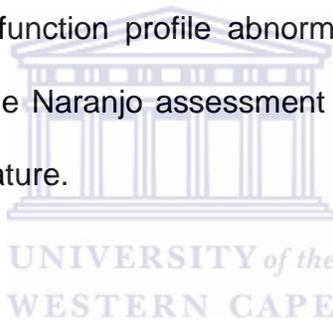


Physiologic antagonism

Describes a situation where two drugs with opposing effects tend to cancel each other's effect out (Rang *et al.* 2012).

Terminology scope of use in this study

Hematological, liver and renal function profile abnormalities in this study were classified as adverse effects. There is evidence that many of the adverse effect ascertained by the study will fall in the 'possible' adverse drug reaction range of the Naranjo assessment scale (Doherty, 2009), however the limitations in the study methodology makes it difficult to establish causality. The classification of hematological, liver and renal function profile abnormalities as adverse effects is therefore assumed based on the Naranjo assessment scale which is mostly based on the available supporting literature.



2.3.1. List of drugs

The first line ARV regimen in Namibia include Tenofovir (TDF), Lamivudine (3TC), Nevirapine (NVP), Efavirenz (EFV), Zidovudine (AZT), (*Ministry of Health* 2010). Stavudine (D4T) is also part of the first line ARV medications. However, due to its undesirable adverse effects such as lipodystrophy, it is no longer recommended to be taken for over two years (*Ministry of Health* 2010). D4T is excluded from the discussions below as the reason given above does not allow it to be part of this retrospective study. The following first line ARV regimen combinations are recommended; (TDF/3TC/EFV), (TDF/3TC/NVP), (AZT/3TC/EFV), (AZT/3TC/NVP). Second line drugs which are not part of this study include: (AZT/TDF/3TC/LPV/r)

with the addition being Lopinavir boosted with Ritonavir (LPV/r) (*Ministry of Health* 2010).

2.3.2. Zidovudine

(i) Mechanism of action

Zidovudine (AZT) is a nucleoside reverse transcriptase inhibitor prodrug which acts as a false substrate for the reverse transcriptase enzyme and terminates the DNA chain (*University of Cape Town* 2012). In other words, the synthetic thymidine analogue from the AZT competes with the endogenous nucleoside for use by the HIV reverse transcriptase enzyme. The use of the synthetic nucleoside results in the termination of the viral DNA which then terminates the infection process (*Rang et al.* 2012).



(ii) Pharmacokinetics

Zidovudine is metabolised in the liver to inactive glucuronide, about 20% of the active form is excreted in the urine (*Rang et al.* 2012). The plasma half-life is about one hour; the intracellular half-life is three hours (*Rang et al.* 2012).

(iii) Adverse effects

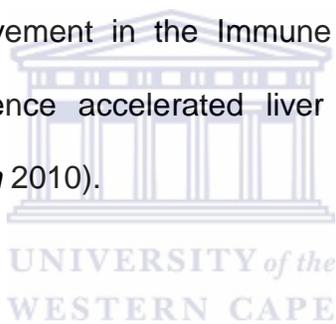
Some of the common adverse effects of AZT include severe anaemia, neutropenia and lactic acidosis (WHO, 2008). Other adverse effects of this drug are presented in appendix 3.

(iv) Drug - drug interactions

Significant drug interactions of ARVs with other medications are well documented. It is noted that, many interactions will occur between ART and various medications used in the treatment of opportunistic infections and short-term illness, such as short courses of antibiotics. For the sake of this study focus is made on the drug interactions that are likely to be encountered in the study, such as interaction with anti-tuberculosis medications and other common opportunistic infection treatments and prophylaxes such as cotrimoxazole.

The majority of the first line ARV medicines are Nucleoside Reverse Transcriptase Inhibitors (NRTI), and generally NRTIs have lower drug interaction profiles than the NNRTIs which mostly use the CYP450 system for metabolism (*Ministry of Health* 2010). One of the common medications likely to be administered with AZT is cotrimoxazole. Cotrimoxazole is given as a standard prophylaxis for opportunistic infections such as bacterial pneumonia, bacteria diarrhoeas, etc. (*Ministry of Health* 2010). Co-administration of AZT and cotrimoxazole has been shown to increase bone marrow suppression, hence the need to monitor such clients (Pham and Flexner, 2005). There have been reports of a decrease in the area under the serum drug concentration-time curve (AUC) of AZT when used together with rifampicin a common anti-tuberculosis medication. However, this decrease is reported to have unknown clinical effect (Pham and Flexner, 2005), and therefore no dosage adjustments are recommended (Burman, Gallicano and Peloquin, 1999). Another common medication likely to be given to clients on the first line ART is fluconazole

given as a secondary prophylaxis to clients who suffer from cryptococcal meningitis (*Ministry of Health 2010*). A slight increase in AZT serum levels is expected when co-administered with fluconazole; however this interaction is described as clinically insignificant (Pham and Flexner, 2005). The risk of Immune Reconstitution Syndrome (IRIS) is increased with the co-administration of AZT, nevirapine, efavirenz and lamivudine (*Medscape Reference 2011*). IRIS is a dramatic increase in the inflammatory response to antigens from untreated or partially treated infections, occurring in the first few weeks of treatment with HAART (*Ministry of Health 2010*). Symptoms are a mimic of the particular untreated infections while the body undergoes robust improvement in the Immune system (*Ministry of Health 2010*). Patients may experience accelerated liver damage following Immune reconstitution (*Ministry of Health 2010*).



(v) Drug - food interactions

Drug food interactions are a common occurrence in people taking HIV medications. Drug food interaction can take place through the pharmacodynamic phase as well as the pharmacokinetic phase (Rang *et al.* 2012). According to Rang *et al.* (2012), medications that increase gastric motility and vice versa influence how much of the drug will be absorbed. Nausea, vomiting and diarrhoea being common side effects of many ARV drugs (*University of Cape Town 2012*), will not only lead to less absorption of food nutrients but also influence client's adherence to medications. Generally, the presence of food in the GI tract can influence the absorption of medications into the system and while as some foods such as grapefruit can inhibit

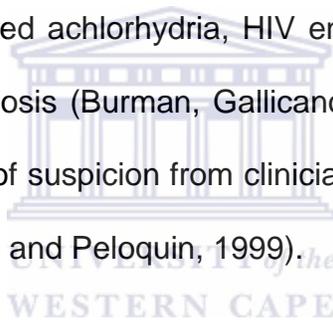
the Cytochrome (CYP) 450 3A4 enzymes (Pronsky and Crowe, 2004). Such an inhibition could lead to increased levels of drugs metabolised by CYP 450 system in the body resulting in increased adverse effects or toxicity. There are significant interactions between many HIV drugs, however only drugs in the first-line ARV treatments are included here.

A liquid fatty meal has been shown to decrease the AUC of AZT by 57%, however its clinical significance is unknown, and therefore administration with food is recommended as it improves tolerability (Pham and Flexner, 2005).

(vi) Drug - disease interactions

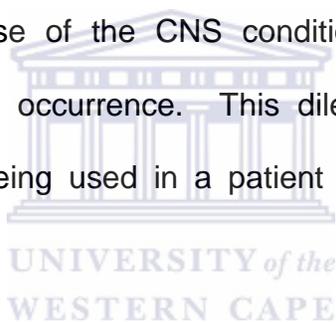
Drug disease interaction refers to a situation in which medications have potential to make a pre-existing disease or condition worse (Lindblad *et al.* 2005). HIV infected patients can have various pre-existing conditions such as hypertension, diabetes, etc., which have potentials of interacting with anti-retroviral therapy. It is well acknowledged from the literature, besides pre-existing conditions that can be made worse by ARV medications, that HIV can also affect various organs in the body which in turn can have many interactions with drugs. Short term and long terms effects of ART can cause structural changes in the body and worsen other conditions or diseases a person may encounter before or after being diagnosed with HIV. For the sake of this study, focus will be on conditions that are likely to be exacerbated by the use of ART based on the most eminent and common adverse effects of the drugs under study i.e. first line treatment.

HIV associated opportunistic infections can lead to condition such diarrhoea and malnutrition. Diarrhoea can in turn limit the absorption of ARVs (Burman, Gallicano and Peloquin, 1999) thus leading to medication sub-therapeutic levels. This condition can also be exacerbated by medications whose adverse effect is diarrhoea. Although there seems to be unreliable methods of measuring malabsorption, gastro-intestinal disturbances and low CD4 counts have been associated with significant malabsorption (Burman, Gallicano and Peloquin, 1999). Some conditions that usually affect people living with HIV that often result in drug malabsorption include HIV-related achlorhydria, HIV enteropathy, and opportunistic infections such as cryptosporidiosis (Burman, Gallicano and Peloquin, 1999). This situation warrants a high index of suspicion from clinicians in patients with advanced HIV disease (Burman, Gallicano and Peloquin, 1999).



Skin conditions are also common among patients with HIV, a study by Serge *et al.* (1993) Using review of records found that skin manifestation in the HIV infected population were higher than in their non HIV infected counterparts, and that skin disorders increased as the disease progressed. Once a diagnosis of skin infections is made, the patient often needs drug therapy, which in turn poses a risk for drug skin eruptions (Serge *et al.*1993). From this study it can be seen that proper clinical judgement will need to be made to ascertain if the cause of a skin condition is related to skin infection or drug adverse effects.

HIV is also associated with an increased risk of psychiatric disorders, including depression, mania, psychosis, and substance abuse (Treisman, 2002). Zidovudine has been associated with mania shortly after its initiation, even occurring in patients without any psychiatric history (Treisman, 2002). Besides the increased risk of psychiatric disorders caused by ARVs; complications of HIV may also lead to psychiatric disorders. Among these, are opportunistic infections of the Central Nervous System (CNS), tumors, systemic and advanced disease (Treisman, 2002). Zidovudine and efavirenz not only have good CNS penetration but also have adverse effects that affect the CNS (Treisman, 2002). This situation may be difficult to judge as to what the cause of the CNS condition is related to, and what medication to use under such occurrence. This dilemma will also need to be considered when HAART is being used in a patient with pre-existing psychiatric disorder.



One of the common complications of HIV is anaemia. Anaemia is reported to be affecting about 60 to 80 percent of people living with HIV especially in the late stages of the disease (Friel and Scadden, 2011). It is also reported to be associated with faster progression to AIDS (Sullivan *et al.* 1998). According to Subbaraman *et al.* (2009), a study done in India in which blood samples were collected from HIV positive patients showed that; 41% had anaemia, and of the anaemic patients, 20% had CD4 counts above 500 mm³ and 64% had CD4 counts below 100 mm³. Unexplained anaemia is classified as stage 3 under the World Health Organisation's HIV clinical staging (WHO, 2007). Causes of anaemia in HIV infected patients are

varied and may range from changes in cytokine production with subsequent effects on hematopoiesis, opportunistic infections, chemotherapeutic agents such as zidovudine and trimethoprim-sulfamethoxazole, cancers, autoimmune destruction of red blood cells etc. (Sullivan *et al.* 1998). To ensure that there is no exacerbation of anaemia, the Ministry of Health in Namibia, recommends that HIV positive clients be assessed for anaemia before commencement of treatment with AZT, only clients with haemoglobin levels above 8 gm/dl can start such a treatment with periodic monitoring (*Ministry of Health* 2010).

2.3.3. Tenofovir

(i) Mechanism of action

Tenofovir is a new addition to the first line ARVs, it is not included in this study due to fewer number of patients placed on it. Its inclusion here is made for completion purposes only. Tenofovir is an analogue of adenosine (*University of Cape Town* 2012) and falls under the category of nucleoside reverse transcriptase inhibitors. It is different from most of the NRTIs because it is monophosphorylated making it to be called a nucleotide reverse transcriptase inhibitor. Tenofovir's mechanism of action is similar to all NRTIs. It acts as a synthetic building block of the HIV DNA synthesis (Hoffman, Rockstroh and Kamps, 2007).

(ii) Pharmacokinetics

Bioavailability of tenofovir is about 25% fasting and increased to 40% with a high fat meal and largely excreted unchanged in the urine through glomerular filtration and tubular secretion. The plasma half-life of tenofovir is about 17 hours (*University of*

Cape Town 2012) and it is not metabolised by the P450 system (*Medscape news* 2012).

(iii) Adverse effects

Adverse effects of tenofovir are presented in appendix 3.

(iv) Drug - drug interactions

Serum levels of tenofovir can be increased by drugs that reduce renal functions such as acyclovir, ganciclovir etc. (*University of Cape Town* 2012). In this instances caution should be observed when co-administration is warranted.

(v) Drug - food interactions

Bioavailability of tenofovir is about 25% fasting and increased to 40% with a high fat meal (*University of Cape Town* 2012), except for the changes in bioavailability no other significant food interactions were found.

(vi) Drug - disease interactions

Another common complication of the HIV infection is HIV nephropathy. Renal disorder can occur at any stage of the HIV infection and ranges from electrolyte imbalances to end-stage renal disease (Choi and Rodriguez, 2008). HIV associated nephropathy (HIVAN) has been demonstrated in about 60% of the black race living with HIV, and almost none existence in whites (Szczech, 2007). According to Szczech (2007), the pathophysiology of HIV associated nephropathy is likely to be

related to direct uptake of the HIV into certain cells of the kidney. Improvements have been reported after HAART is started, whereas higher viral load and low CD4 counts are linked to faster progression of the HIVAN (Szczzech, 2007). Symptomatic HIVAN is classified as a stage four condition under the WHO clinical staging for HIV (WHO 2007). Apart from HIVAN, there are other primary kidney diseases associated with HIV such as IgA nephropathy, Immune-complex glomerulonephritis, amyloidosis etc. (Szczzech, 2007). Medications such as tenofovir, adefovir, and cidofovir, aminoglycoside antibiotics, acyclovir, and amphotericin etc., have all been associated with acute tubular necrosis in HIV-positive patients (Choi and Rodriguez, 2008). In Namibia, tenofovir whose major adverse effect is nephrotoxicity (*University of Cape Town 2012*) is part of the first-line of anti-retroviral therapy (*Ministry of Health 2010*). There is therefore a need to assess the renal function of a patient before tenofovir is prescribed. Ministry of Health (2010) recommends a six monthly creatinine clearance monitoring for clients on a tenofovir based regimen. Caution and close monitoring should be exercised when tenofovir is to be used in clients with renal insufficiencies (*Ministry of Health 2010*). Clients with renal impairment are generally at risk of toxicities when NRTI are used, this warrants a need for close monitoring (*Drug Information Online 2012*).

2.3.4. Lamivudine

(i) Mechanism of action

Lamivudine (3TC) undergoes anabolic phosphorylation by intracellular kinases to form lamivudine 5 triphosphate an active anabolite (Johnson *et al.* 1999). Lamivudine is also a nucleoside reverse transcriptase inhibiting substance. Its

mechanism of action resembles the one described above under AZT but differs in that; it is an analogue of cytosine (Rang *et al.* 2007).

(ii) Pharmacokinetics

Lamivudine has a high oral bioavailability reaching maximum serum concentrations usually within 0.5 to 1.5 hours after the dose (Johnson *et al.* 1999). The absolute bioavailability is approximately 82% and 68% in adults and children respectively; about 70% of an oral dose is eliminated unchanged by kidneys (Johnson *et al.* 1999). And about 5-10% of the drug is excreted as inactive trans-sulfoxide metabolite (Johnson *et al.* 1999; *Pharmacogenomics. Knowledge. Implementation*, 2012).



(iii) Adverse effects

Adverse effects of lamivudine are presented in the appendix 3.

(iv) Drug - drug interactions

No clinically significant interaction of this medicine is documented by Pham and Flexner (2005) and the University of Cape Town (2012). The Medscape Reference (2011) highlights the increased risk of Immune Reconstitution Inflammatory Syndrome when lamivudine is used in combination with any of AZT, nevirapine or efavirenz drugs. Many other drug interactions of lamivudine listed by the Drug Information Online (2012), leading to risks of hepato-toxicity are not likely to be encountered in the scope of this study.

Pham and Flexner (2005) reported an increase in the 3TC area under the plasma drug concentration-time curve (AUC) by 44% if co-administered with cotrimoxazole but also indicated this effect as clinically non-significant. Trimethoprim has also been shown to decrease the renal clearance of 3TC whereas 3TC does not have the same effect on trimethoprim (Johnson *et al.* 1999).

(v) Drug - food interactions

Limited information was found on the interaction between lamivudine and food. According to Johnson *et al.* (1999), food does not seem to alter the AUC of lamivudine.

(vi) Drug - disease interactions

Patients with known risk factors for pancreatitis should be monitored closely if on 3TC and discontinuation of 3TC should be done promptly if signs and symptoms suggestive of pancreatitis occur (*Drug information online* 2012). In patients with hepatitis, there is a risk of rebound hepatitis following withdrawal of lamivudine (*University of Cape Town* 2012).

2.3.5. Nevirapine

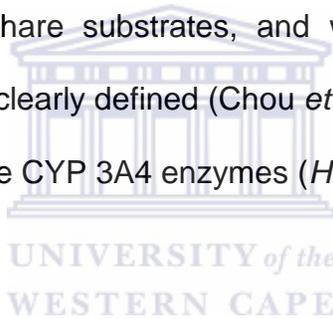
(i) Mechanism of action

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor, and works by attaching to the viral reverse transcriptase enzyme and denatures it; this in turn stops the progression of the virus replication (Rang *et al.* 2012).

(ii) Pharmacokinetics

Nevirapine has a bioavailability of about 90%; the plasma half-life is about 45 hours which is reduced by auto-induction to 20 – 30 hours. It is heavily metabolised in the liver by the cytochrome P450 system (Rang *et al.* 2012; *University of Cape Town* 2012). Metabolites are renally excreted (Rang *et al.* 2012; *University of Cape Town* 2012).

Nevirapine is 60% plasma protein bound and its elimination is mainly through oxidative metabolism involving CYP3A and CYP2B6 enzyme (Chou *et al.* 2010). Both CYP3A4 and CYP3A5 share substrates, and whether this is the case in nevirapine metabolism, it is not clearly defined (Chou *et al.* 2010). Nevirapine is both an inducer and a substrate of the CYP 3A4 enzymes (*HIV guidelines* 2012).



(iii) Adverse effects

Adverse effects of nevirapine are presented in appendix 3.

(iv) Drug - drug interactions

Nevirapine and rifampicin are not given together in accordance with the Ministry of Health and Social Services in Namibia ART guidelines (2010). This is because of the resulting interaction that leads to reduced nevirapine level from the enzyme induction capabilities of the rifampicin (Lalloo, 2009). Another drug likely to be given with nevirapine is fluconazole. There is an elevated risk of hepatitis occurring as a result of increased serum levels of nevirapine caused by fluconazole which inhibits

the P450 system (*University of Cape Town* 2012). This potential adverse effect should be monitored in cases of nevirapine and fluconazole co-administration (Pham and Flexner, 2005). Serge *et al.* (1993), reports more drug eruption being mostly related to cotrimoxazole therapy, a situation that also needs to be assessed careful in case cotrimoxazole is given concurrently with other medicine that can cause drug eruptions such as nevirapine.

Although no dose adjustment is required in the NVP, there is a reported increase in the NVP Area under Serum drug Concentration-Time Curve (AUC) with the use of depo-medroxy-progesterone acetate (DMPA) (Pham and Flexner, 2005). On the other hand, ethinyl estradiol's AUC is decreased by about 23%, and alternative form of contraceptives especially barrier methods are recommended (Pham and Flexner, 2005). Efficacy of oral contraceptives may be reduced by the NVP cytochrome P450 enzyme induction (*University of Cape Town* 2012). There is a 35% increase in NVP clearance if administered with St. John's Wort (Pham and Flexner, 2005).

(v) Drug - food interactions

No clinically significant interactions documentation was found on nevirapine and food (Pham and Flexner, 2005; *University of Cape Town* 2012).

(vi) Drug - disease interactions

Hepatitis and many other liver disorders can be complicated by the use of HAART. The clinical course of a chronic liver disease is likely to be more aggressive in the

presence of HIV infection, than in non HIV infection (Klatt, 2011). Though it is known that HAART improves the clinical course of some liver disorders such as Hepatitis C Virus (HCV), some drugs such as nevirapine, and D4T should be used with caution as they can aggravate hepatotoxicity (Hoffmann, Rockstroh and Kamps, (ed.) 2007). Hepatotoxicity often presenting in the form of hepatitis, hepatic steatosis or hepatic necrosis is often associated with most of the classes of HAART medication such as NNRTI, NRTIs and PIs (Klatt, 2011; U.S. *Department of Health and Human Services* 2005).

People living with HIV are more at risk of developing HAART-related hepatotoxicity if co-infected with hepatitis B (Hoffmann, Rockstroh and Kamps, (ed.) 2007). Reactivation of hepatitis B has been described following immune reconstitution after initiation of HAART (Hoffmann, Rockstroh and Kamps, (ed.) 2007).

Another common syndrome occurring as a result of drug disease interaction is the Immune Reconstitution Inflammatory Syndrome (IRIS).

2.3.6. Efavirenz

(i) Mechanism of action

Efavirenz is also a non-nucleoside reverse transcriptase inhibitor and has a similar mechanism of action to that of nevirapine described above (Rang *et al.* 2012).

(ii) Pharmacokinetics

Taking efavirenz with a fatty meal has potential to increase the bioavailability to about 50%, protein binding is 99% with the plasma half-life reaching the ranges of 52 – 76 hours (*University of Cape Town 2012*). Efavirenz is metabolised by auto induction via the P450 system and is renally and fecally excreted (*University of Cape Town 2012*). A genetic study presented in *Pharmacogenomics. Knowledge. Implementation (2012)* refers to CYP2B6 as the enzyme with most activity on efavirenz. According to Leung *et al* (2009), efavirenz is about 90% cleared by the CYP2B6 and is metabolized mainly by cytochrome P450 2B6 (CYP2B6) and possibly CYP3A4 or other CYP isoforms to a less extent. It is also an inducer of the CYP2B6 and CYP3A4 (Auto-Induction) (Zhu *et al.* 2009).

(iii) Adverse effects

Common side effects of this medication are presented with codes in appendix 3.

(iv) Drug - drug interactions

The interaction between efavirenz and rifampicin has been reported to be minimal during clinical trials with some studies recommending an increase in the efavirenz dose and others not (*MIMS 2010*). In Namibia efavirenz is the selected drug of choice for patients on the first line treatment and taking rifampicin (*Ministry of Health 2010*), as efavirenz is seen to have lesser interaction with rifampicin. Caution should be exercised for women of child bearing age, as efavirenz may reduce the efficacy of oral contraceptives (*University of Cape Town 2012*). The St. John's Wort is known

to induce the metabolism of efavirenz and may lead to its decreased plasma levels (*University of Cape Town 2012*).

(v) Drug - food interactions

There is a reported increase in the AUC of EFV if taken with fatty meal, with about 79% increases in serum concentration (C_{max}) after a fatty meal, for this reason, manufacturers recommend taking EFV on an empty stomach to reduce side effects (*Pham and Flexner, 2005*).

(vi) Drug - disease interactions

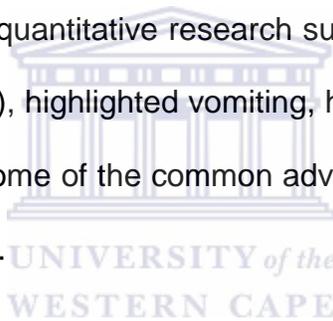
There have been reports of an increase in total cholesterol of about 10 to 20% in studies involving non infected volunteers given efavirenz (*Drugs online 2012*), the Namibian guideline on ART (*Ministry of Health 2010*) requires that clients on efavirenz be monitored for fasting cholesterol and triglyceride at 12 months and yearly thereafter. This is because efavirenz has been shown to cause an increase in total cholesterol (*Maartens et al. 2008*). In anticipation of this interaction, clients with pre-existing hyperlipidemia may therefore need to be closely monitored if efavirenz is to be used (*Drugs online 2012*).

Since efavirenz is largely metabolised in the liver, clients with liver disorders are at risk from low drug metabolism and drug toxicity, this will call for regular liver function monitoring (*Drugs online 2012*). Therapy with efavirenz should also be cautiously

administered in clients with past and present history of psychiatric disorders and discontinuation may be necessary if symptoms worsen (*Drugs online* 2012).

2.4. Common adverse effects experienced by patients on ARV treatment in Namibia

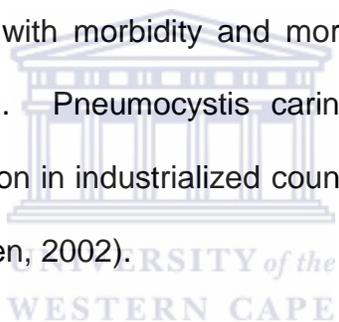
According to a survey by Ibis Namibia, Lironga Eparu and the Rainbow Project (2005), about 57% of clients interviewed had at one point or the other experienced adverse effects of which 55% of these clients had reported such side-effects to a health care provider. A similar quantitative research survey done in eight regions of Namibia by Van Zyl *et al.* (2008), highlighted vomiting, headaches, diarrhoea, itching and peripheral neuropathy as some of the common adverse effects (AE) reported by people living with HIV and AIDS.



Many adverse effects of ARVs are well known and well documented. They include serious and less serious self-limiting adverse effects. Examples of the serious adverse effects of ARVs include pancreatitis, Hypersensitivity reactions, toxic epidermal necrolysis, hepatotoxicity, haematological toxicities etc. (*Ministry of Health* 2010). Other classifications include disabling and long term AE such as peripheral neuropathy and lipodystrophy respectively (*Ministry of Health* 2010).

2.5. Opportunistic infections commonly seen in HIV infected patients and their treatment

Opportunistic infections (OIs) are diseases or infections that do not usually cause illness in human, but will usually result in illness when there is a reduction in the competency of the immune system (*Ministry of Health* 2011). Organisms causing opportunistic infections are usually of low or non-virulence in people with intact immune systems and may present with an unusual clinical manifestation in immunodeficient people (*WHO* 2009). This means that the level of immune system determines what types of opportunistic infection is likely to be experienced (Hoffmann, Rockstroh and Kamps, (ed.) 2007; *WHO* 2009). OIs may be regional, age or gender associated (Klatt, 2011; Maartens, 2002; *WHO* 2009). Tuberculosis is the commonest OI associated with morbidity and mortality in Sub-Saharan Africa (*WHO* 2010; Maartens, 2002). *Pneumocystis carinii* pneumonia which is the commonest opportunistic infection in industrialized countries is uncommon in African adults with HIV infection (Maarten, 2002).



Namibia has one of the highest TB burdens in the world. In 2012, Namibia had a case notification rate of 655 per 100 000 population (*WHO* 2013), with a 45% prevalence of HIV among TB patients (*Ministry of Health* 2013). Few studies highlight the common OIs experienced by HIV positive clients from a Namibian context; however the Ministry of Health and Social Services (2010) had listed common OIs that are mostly seen in immune reconstitution inflammatory syndromes, presented in the table 1 below:

Table 1: Opportunistic infection mostly seen in Immune Reconstitution Inflammatory Syndromes

Opportunistic Infection	Treatment
Mycobacterium Avium Complex	-Azithromycin, Ethambutol, Quinolones or Amikacin
Cytomegalovirus	Valganciclovir and Steroids
Tuberculosis	First line TB treatment include Rifampicin, Isoniazid, Pyrazinamide, Streptomycin and Ethambutol
Cryptococcosis	Amphotericin B, Fluconazole
Hepatitis B Virus	HAART, to include Lamivudine and Tenofovir
Herpes Zoster	Oral Acyclovir
Progressive multifocal leukoencephalopathy (PML)	HAART

Ministry of Health: 2010

2.6. Relationships between gender and ARV adverse effects

Some adverse effects are reported to be more common in a particular gender than the other. For example, the osteopenia and osteoporosis mostly associated with the PIs class of medicines are more common in females than their male counterparts (*US Department of Health and Human Services 2005*). Nevirapine adverse effects are likely to be experienced at CD4 counts above 400 cell/ml in male and above 350 cell/ml in females (*Panel on Antiretroviral Guidelines for Adults and Adolescents 2011; Ministry of Health 2010*). The female sex is also reported to be a risk factor for lactic acidosis (Hoffmann, Rockstroh and Kamps, 2007). A number of adverse effects common to female and peculiar to males have been reported and include, higher blood levels of ARV medicines due to more fat deposits, abnormal fat distribution (lipodystrophy), exaggerated symptoms of osteoporosis etc. (*Southern Africa HIV and AIDS Information Dissemination Service 2008*).

2.7. Relationships between ARV adverse effects and treatment regimens

Different ART regimens are found to present with different types of side effects and toxicities. According to WHO (2008), and Hoffmann, Rockstroh and Kamps, (ed.) (2007), mitochondrial toxicity adverse effects are usually associated with NRTI, whereas metabolic reactions adverse effects are associated with PIs. On the other hand hypersensitivity reactions are mostly associated with NNRTIs. Although there are medicine class specific known adverse effects, most of the adverse effects are seen to be drug specific, such as haematological toxicities associated with AZT and renal toxicities associated with tenofovir (WHO 2008).

2.8. Relationship between adverse effects and duration of treatment

Adverse effects to antiretroviral medicines have been reported to manifest in different trends according to the regimen used. NRTIs, NNRTIs and PIs are known to be associated with earlier gastro-intestinal adverse effects (Hoffmann, Rockstroh and Kamps, (ed.) 2007), gastro-intestinal adverse effects occurring later during the course of treatment need to be investigated as this could be due to some other pathologies (Hoffmann, Rockstroh and Kamps, (ed.) 2007). Some adverse effects are expected earlier while others occur later during the course of treatment (*Ministry of Health* 2010). Examples include hypersensitivity reaction (HSR) occurring within 12 weeks of treatment of NNRTI and abacavir HSR that usually occurs in a median of eight days (Hoffmann, Rockstroh and Kamps, (ed.) 2007). Nucleoside reverse transcriptase inhibitors related hepatic steatosis is known to be occurring later than 6 month of treatment (Hoffmann, Rockstroh and Kamps, (ed.) 2007).

2.9. Relationship between CD4 count level and ARV adverse effects

The review had found significant amount of information on studies that looked at the relationships between CD4 counts and the types of adverse effects experienced. A prospective study aimed at finding the relationship between CD4 counts and ARV toxicities could not yield much information. In this study, a low CD4 count nadir was not associated with higher risks of ARV toxicities (Colette *et al.* 2005). On the contrary, clients starting nevirapine (NVP) with a higher CD4 count are found to be at risk of drug related Hepatitis and pathologic dermatological manifestations (WHO 2008). Starting clients with a higher CD4 counts on NVP has shown to be associated with more serious toxicities (*Panel on Antiretroviral Guidelines for Adults and Adolescents* 2011; *Ministry of Health* 2010). However this seems to be challenged in a prospective cohort study by Peters *et al.* (2010) who concluded that, hepatotoxicity and rash after NVP initiation are more related to abnormal baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as opposed to higher CD4 counts. Although this study reported several limitations, other studies seemed to have arrived at similar conclusion (Kondo *et al.* 2008; Knobel *et al.* 2008).

At times, CD4 count levels may remain low despite a responsive reduction in the viral load; this could be associated to neutropenia, an adverse effect of medicines such as zidovudine (Hoffmann, Rockstroh and Kamps, (ed.) 2007). A low CD4 nadir, has also been identified as a risk factor for lactic acidosis (Hoffmann, Rockstroh and Kamps, (ed.) 2007). Immune Reconstitution Syndrome (IRIS) is another adverse effect that is related to the ability of the body to mount an immune

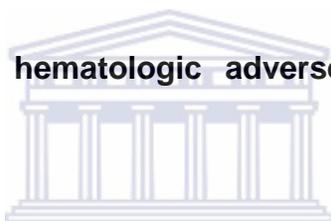
response to existing pathologies (*WHO* 2008). This condition related to use of ARVs is most commonly reported in clients who start ART with CD4 below 50 (*WHO* 2008).

2.10. Relationship between viral load and ARV adverse effects

In a multivariate analysis of a prospective French study involving clients put on protease inhibitors, a viral load of 100 000 copies /ml was independently associated with severe adverse effects ($P= 0.03$). Other independent variables in the same study that were associated with severe adverse effects were, creatinine clearance below 70ml/min ($p=0.007$), taking indinavir ($p.0.008$) and hepatitis B or C infection (Carter, 2004). The preliminary result of the AIDS clinical trial group (ACTG) 5202, revealed that there was a difference in the amount and type of adverse effects experienced by population starting treatment with viral load below and above 100 000 copies per ml. This study was presented at the International AIDS Conference in 2008. In this study, the population starting ARV treatment with viral load above 100 000 per ml using the regimen that contained abacavir, lamivudine and ritonavir boosted atazanavir or efavirenz developed adverse effects 1.89 times faster compared to the tenofovir, emtricitabine and efavirenz or ritonavir boosted atazanavir regimens. These results were not ascertained when comparison of the same regimens were made in the population starting ARV treatment with viral loads lower than 100 000 per ml (Horn, 2008). There were also differences in the amount of adverse effects, where 130 moderate to severe adverse effects were experienced in the former regimen group compared to 78 of the later (Horn, 2008). On the other hand, an analysis made by GlaxoSmithKline to challenge the ACTG 5202 results

revealed lesser differences and regarded these differences as statistically insignificant (Horn, 2008). The abacavir, lamivudine and ritonavir boosted atazanavir or efavirenz regimens in the category of clients starting ARV treatment with pre-treatment viral loads above 100 000 per ml was later dissolved due to insufficient viral suppression. However the same regimens in the study population starting ART with viral loads below 100 000 copies per ml was allowed to continue as this study population did not show challenges of increased adverse effects or insufficient viral suppression at the study pre-evaluation time. This may be a representation that, higher viral loads are associated with increased adverse effects.

2.11. Hepatic, renal and hematologic adverse effects of antiretroviral treatment



Alanine transaminase enzyme (ALT) test is not necessarily a liver function test; it is mostly used to indicate some degree of liver injury (Haghighat, 2014). In patients taking ARVs, hepatotoxicity is always encountered. Manuela *et al.* (2012) reported that elevated ALT was commonly associated with nevirapine compared to efavirenz. According to Manuela, *et al.* (2012), increases in ALT or and aspartate aminotransferase (AST) are common symptoms of hepatotoxicity (Manuela *et al.* (2012).

Serum creatinine levels are often used to determine renal function of patients. Although this method provide the much needed information for patient management, other test such as the glomerular filtration rates are necessary

to recognise renal dysfunction (Duncan *et al.* 2000). A study on the creatinine levels of patients placed on HAART treatment in South Eastern Nigeria, showed elevation in mean creatinine level in 28% of the patients from baseline mean range of 1.24mg/dl and 50.71mg/dl to 3.92mg/dl and 71.6mg/dl at 18 months (Alo, *et al.* 2012). This study does however not mention which types of antiretroviral combinations were the patients taking.

Various studies have demonstrated that there are hematologic adverse effects associated with antiretroviral medications. A study by Romanelli (2004) showed that 77% of the patients who were adherent to zidovudine had macrocytosis compared to 18% who were not adherent. Macrocytosis, anaemia, thrombocytopenia were among the commonest haematological adverse effects associated with zidovudine in a study by Oshikoya (2012).

2.12. Summary

Many literatures reveal that patients on ARVs experience more adverse effects especially in the initial phases of treatment (Hardon *et al.* 2006), which tends to improve as treatment goes on. This is related to physiological adaptation (Rang *et al.* 2012). Literature also still document that patients on ARV treatment will experience different adverse effects, manifesting as short term and long term (also

called delayed) adverse effects (*Ministry of Health* 2007; Edward and Aronson, 2000).

Given the differences in settings in which many of the reviewed studies took place, a research from this part of the world does not guarantee similar results. In consideration are facts such as limited resource settings, nutrition, geographical location, genetic influences, people's habits, existence of co-morbidities, reliance on local alternative or traditional medicines, levels of training of the human resource managing clients on ARVs, existence of medicine safety regulatory systems etc. These independent factors may play a role in the results ascertained in this study.



Chapter 3: Materials and methods

3.1. Study design and site

This study was done at Keetmanshoop ARV clinic; the researcher used a retrospective quantitative study design, in which patients' files were used to examine follow-up care in the past four years. Patients who started treatment between the 1st of November 2007 and 1st of December 2008 were enrolled into the study. This period was chosen to match the study design, as these patients would have attained at least four years of treatment by the time of data collection. This study period was also suitable because it was least affected by changes in the Namibian Ministry of health and Social Services ART guidelines (2007) that prescribed for a change in the treatment of patients who were placed on stavudine for more than two years. The Namibian Ministry of Health and Social Services ART guidelines (2010) allowed patients who were stable on the first line treatment of AZT, 3TC and NVP/ EFV based regimens to continue such treatment. Thus making these patients eligible to be included in the study criteria. Common adverse effects (clinical and laboratory findings) experienced at various levels of the first line treatment were looked at. It is presumed that clinicians will order certain tests, or do certain exams related to what patients complain of, on this ground the findings of such assessment were reviewed for inclusion in the study. Haematological and biochemical evaluations were done using reference ranges set by the country's reference laboratory, i.e. the Namibia Institute of Pathology (NIP). Figures outside these set ranges were evaluated and considered as adverse effects. A list of the NIP ranges is attached in Appendix 4.

3.2. Inclusion criteria

The inclusion criteria included all patients male and female, fifteen years and older starting the first line ARV treatment or that had stabilised on a first line regimen after being changed from earlier treatment regimens that are not part of the study. Patients should have attained at least four years (36 – 48 month) of documented uninterrupted treatment on the same first line regimen. The fifteen years age group cut off was chosen as it was the age at which children were likely to be placed on adult regimens, than the paediatric regimens which starts with stavudine, and would be later changed to other regimens (*Ministry of Health 2010; Ministry of Health 2007*). An adverse effect was defined as a deviation (reported, clinical, laboratory or biological finding) from the normal findings.

3.3. Exclusion criteria

Patients who did not meet the above criteria were not included in the study. Patients whose ART was switched from first to second line ARV treatment were also excluded.

3.4. Sampling and sample size

According to the electronic dispensing system (Electronic Dispensing Tool), 429 patients, fifteen years and older were started on treatment between the 1st November 2007 and 1st December 2008. Of this number, 294 patient records were found. The ascertained patient records were numbered and a random number generator using Stata 12.1 was done to select the records to be included in the

study. The Taro Yamane simplified formula was utilized to calculate the sample sizes for proportions as follows (Israel, 2008):

$$n = \frac{N}{1 + N(e)^2}$$

Sample sizes was calculated for +/- 5% precision levels where confidence intervals is 95% and a maximum variability (P = .5).

N = Population size

n = Sample size

e = required size of standard error

Size of population (N)	Sample Size (n) for Precision (e) of:		
	±5%	±7%	±10%
100	80	57	36
125	95	65	39
150	109	71	42
175	122	76	43
200	133	81	45
225	144	84	46
250	154	88	47
275	163	91	48
294	169	93	48
325	179	95	49

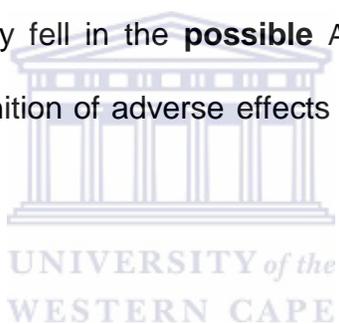
3.5. Data collections

Data collection was done from 21st December 2012 to the 4th January 2013. Two nursing staff were trained on data collection and assisted with the data collection under guidance of the researcher. Patient files were used to generate data which was entered into the data collection tool. Any other significant adverse effects were entered into the data collection tool. Entry into the data collection tool (Appendix 5)

was according to months the treatment was started. For example, month one, is the month when the patient was started or transitioned to the first line treatment under the study.

3.6. Classification and ranking of adverse effects

Classification of adverse effects was done using the Naranjo adverse drug reaction probability scale (Doherty, 2009). Although the Naranjo scale is more applicable when assessment are done in a controlled environment such as a situation where re-challenge of the suspected medication is achievable, assessment of the adverse effects ascertained in this study fell in the **possible** Adverse Drug Reaction (ADR) category. Consequently a definition of adverse effects instead of ADR was used in the study.



3.7. Parameters assessed

The following parameters were assessed and used in various statistical tests:

3.7.1. Demographic characteristics

The demographic characters that were assessed are gender and age.

3.7.2. Pharmacotherapeutic characteristics

The pharmacotherapeutic characters that were assessed are regimen types and duration of treatment. Assessment was also done on the implications of earlier exposure to ART compared to no exposure.

3.7.3. Hematologic and Immunologic profile

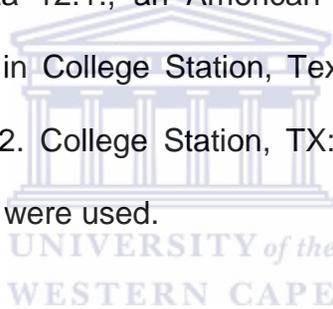
Hematologic and immunologic profile assessed included haemoglobin levels, red cell counts, mean cell haemoglobin, CD4 counts and white cell counts etc.

3.7.4. Biochemical characteristics

Biochemical parameters assessed the liver and renal function status by looking at the alanine transaminase enzymes and creatinine levels, abnormality of which was classified as adverse effects.

3.7.5. Data analysis

Data was analysed using Stata 12.1., an American statistical software package produced by StataCorp based in College Station, Texas. (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Using this software various statistical tests were used.



3.7.6. Ethics approval

The information obtained was handled with strict confidentiality, with no use of patient names for anonymity purposes. The study was approved by the ethics committee of the University of the Western Cape (Ethics certificate number: 12/6/45) and the Namibian Ministry of Health and Social Services (see appendixes 1 and 2).

3.8. Limitations

The major limitation of this study was the low numbers of patients that resulted in wider confidence intervals. Other parameters could not be assessed due to low numbers, e.g. patients who had viral load results were few.

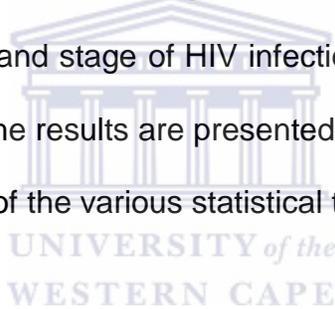
Results are based on the recorded information from health workers, whereas it is mandatory for health workers attending to the patient to record findings from patient assessments, it is also common knowledge that variation in what health workers will consider as important information to be recorded can occur. Thus, the result of a retrospective record based study is limited to existing data and is as good as the quality of the recordkeeping. Furthermore, this study also suffers from weakness of retrospective studies in determining causation i.e. some other factors such as alcohol or lifestyle or none recorded medications taken by the studied patients could have contributed to the abnormal findings. Abnormal findings could also relate to the disease process or any pathologies and not necessarily to the medications. However there are agreements between this study and many other studies that point to consistencies in the results.

Cotrimoxazole was recorded to have been used in 91% of the patients; this means some adverse effects ascertained in the study could also relate to it.

Chapter 4: Results

4.1. Introduction

The study aimed at finding common adverse effects experienced by HIV-positive patients treated with first line ARV treatment at Keetmanshoop ART Clinic. The study also aimed at assessing the risk factors for development of adverse effects in HIV-positive patients on antiretroviral therapy (ART). Specific objectives of the study were to determine if there is any association between adverse effects (clinical and laboratory findings) and any of the following factors: patient gender, drugs used, treatment duration, patient age and stage of HIV infection. This chapter present the various findings of the study. The results are presented starting with the background of the patients and later results of the various statistical tests performed.



4.2. Demographics characteristics

The gender and age distribution of the 94 studied patients is presented in table 2 below. The median age was 38, with age ranges of 18 to 69.

Table 2: Demographic characteristics of the studied patients		
Demographic Factor	Number	Percent
Gender distribution		
Male	33	35
Female	61	65
Age distribution		
18 – 24	4	4.3
25 – 34	30	31.9
35 – 44	31	32.9
45 – 69	29	30.9

4.3. Therapeutic and clinical profile

Table 3 below shows the therapeutic and clinical profiles of the 94 studied patients. Among a total of 94 studied patients, 54% remained on the first line ARV treatment (herein classified as first treatment) under study for a period up 36 to 48 month, while 46% of the patients were transitioned (herein referred to as transitioned) from a different regimen and stabilised on one of the first line alternative treatment for the duration of the studied period. For a list of the first line drugs see section 2.3.1. Only 6% of the 94 patients were found with records of being on chronic medications other than ARVs, they included five patients on amiloride hydrochloride, and one patient on an unmentioned anti-asthmatic medication.

As a measure of liver function abnormality as an adverse effect, about 40% of the studied patients had one or more elevated ALT test results during the duration of the treatment. This was measured by aggregating into one group, the patients who experienced one or more elevations in the measured ALT tests throughout the study period, compared to the group of patients that never experienced any elevation in the measured ALT tests during the study period. Using this same principle in measuring the renal function of the studied patients, 59% of the patients experienced an elevation in their creatinine test result.

Table 3: Therapeutic and Clinical profile of the studied patients		
Therapeutic/Clinical Factor	Number	Percent
Regimen base		
AZT/3TC/NVP	72	77
AZT/3TC/EFV	22	23
Treatment status		
First treatment	51	54
Transitioned	43	46
Cotrimoxazole use		
Recorded	86	91
No record	8	6
Median CD4 Counts		
0 - 300	36	38
> 301	58	62
Average high ALT		
None	56	60
Positive	38	40
Average high creatinine		
none	16	41
Positive	23	59

4.4. Prevalence of patient reported adverse effects

Only 44 out of 94 (46%) patients had reported an adverse effect during their visits to the ARV clinic in the period of 36 – 48 months. Of these patients, 31 were females and 13 were males. Out of the 44 patients, 33 were on the NVP based regimen and 11 were on efavirenz. The statistical significant relationship between prevalence of patient reported adverse effects and type of regimen and CD4 count were tested using the Pearson chi square test. CD4 count medians achieved at 36 – 48 month of treatment were calculated for each patient and categorized into CD4 count of 1 – 300 and 301 and above. There were no statistically significant associations between the regimen base patients were on and the reported adverse effects. There was also no statistically significant association between the reported adverse effects and patient CD4 counts. Table 4 below shows the five most reported adverse effects,

percentages calculated from the numbers of patients with recorded adverse effects and the p-values of the Pearson chi-square test used to test for associations.

Table 4: Commonly reported adverse effects by patients on first line ART treatment

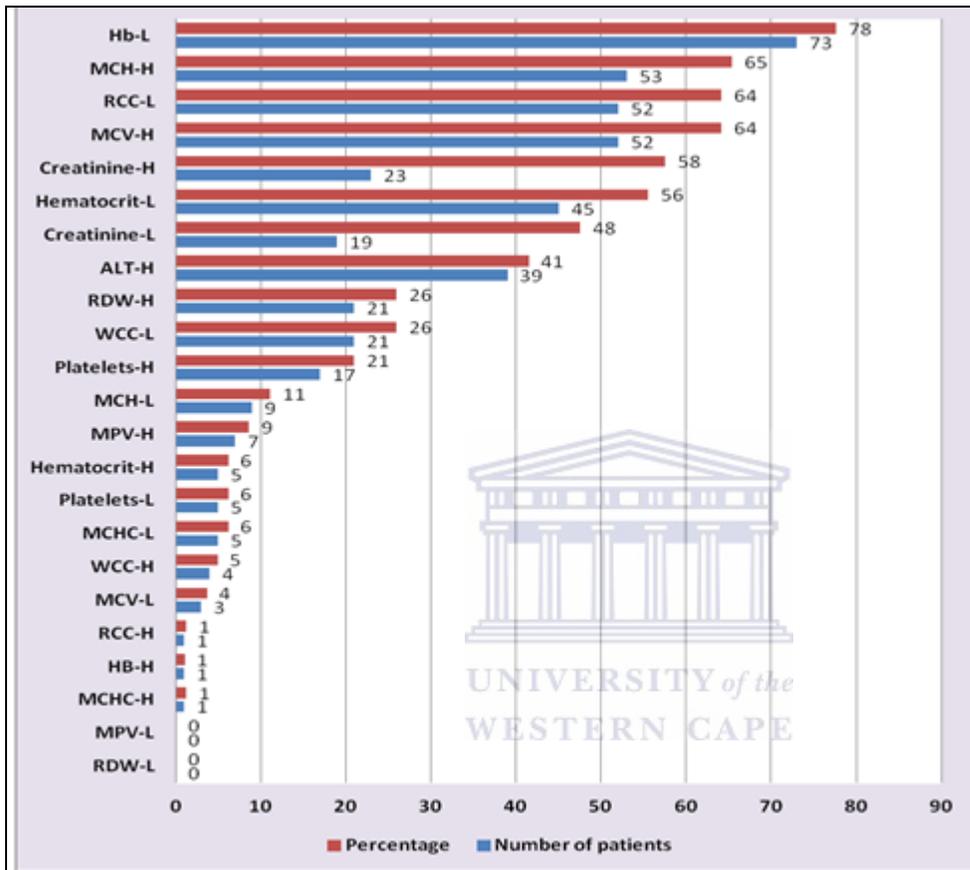
Complaints	Number of patients reporting the adverse effect at any period	%	Association with regimen P-value:	Association with CD4 P-value:
1. Musculoskeletal Disorder	11	25	0.747	0.467
2. Skin disorder	9	20	0.459	0.799
3. Cough	9	20	0.930	0.088
4. Gastro intestinal disorders	8	18	0.446	0.122
5. Headache	7	16	0.750	0.607

4.5. Prevalence of haematological, renal and liver function adverse effects in the studied patients

All 94 patients were assessed for haematological, renal and liver function related adverse effects using the recorded blood results. The Namibian Institute for Pathology (NIP)'s reference ranges were used to classify the disorders from the norm. The disorders were then classified as adverse effects and were taken from any stage of treatment period per patient i.e. patients who would have had an abnormality in the haematological profile at any stage would be classified as positive for that particular hematologic test at the end of the assessment period of 36 – 48 months. The common haematological, renal and liver function related adverse effects as ascertained from the full blood counts are illustrated in figure 3 below. The most common haematological adverse effect ascertained was the low HB, followed by higher mean cell haemoglobin (MCH). The least common adverse effect

was the low Mean Platelet Volume (MPV) and low Red cell Distribution Width (RDW).

Figure 1: Common haematological, renal and hepatic adverse effects ascertained



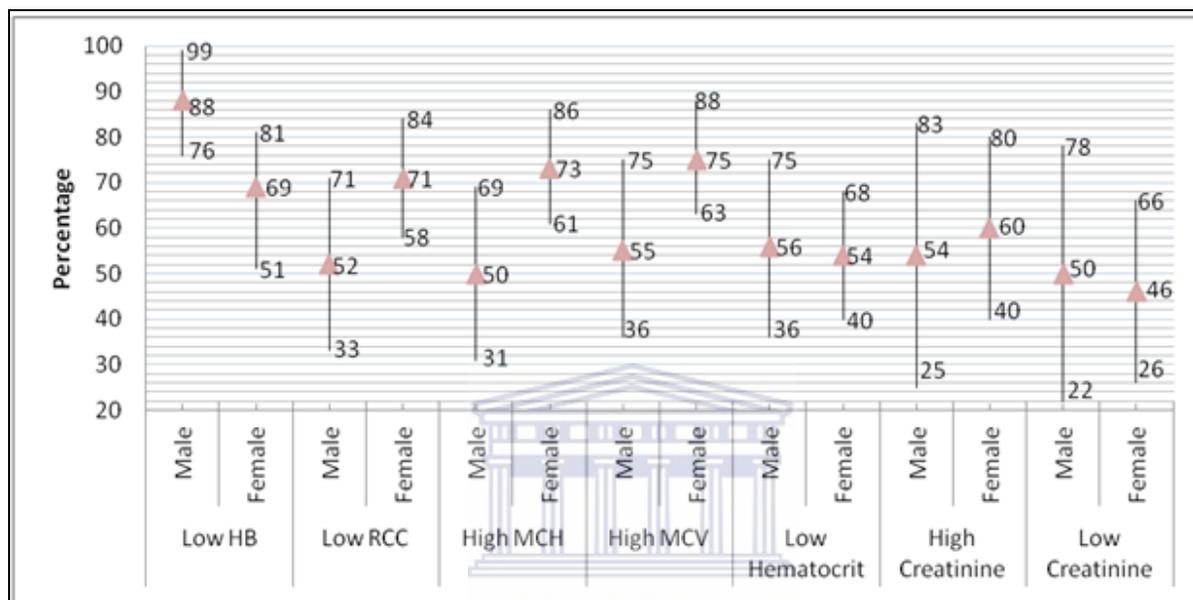
Key: H=High, L=Low

4.6. Association between haematological, renal and liver function adverse effects and the gender of the studied patients

To understand if some haematological or renal and liver function adverse effects were more common in male or female patients, a Pearson chi square test was performed to test for statistical significance in selected prominent adverse effects. A

null hypothesis of no association was assumed. Figure 5 depicts the point prevalence and confidence intervals of selected adverse effects.

Figure 2: Common haematological and renal adverse effects among adult male and female patients showing point estimates and 95% confidence intervals



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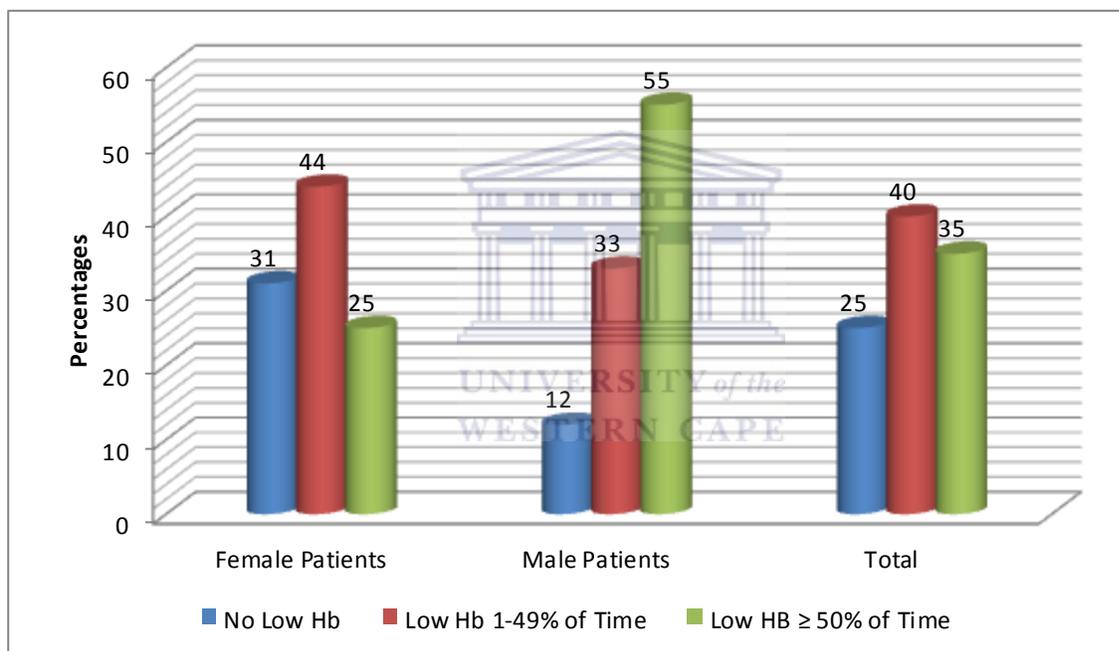
4.6.1. Association between gender and low hemoglobin levels

All 94 patients had a haemoglobin (HB) test done at most times during their follow up visit to the ART clinic, 61 were females and 33 were males. More male patients (88%, 95%CI: 76.4 – 99.3) experienced low haemoglobin compared to female patients (69%, 95%CI: 56.9 – 80.7). This difference was statistically significant ($p < 0.04$) and rejects the null hypothesis of no association.

The low haemoglobin was further divided into three categories, i.e. patients who had no low HB, patients who had low HB in 1 to 49% of the tests done, and patients who had low HB in 50% and more of the tests performed. This was done to try and

classify low HB as an adverse effect if it persisted for up to 50% or more of the tests done. As highlighted in figure 3, more males than female patients were still found to have low HB persisting in 50% and more of the total tests taken, 55% (95%CI: 37.0 – 72.0) and 25% (95%CI: 13.5 – 35.6) respectively ($p=0.004$). When adjusted for regimen type, a male patient was three times likely to have a low haemoglobin level compared to a female patient (OR: 3.29, 95% CI: 1.3 – 8.3).

Figure 3: Changes in haemoglobin levels in relation to gender



4.6.2. Association between gender and high mean haemoglobin (MCH) levels

Another statistically significant test was the association between gender and high MCH. Only 77 out of the 94 patients were found to have ever had an MCH test. Of the tested patients, there were 49 females and 28 male patients. More of the female patients (73%, 95%CI: 60.7 – 86.1) were found to have ever recorded an elevated MCH compared to male patients (50%, 95%CI: 30.8 – 69.1). This difference was

statistically significant ($p < 0.05$) (OR: 0.36, 95%CI: 0.13 – 0.95%). With adjustment for regimen, a male patient was still found to be 69% times ($0.31 - 1 \times 100 = 69\%$) less likely to have a higher MCH result compared to a female patient (OR: 0.31, 95% CI: 0.11 – 0.87).

4.6.3. Association between gender and other various hematological, renal and liver function adverse effects of the studied patients

No statistically significant differences were ascertained when a Pearson chi square and a Fischer's exact test were performed on the association between genders and further haematological, renal and liver function related adverse effects. These results are depicted in table 5 below.

Table 5: Statistical significance testing results between male and female patients and various haematological, renal and liver function adverse effects

Hematologic Disorder	SEX	Ever experienced an abnormality	Patient Denominator (Total number of patients)	Statistical significance
Low Red Cell Count (RCC)	Females	36 (71%)	51	None (P=0.092)
	Males	15 (52%)	29	
High Mean Cell Volume (MCV)	Females	37 (76%)	49	None (P=0.073)
	Males	15 (56%)	27	
Low Hematocrit	Females	27 (54%)	50	None (P=0.896)
	Males	15 (56%)	27	
High Creatinine	Females	15 (60%)	25	None (P=0.715)
	Males	7 (54%)	13	
High Alanine transaminase (ALT)	Females	21 (34%)	61	None (P=0.107)
	Males	17 (52%)	33	

4.7. Association between haematological, renal and liver function adverse effects and drug groups

Patient's parameters were assessed to demonstrate differences in the common haematological, renal and liver function adverse effects experienced between nevirapine and efavirenz based treatment groups. The denominators was not the same for all haematological and biochemical tests performed. There were 22 patients on efavirenz and 72 on nevirapine based regimen.

The most prominent results as presented in figure 4 were selected to test for statistical significance of association between nevirapine and efavirenz based treatment groups using Pearson chi square test. The null hypothesis of no association was assumed.

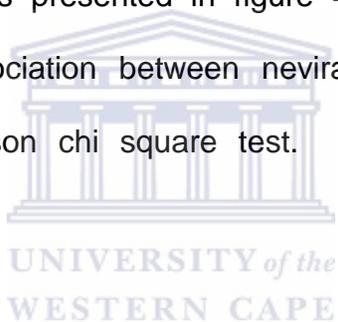
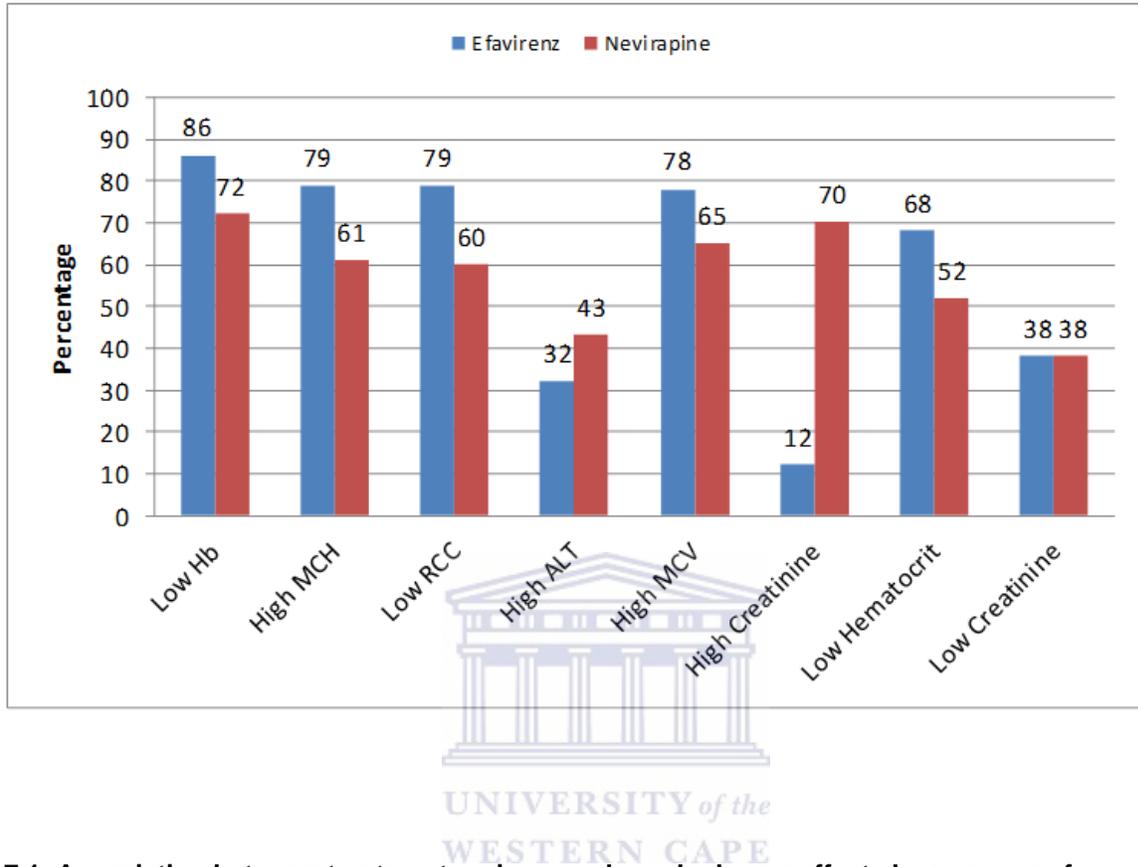


Figure 4: Association between NVP and EFV based treatment and the haematological, renal and hepatic adverse effects



4.7.1. Association between treatment regimen and renal adverse effects by measure of creatinine level

To assess the renal function related adverse effects of the studied patients, an association between high creatinine levels and regimen status was tested using the Pearson chi square exact test and the result showed that there was a statistically significant association between the regimen base patients were on and an elevated creatinine levels ($p < 0.003$). More patients on nevirapine base (70%, 95%CI: 54.1 – 87.7) experienced elevated creatinine levels compared to efavirenz base (12%, 95%CI: 12.0 – 37.8). A patient on nevirapine was more likely to experience an elevated creatinine level compared to a patient on efavirenz (OR 36.0, 95% 2.02 –

62: adjusted for gender, age and CD4 count median), this was statistically significant at $p=0.0027$. This finding rejects the null hypothesis of no association and suggests that a patient on nevirapine base was more likely to experience elevated creatinine levels than a patient on efavirenz.

4.7.2. Association between treatment regimen and other hematological and liver function adverse effects

There was no statistically significant association between regimen base and various haematological and liver function adverse effects, low haemoglobin ($p= 0.191$), high ALT ($p= 0.347$), high MCV ($p= 0.254$), high MCH ($p = 0.714$), low red cell count ($p= 0.502$) and low Hematocrit ($p= 0.162$).

4.8. Association between duration of treatment and haematological, renal and liver function adverse effects of the studied patients

This section looks at the haematological, renal and liver function adverse effects in two groups of patients. The first group of patients were started on the first line treatment and were kept on this line for a period of 36 to 48 months, herein referred to as “first treatment”. The second group are patients who had some exposure to ART treatment and were transitioned and stabilised on the first line treatment under the study for a period of 36 to 48 month, herein referred to as “transitioned”. A Pearson chi square test was performed to test for statistical significant associations between haematological, renal and liver function adverse effects of the two groups. Two points were compared, i.e. the frequency of a particular adverse effect at treatment initiation (baseline) and the overall frequency if a patient have ever

recorded a particular adverse effect at any time during the treatment period which was evaluated at 36 to 48 month of treatment. The baseline period for the patients who were transitioned was the tests performed when they were being transitioned to the standard first line treatment under study. This information is summarised in table 6 below.

Table 6: Association between treatment status and commonly experienced haematological, renal and liver function adverse effects at baseline and at 36 to 48 month evaluation

Hematologic Disorder	Treatment Status	Patients with Baseline abnormal Results	Statistical significance	Ever experienced an adverse effect	Statistical significance
Low hemoglobin	First treatment	32 (80%)	Yes (P=0.003)	43 (84%)	Yes (P=0.031)
	Transitioned	12 (44%)		28 (65%)	
High Mean Cell Hemoglobin	First treatment	6 (17%)	Yes, (P=0.000)	21 (50%)	Yes, (P=0.003)
	Transitioned	17 (68%)		29 (83%)	
Low Red Cell Count (RCC)	First treatment	13 (37%)	Yes, (P=0.040)	25 (58%)	No, (P=0.260)
	Transitioned	16 (64%)		26 (70%)	
High Mean Cell Volume (MCV)	First treatment	6 (17%)	Yes, (P=0.000)	23 (56%)	Yes, (P=0.012)
	Transitioned	17 (68%)		29 (83%)	
Low Hematocrit	First treatment	24 (69%)	Yes, (P=0.012)	27 (64%)	No, (P=0.060)
	Transitioned	9 (36%)		15 (43%)	
High creatinine	First treatment	2 (50%)	No, (P=0.361)	11 (52%)	No, (P=0.444)
	Transitioned	0 (0%)		11 (65%)	
High Alanine transaminase (ALT)	First treatment	4 (10%)	No, (P=0.164)	22 (43%)	No, (P=0.560)
	Transitioned	7 (21%)		16 (37%)	

The most common type of haematological adverse effects in the first treatment group at baseline was low haemoglobin (80%); low hematocrit (69%) and low red cell count (37%). This differed with the treatment exposed (transitioned) group in which the

most common haematological adverse effect at baseline was the high mean cell volume and high mean cell haemoglobin of 68% respectively. This is followed by low red cell count (64%), low haemoglobin (44%) and low Hematocrit (36%).

At baseline, a patient who was exposed to prior ART treatment had a 67% reduced risk of having lower haemoglobin level, compared to a patient who had no prior ART exposure (RR: 0.33, 95%CI: 0.37 - 0.81). However this risk was reduced to 23% when the two groups were evaluated at 36 – 48 month of treatment (RR: 0.77, 95CI: 0.60 – 0.97).

On the contrary, at baseline, a patient who had prior exposure to ART had a three times increased relative risk of experiencing a high mean cell haemoglobin (MCH) compared to a patient with no ART exposure (RR: 3.6, 95%CI: 1.91 – 7.14). However, at 36 – 48 month of treatment, this risk reduced to 1.65 (RR, 95%CI: 1.18 – 2.30) between the two groups.

After adjustment for gender, regimen, CD4 count and age, at baseline, a patient who had prior exposure to ART (transitioned group) had 81 times (adjusted OR: 81.4, 95%CI: 5.3 – 119, p-value=0.00) increased odds of experiencing a high mean cell volume (MCV) compared to a patient with no ART exposure (first treatment). However at 36 – 48 month of treatment, with the same adjustment, this risk has reduced to 2.89 times (95%CI: 0.87 – 9.07, p-value=0.08).

At baseline, a patient who had prior exposure to ART was found to have a three times increased odds of experiencing a low red cell count compared to a none ART exposed patient (unadjusted OR: 3.0, 95%CI: 1.03 – 8.73). However at 36 – 48 month of treatment evaluation, the findings were not statistically significant at p-value of 0.262 (unadjusted OR: 1.70, 95%CI: 0.67 – 4.31).

4.9. Association between age and various hematological, renal and liver function adverse effects of the studied patients

Correlation between age and the various haematological adverse effects was not possible as it was difficult to use parametric tests due to the skewness of the data distribution. To assess for association between age and various haematological adverse effects, the age categories were disaggregated into the ages of 18 – 24, 25 – 34, 35 – 44, and 45 – 70. The patient's categorical ages were then used to test for association between age groups and various adverse effects using the Pearson chi square test. There were no statistically significant associations between age and any hematologic, renal and liver function adverse effects. The results showing the p-values are summarised in table 7 below.

Table 7: Association between patient age and selected common haematological, renal and liver function related adverse effects using Pearson chi square test

Hematologic Adverse effects	Statistical significance
CD4 count median	No, (P=0.869)
Low Haemoglobin	No (P=0.376)
High Mean Cell Hemoglobin	No (P=0.296)
High Mean Cell Volume (MCV)	No, (P=0.518)
High creatinine	No, (P=0.576)
High Alanine transaminase (ALT)	No, (P=0.721)

4.10. Association between CD4 count and haematological, renal and liver function adverse effects of the studied patients

To answer the question of whether there were associations between CD4 counts and the various hematological, renal and liver function adverse effects of the studied patients, CD4 count medians achieved at 36 – 48 month of treatment were calculated for each patient and categorized into CD4 count of 1 – 300 and 301 and above. Various hematologic, renal and liver function related adverse effects were then also stratified into never recorded an adverse effect and ever recorded an adverse effect at 36 – 48 month evaluation. This was done for all tests results shown in table 8 in exceptions of the lower hemoglobin and high ALT variable. The lower hemoglobin and high ALT variables were stratified into patients who experienced low hemoglobin and high ALT in 1 – 49% percent of the tests done during the treatment period, and those who experienced low hemoglobin and ALT in 50% and above of the tests done during the treatment period. This was done

because lower hemoglobin and high ALT test results were recorded more frequently than other tests, and therefore warranted better classification. A Pearson chi square test was then performed to determine if there were any associations between CD4 count categories and various hematologic, renal and liver function adverse effects. Results of these tests are show in table 8 below.

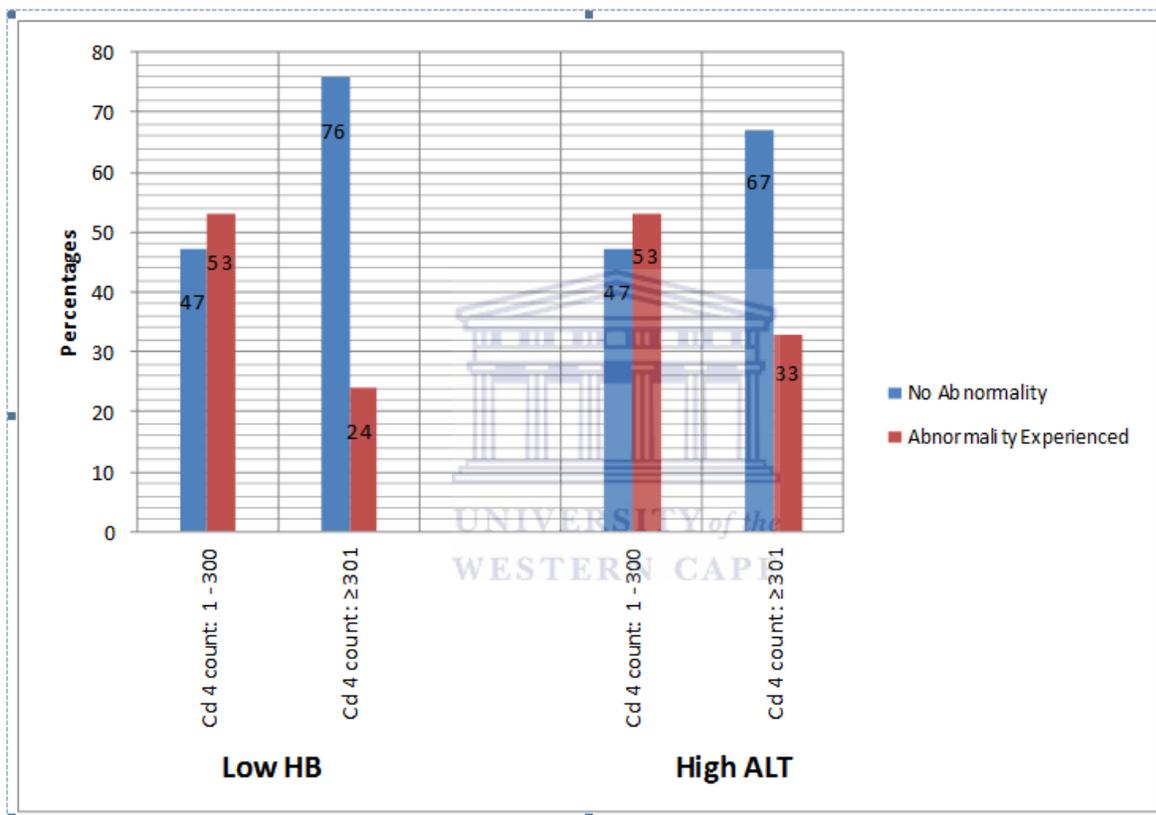
Table 8: Association between CD4 count and selected common haematological, **renal and liver function adverse effects** using Pearson chi square test

Hematologic Disorder	CD4 count	Ever experienced an abnormality	Patient Denominator (Total number of patients)	Statistical significance
Low hemoglobin	1 – 300	19 (53%)	36	Yes (P<0.05)
	≥ 301	14 (24%)	58	
High Alanine transaminase (ALT)	1 – 300	19 (53%)	36	Yes (marginal) (P=0.055)
	≥ 301	19 (33%)	58	
High Mean Cell Volume (MCV)	1 – 300	20 (69%)	29	None (P=0.936)
	≥ 301	32 (68%)	47	
Low hematocrit	1 – 300	19 (66%)	29	None (P=0.133)
	≥ 301	23 (48%)	48	
High creatinine	1 – 300	10 (71%)	14	None (P=0.197)
	≥ 301	12 (50%)	24	
Low Red Cell Count	1 – 300	17 (55%)	31	None (P=0.187)
	≥ 301	34 (69%)	49	

As can be seen from the table above, patients with higher CD4 counts were less likely to experience low hemoglobin levels compared to patients with low CD4 counts (24%, 95%CI: 12 - 35 vs. 53%, 95%CI: 36 - 69) (p<0.05), When adjusted for regimen type and treatment status the OR was 0.31 (95%CI: 0.12 – 0.77). Patients with higher CD4 counts were also less likely to experience elevated ALT enzyme levels

compared to patients with low CD4 count (33%, 95%CI: 20 - 45 vs. 53%, 95%CI: 36 - 69) ($p= 0.055$). The unadjusted OR was 0.22 (95%CI: 0.06 – 0.78). After adjustment for treatment status and regimen type, the OR was 0.20 (95%CI: 0.05 – 0.76).

Figure 5: Association between median CD4 counts and low hemoglobin level and high ALT



Chapter 5: Discussion

5.1. Prevalence of adverse effects

Out of the 94 eligible patients records assessed, only 44 patients were found to have reported an adverse effect. Much could not be deduced from these findings due to low numbers of ascertained records with reported adverse effects. This made further analysis and test for association to be inconclusive; hence no further stratification is reported. The low number of reported adverse effects could indicate the need for improved recordkeeping. It may also indicate the less attendance of patients to the ARV clinic when experiencing a complaint, i.e. patients may at the time when experiencing adverse effects use other health facilities. Lesser information is available to classify musculoskeletal disorder ascertained as a commonly reported adverse effect among patients in this study. Musculoskeletal adverse effect was a culmination of various musculoskeletal adverse effects reported; therefore there is a likelihood that this finding may related to advanced age, chance finding or other pathologies in the studied patients. The lack of association between reported adverse effects, CD4 counts and regimen could also suggest a weak association or inconsistencies in reporting or recording of adverse effects. Despite these limitations, our study agrees with the study by Van Zyl *et al.* (2008), which concluded that the common adverse effects affecting patients on ART included headaches, nausea, diarrhoea, itching etc.

5.2. Prevalence of haematological, renal and liver function adverse effects in the studied patients

The most common haematological adverse effect ascertained was a low HB, followed by higher mean cell haemoglobin (MCH), higher mean cell volume (MCV) and low red cell counts. This finding agrees with many other studies that highlighted low haemoglobin to be the most common blood disorder in HIV infected patients (Friel and Scadden 2011). Owiredu *et al.* (2011) highlighted the prevalence of lower haemoglobin in HAART naive HIV positive patients to be 70%, which is consistent with 80% ascertained in this study. Causes of anaemia in HIV infected patients are varied and may range from changes in cytokine production with subsequent effects on hematopoiesis, opportunistic infections, chemotherapeutic agents such as zidovudine and trimethoprim-sulfamethoxazole, cancers, autoimmune destruction of red blood cells etc. (Sullivan *et al.* 1998).

5.3. Association between haematological, renal and liver function adverse effects and the gender of the studied patients

Our study ascertained that anaemia was more prevalent in males than females patients, (adjusted OR: 3.29, 95% CI: 1.3 – 8.3) ($p < 0.04$). A study by Omoregie *et al.* (2009), reported a higher prevalence of anaemia in HAART naive HIV positive male patients than female patients (76% vs. 63%), however this study did not report a statistically significant differences in anaemia between the two sexes when patients were on HAART. Many factors may account for statistical difference in low haemoglobin between male and female patients on ART, as ascertained by this

study. Among others are possibilities that adherence to treatment between male and female patient is different. An extreme classification of abnormal haemoglobin levels by the reference laboratory which may not be reflective of the community averages is another hypothesis. These areas may need to be investigated further. A finding in contrast to our study, of HIV negative Ugandan by Lugada *et al*, (2004) highlighted that after age 13, males were more likely to have higher haemoglobin levels compared to females. This finding agrees with a cross sectional study by Messanh *et al*, (2011) that assessed haematological reference values in health individuals in Togo. The study ascertained that male health individuals generally had higher haemoglobin and higher MCH compared to female individuals (Messanh *et al*. 2011).

In the presence of HIV and ART, causes of anaemia are varied and could be both due to disease process and use of ARVs and other chemotherapeutic agents (Sullivan *et al*. 1998). In our study more female patients were found to have experienced higher MCH than male patients 73% (95%CI: 60.7 – 86.1) and 50% (95%CI: 30.8 – 69.1) respectively. The MCH test is said to be identical with the MCV test in providing information related to the diagnosis of anaemia (WHO 2004). An elevated MCH is always associated with macrocytic anaemia which is common in people using zidovudine and related medications among other possible causes (Claster, 2002). It is difficult to speculate the cause of the statistical difference in MCH between males and female patients with lesser available literature. One theory could be that the difference in MCH between males and female patients could point to the differences in adherence levels. A study by Mugisha *et al*. (2012) reported an

elevated MCV levels to be a possible marker for adherence and response to AZT containing therapy. According to the Southern Africa HIV and AIDS Information Dissemination Service (2008), Numbers of adverse effects common to female and peculiar to males have been reported and include, higher blood levels of ARV medicines due to more fat deposits, abnormal fat distribution (lipodystrophy) and exaggerated symptoms. Our study agrees with studies that highlighted that HIV-infected male patients had increased risks of having anaemia than female patients (Omoregie *et al.* 2009).

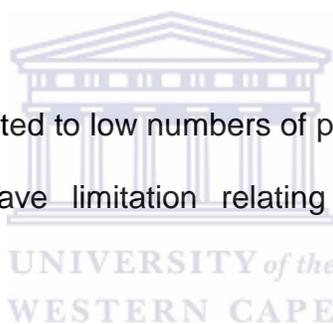
5.4. Association between haematological, renal and liver function adverse effects and drug groups

There was no association between regimen type and these haematological and liver function adverse effects; HB ($p=0.177$), ALT ($p=0.347$) and MCV ($p= 0.254$). However more patients on nevirapine base (70%) experienced elevated creatinine levels compared to efavirenz base (12%), ($p<0.003$). This finding suggests increased risk of renal adverse effects for patients on nevirapine. However there might be a need to study this risk with a stronger sample size.

This finding is closely supported by findings of a prospective study by Namu (2013) which ascertained an increase in creatinine levels associated with the use of ARVs (mean increase of 1.03mg/dl at baseline to 1.37mg/dl at 6month). ARVs in this setting were zidovudine, stavudine and nevirapine. A study on the creatinine levels of patients placed on HAART treatment in South Eastern Nigeria,

showed elevation in mean creatinine level in 28% of the patients from baseline mean range of 1.24mg/dl and 50.71mg/dl to 3.92mg/dl and 71.6mg/dl at 18 months (Alo, *et al.* 2012). Namu *et al.* (2013), also cited a study by Hirsch and Gunthad, (2005) which did not find a significant increase in creatinine levels in patients who were taking cotrimoxazole. This lessens the possibility of the elevated creatinine levels to be associated with the use of cotrimoxazole, which is a common medication found to have been used in 91% of the patients under this study. An ongoing online study by eHealthMe (2013) based on reports from patients taking nevirapine revealed a 0.77% (40 out of 5 171) prevalence of elevated creatinine.

Although there is limitations related to low numbers of patients used in our study, the eHealth (2013) study also have limitation relating to lack of control in the environment.



These finding raises interest to which the author recommends further controlled studies that will compare the nevirapine and efavirenz regimens and creatinine elevation.

5.5. Association between duration of treatment and haematological, renal and liver function adverse effects of the studied patients

An ART exposed patient was less likely to experience a low haemoglobin than an ART naïve patients, (1.65, RR: 95%CI: 1.18 – 2.30) ($p < 0.003$). This finding suggests that there is an improvement in patient's health status related to the use of

ARVs and agrees with a study by Owirendu *et al* (2011) who reported a higher prevalence of anaemia in HAART naïve patients compared to patient on HAART.

At baseline ART naïve patients were also less likely to experience elevated mean cell volume (MCV) and MCH than ART exposed patients, 17% versus 68%, ($p < 0.00$). At 36 – 48 month evaluation after being on treatment, the category of patients who were earlier exposed to ART had experienced elevated MCV more times than the patients who were ART naïve at baseline, 83% versus 56% p -value=0.012. This finding suggests a cumulative and more macrocytic picture occurring as treatment advances and may be suggestive of bone marrow depression related to the use of AZT and Cotrimoxazole. Hypothetically, anaemia experienced in the initial phases could relate to iron deficiency, anaemia of the chronic disease or vitamins and nutrients deficiency. Anaemia occurring during the later period of treatment points to a more macrocytic cause, which can relate to the use of AZT, cotrimoxazole and bone marrow suppression. This hypothesis is also highlighted and supported by Owiredu (2011). Further studies aimed at understanding the cause and implications of this scenario are recommended.

5.6. Association between CD4 count and haematological, renal and liver function related adverse effects of the studied patients

This study ascertained that there is an association between CD4 count and low haemoglobin. Patients with higher CD4 counts had reduced chances of experiencing

lower haemoglobin levels compared to patient with lower CD4 counts. This supports other findings highlighted earlier that, treatment with ART, which is always related to improved CD4 counts reduces the likelihood of having anaemia and abnormal liver enzymes. Our study agrees with findings of a study by Meidani *et al.* (2012), that ascertained that Anaemia was more prevalent in patients with lower CD4 counts (CD4 count of <100, (77%), 100 – 249, (83%) >250 (54%)).



Chapter 6: Conclusions and Recommendations

6.1. Conclusions

This document presented findings of a retrospective study done to ascertain the adverse effects experienced by patients on first line antiretroviral treatment at Keetmanshoop Hospital. Adverse effects associated with antiretroviral treatment were looked at in terms of clinical, immunologic, hematologic and biochemical changes (renal and liver function).

The most commonly reported adverse effect was musculoskeletal disorders (25%), followed by skin disorders and cough at 20% respectively. The most common haematological adverse effects were lower haemoglobin, high mean cell haemoglobin and lower red cell count. Male patients had higher prevalence of low haemoglobin compared to female patients. Patient on nevirapine based NNRTI had about five times increased risk of elevated creatinine level compared to patients on efavirenz. Elevated mean cell haemoglobin was more common in later treatment periods than initial treatment periods. Lower haemoglobin and elevated ALT were less common in patients with Higher CD4 count compared to patients with lower CD4 count.

6.2. Recommendations

Low numbers of patients with recorded adverse effects led to inconclusive results on what is the most common adverse effect raised by patients on ART, clinicians may need to inquire more and record the client's complaints. Conducting a prospective or a random controlled study with higher sample size may yield better result in this area.

Factors that may results in a statistical difference in Anaemia between male and female patients on ART can also be explored.

Creatinine was found to be higher in patients on the nevirapine based regimen compared to patients on the efavirenz base. The author recommends further studies with higher sample size to confirm whether higher creatinine levels were more in patients on nevirapine compared to efavirenz; this will have clinical implications especially in patients with impaired renal system.

Antiretroviral treatment increases chances of developing macrocytosis, clinical implication of this condition is unknown and will need to be investigated.

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8. Appendices

Appendix 1: Ministry of Health Ethical Approval

9 - 0/0001



REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198
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Ministerial Building
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Date: 19 October 2012

Enquiries: Mr .M. Simasiku Ref: 17/3/3

OFFICE OF THE PERMANENT SECRETARY

Mr. Nicholus Mutenda
P.O. Box 380
Keetmanshoop
Namibia

Dear Mr. Mutenda

Re: Adverse effects experienced by patients on first line antiretroviral drugs used at Keetmanshoop hospital, Namibia.

1. Reference is made to your application to conduct the above-mentioned study.
2. The request has been evaluated and found to have merit.
3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**
 - 3.1 The data collected must only be used for purpose stated in the proposal and the permission requesting letter;
 - 3.2 No other data should be collected other than the data stated in the proposal;
 - 3.3 A quarterly report to be submitted to the Ministry's Research Unit;
 - 3.4 Preliminary findings to be submitted upon completion of study;
 - 3.5 Final report to be submitted upon completion of the study;
 - 3.6 Separate permission to be sought from the Ministry for the Publication of the findings.

Yours sincerely,

MR. A. NDISHISHI
PERMANENT SECRETARY



"Health for All"

Appendix 2: University of the Western Cape Ethics Certificate

Ref: Nb 12/6/45



Appendix 3: Codes for adverse effects

First line Regimens;

Tenofovir (TDF), Lamivudine (3TC) and Nevirapine (NVP)

First line alternatives

Tenofovir (TDF), Lamivudine (3TC) and Efavirenz (EFV)

AZT, 3TC and NVP

AZT, 3TC and Efavirenz (EFV)

Known or expected adverse effects of first line antiretroviral medications (ARVs) (Division of Pharmacology, Faculty of Health Science, University of Cape Town. 2005).

Zidovudine (AZT) adverse effects

- A1. Anemia
- A2. Leucopenia
- A3. Neutropenia
- A4. Myalgia
- A5. Insomnia
- A6. Myopathy
- A7. Seizures
- A8. Confusion
- A9. Mania
- A10. Hepatotoxicity
- A11. Acidosis
- A12. Depression



Lamivudine (3TC) adverse effects (Infrequent)

- L1. Pancreatitis
- L2. Diarrhoea
- L3. Malaise
- L4. Upper Abdominal Pain
- L5. Alopecia
- L6. Parasthesia

Tenofovir adverse effects

- T1. Mild to moderate gastro-intestinal disturbances
- T2. Nephrotoxicity
- T3. Rarely: hypersensitivity reaction, hyperlactaemia and hepatic steatosis

Nevirapine (NVP) adverse effects

- N1. Clinical Hepatitis
- N2. Granulocytopenia
- N3. Gastrointestinal Intolerance

Adverse effects shared by AZT, 3TC and NVP

- ALN1. Peripheral Neuropathy
- ALN2. Nausea and Vomiting
- ALN3. Headaches
- AL4. Hyperlactaemia

AL5.	Hepatic Steatosis
LN6.	Rash
LN7.	Fever
LN8	Fatigue

Adverse effects of Efavirenz

- E1. Rash
- E2. Headache
- E4. Abnormal dreams
- E5. Dizziness
- E6. Insomnia
- E7. Depression
- E8. Nausea & Vomiting
- E9. Gynaecomastia
- E10. Elevated liver enzymes



Appendix 4: Namibia Institute of Pathology Haematological Reference Ranges

Full Blood Count

Test	Male Ref ranges	Females Ref Ranges
White Cell Count	4.00 – 11.00 X10 ⁹ /L	4.00 – 11.00 X10 ⁹ /L
Red Cell Count	4.20 – 6.50 X10 ¹² /L	3.80 – 5.40 X10 ¹² /L
Haemoglobin	14.00 – 18.80 g/dL	12.00 – 16.90 g/dL
Haematocrit	40.00 – 54 %	37.00 – 44.00 %
Mean Cell Volume	80 – 100 fl	80 – 100 fl
Mean Cell Haemoglobin	27.00 – 32.00 pg	27.00 – 32.00 pg
Mean Cell Haemoglobin Concentration	32.00 – 36.00 g/dL	32.00 – 36.00 g/dL
Red Cell Distribution Width	0.00 – 16.00 %	0.00 – 16.00 %
Platelets	150.00 – 400.00 X10 ⁹ /L	150.00 – 400.00 X10 ⁹ /L
MPV	6.00 – 9.00 fl	6.00 – 9.00 fl

Biochemistry

Creatinine	62.00 – 106.00 umol/L	44 – 80 umol/L
ALT	1 – 41 IU/L	1 – 41 IU/L

Appendix 5: Example of the data collection tool

Data Collection tool

Client code	Age	Rx Regimen	Sex	Adverse Effects Reported (Every 3 Months)														
				Quarters	1	2	3	4	5	6	7	8	9	10	11	12		
1 ST	28	1b	M	Cd 4 count										92	57	256		
				Viral Load														
				ALT						50				50				
				HB										15		14		
				WT											48	50		
				Co morbid	HBSA-	RPR-												
				INH														
				CTX		CTX												
				FP														
				WCC														
				RCC														
				HEMATOCRIT														
				MCV														
				MCHC														
				RDW														
				PLATLET							107							
				MPV														
				ADHERE	GOOD	GOOD	GOOD	GOOD	GOOD	GOOD	POOR	GOOD						
				Cd 4 %														
				CREATIN														
Adverse Effects Reported																		