A REVIEW OF TENOFOVIR AND LAMIVUDINE DOSING ERRORS IN PATIENTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY WITH RENAL IMPAIRMENT AT THE UNIVERSITY TEACHING HOSPITAL IN LUSAKA, ZAMBIA.

By

Webrod Mufwambi

A dissertation submitted to the University of Zambia in partial fulfilment of the requirements for the award of the degree of Master of Clinical Pharmacy

THE UNIVERSITY OF ZAMBIA

LUSAKA

2014

DECLARATION

I, **Webrod Mufwambi** hereby declare that the work on which this dissertation is based is original, except where acknowledgements indicate otherwise.

This dissertation is submitted for the award of the degree of Master of Clinical Pharmacy at the University of Zambia. Neither the whole work nor any part of it has been submitted before for any degree or examination at this or any other university.

Signed……..……..…on the…….……..day of ……...…….

CERTIFICATE OF APPROVAL

This dissertation of **Webrod Mufwambi** has been approved as fulfilling the requirements or partial fulfilment of the requirements for the award of Master's Degree in Clinical Pharmacy by the University of Zambia;

Signature for examiner one……....Date…….

Signature for examiner two……....Date…….

Signature for examiner three……..Date……..

Signature for Supervisor ……Date ……

DEDICATION

I dedicate this dissertation to my wife, Maureen Mulenga Mufwambi, my son Lushomo Webrod Mufwambi, my daughter's Bupe Annabelle Mufwambi and Grace Miyanda Mufwambi, my parents Mr. P.W. Mufwambi and Mrs. N.K. Mufwambi and to my brothers and sisters for their love, moral support and unwavering patience during my studies for the time I robbed them.

ABSTRACT

Objectives

Drug dosing errors are common in patients with renal impairment and could cause adverse effects and poor outcomes. The study reviewed tenofovir and lamivudine dosing errors as a component of the highly active antiretroviral therapy (HAART) regimen in patients with renal impairment at the University Teaching Hospital (UTH) in Lusaka, Zambia. The dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate. The aim of the study was to determine the frequency of tenofovir and lamivudine dosing errors in patients on HAART with renal impairment at UTH.

Methodology

A retrospective cross sectional study which involved review of patient files of 76 study patients with renal impairment at the Adult infectious Diseases Center (AIDC) at UTH was undertaken. Data analysis was done using Statistical Package for Social Sciences (SPSS) version 16.0 and association between dosing errors and prescribed dose were executed using Pearson Chi-square tests. Outcome measures were compliance with manufacturers' literature and Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection (2014). Documentation of drug regimen prescribed, dose and frequency were used to measure appropriateness of dose prescribed.

Results

This study did not reveal any tenofovir dosing errors. Tenofovir was dosed correctly in patients (100%, 3/3) with renal impairment. Lamivudine dosing errors were found to be 40% in patients on HAART with renal impairment. Lamivudine was under dosed in 8% of the patients and overdosed in 32% of the patients on HAART with renal impairment. A statistically significant association between the dose of lamivudine prescribed and dosing error type was observed (CI 95, $p < 0.001$).

Conclusion

Tenofovir dosing errors in patients on HAART with renal impairment are not prevalent while lamivudine dosing errors in the same patient population have a prevalence of 40% at the University Teaching Hospital.

ACKNOWLEDGEMENTS

I wish to take this opportunity to thank the following individuals and organizations for their assistance and support during the research work and the final compilation of the work.

I would like to extend my gratitude to my supervisors, Dr. L.T. Muungo and Dr. P. Yassa for assisting me in identifying the intrinsic elements of research and evaluation of literature that made up the contents of this report and their continued support and motivation throughout the whole study. I thank them for their time, guidance and willingness to assist me whenever they were needed.

I am grateful to:

- Mr. Mwangana Mubita, Mr. Chichoni A. Kalungia and all the members of the Department of Pharmacy - UNZA for the guidance during the development of the research
- Dr. Aggrey Mweemba for the great input in fine tuning my research work.
- Mr. Lameck Chirwa for the data input in determining the sample population at the Adult Infectious Diseases Center (AIDC) at the University Teaching Hospital.
- Mrs. Elizabeth Mwamba the Sister in Charge at the Adult Infectious Diseases Center (AIDC) at the University Teaching Hospital.
- Mr. Morton Muchu for assistance in file search at the registry at the Adult Infectious Diseases Center (AIDC) at the University Teaching Hospital.
- My classmates especially Mrs. Mufaweli Kapawa Mwale for the encouragements and the teamwork we enjoyed throughout our training.

I wish to extend my gratitude to the University of Zambia for their moral and financial support during the course of my studies without which my studies would have been impossible.

My gratitude goes to my parents, brothers, sisters and family for their spiritual, moral and financial support. Above all I wish to thank God Almighty for making everything possible for me to complete this work.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AIDC - Adult Infectious Disease Center

AIDS - Acquired Immune Deficiency Syndrome

ARVs - Anti Retroviral Drugs

CG - Cockcroft-Gault Equation

CKD - Chronic Kidney Disease

GFR - Estimated glomerular filtration rate

CrCl – Creatinine Clearance

HAART - Highly Active Anti-Retroviral Therapy

HIV - Human Immunodeficiency Virus

MDRD - Modification of Diet in Renal Disease

MOH - Ministry of Health

NNRTIs - Non Nucleoside Reverse Transcriptase Inhibitors

NRTIs - Nucleoside Reverse Transcriptase Inhibitors

PIs - Protease Inhibitors

UTH - The University Teaching Hospital Zambia

WHO - World Health Organisation

GLOSSARY

Chronic Kidney Disease - is the presence of kidney damage or a reduction in the glomerular filtration rate (GFR) less than 50 mL/min for three months or longer.

Creatinine Clearance - the flow rate of filtered fluid through the kidney

Drug Disposition - the absorption, distribution, metabolism, and excretion of a drug that has been administered

Highly Active Anti-Retroviral Therapy – is a combination of at least three drugs from at least two different classes: for example, any of the following combinations; two (2) Nucleoside Reverse Transcriptase Inhibitors (NRTIs) plus one (1) Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or two (2) NRTIs plus Protease Inhibitors (PI).

Medication error – is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.

Morbidity - the state of being diseased or unhealthy

Mortality - the number of people who died within a population

Pharmacotherapy - the treatment of disease through the administration of drugs

Renal Dysfunction – defined as creatinine clearance less than 50ml/minute

CHAPTER ONE

1.0. INTRODUCTION

Drug dosing errors are common in patients with renal impairment and could cause adverse effects and poor outcomes, (Munar and Singh, 2007). The study reviewed tenofovir and lamivudine dosing errors as a component of the highly active antiretroviral therapy (HAART) regimen in patients with renal impairment at the University Teaching Hospital (UTH) in Lusaka.

Highly Active Antiretroviral Therapy (HAART) consists of a combination of at least three drugs from at least two different classes: for example, a combination of two (2) Nucleoside Reverse Transcriptase Inhibitors (NRTIs) plus one (1) Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or two (2) NRTIs plus Protease Inhibitors (PI). Highly active antiretroviral therapy (HAART) has revolutionized the management of HIV/AIDS. This has been reflected in the reductions in morbidity and mortality across the globe. However, use of antiretroviral drugs has been associated with a number of toxicities, including those affecting the kidney (MoH, 2010; Kalyesubula and Perazella, 2011).

Tenofovir disoproxil fumarate is an orally bioavailable prodrug of tenofovir, an acyclic nucleotide analog of adenosine monophosphate with activity in vitro against HIV type 1 and type 2 (Behar, et al. 2010). Tenofovir is a nucleotide reverse transcriptase inhibitor (NRTI) that is eliminated by the kidneys and can build up to toxic levels in the renal tubules leading to acute tubular necrosis (Lesar, et al. 1997). About 70% of an intravenous dose and approximately 30 to 35% with chronic oral dosing of tenofovir appears in urine, mostly as parent drug, by a combination of filtration and tubular secretion. Tenofovir is poorly bound (1%) to plasma proteins (Kearney, et. al, 2004 and Lyseng-Williamson, et. al, 2005).

Tenofovir is dosed once daily and is usually well tolerated by patients. Tenofovir should be used cautiously in patients with decreased renal function. The dosing of tenofovir should be adjusted in patients with creatinine clearance below 50 mL/min. There is significant clearance with hemodialysis, so the dose of tenofovir should be given after dialysis or on a non-dialysis day (Kearney, Flaherty, and Shah, 2004).

Dose adjustment according to creatinine clearance is an important pharmacotherapy intervention with the use of tenofovir based regimens. The standard reference for the adjusted tenofovir dosing regimen in renal impairment is provided as follows in table 1.0 (McNicholl and Rodriguez, 2012);

Table 1.0 Adjustment of Dosage of tenofovir in adults and adolescents in accordance with Creatinine Clearance

CrCl (mL/min)	Recommended Dosage of tenofovir
≥50	300 mg once daily
30-49	300 mg every 48 hours
10-29	300 mg twice weekly
Haemodialysis	300 mg weekly

Lamivudine is a nucleoside reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV infection. The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. Dosing of lamivudine is adjusted in accordance with renal function.

Dose adjustment according to creatinine clearance is an important pharmacotherapy intervention with the use of lamivudine. The standard reference for the adjusted lamivudine dosing regimen in renal impairment is as in table 2.0 (McNicholl and Rodriguez, 2012);

Table 2.0 Adjustment of Dosage of lamivudine in adults and adolescents in accordance with Creatinine Clearance

CrCl (mL/min)	Recommended Dosage of lamivudine
≥50	150 mg twice daily or 300 mg once daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily

In the United States of America (USA) Munar and Singh (2007) noted that drug dosing errors were common in patients with renal impairment and could cause adverse effects and

poor outcomes. They further emphasized that dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate. They further recommended methods for maintenance dosing adjustments as dose reductions or lengthening the dosing interval, or both.

A study conducted by Taurret, et.al, (2007) which reviewed antiretroviral drug dosing errors in HIV-infected patients undergoing hemodialysis reported that 107 of the 129 patients received a total of 317 ARV drugs, 59% of which were improperly prescribed. The dosing was too low for 18% of the patients and too high for 39% of the patients. Twenty-eight patients (26%) did not receive any of their ARV drugs at the recommended dose. This shows the relevance of reviewing dosing of tenofovir and lamivudine in patients with renal impairment as dosing errors are common and have been associated with development of treatment failure, drug resistance and toxicity in patients with renal impairment.

Shavadia (2009) in a study done in Kenya found that none of the study subjects had a calculated creatinine clearance in their medical records. Fifteen of the 93 patients (16.1%) had no serum creatinine performed in the twelve months preceding the last clinic visit. Nine of the remaining 78 patients (11.5%) had evidence of renal insufficiency (CrCI <60mls/min) as estimated by the Cockcroft Gault method, with six patients (7.7%) requiring dose adjustments to one or more drugs in their antiretroviral therapy (ART) regimen (CrCI <50mls/min)

According to Mulenga et.al, (2008) renal insufficiency at time of HAART initiation was prevalent and associated with increased mortality risk among adults in this population. These results have particular relevance for settings like Zambia, where tenofovir - a drug with known nephrotoxicity is part of first-line therapy.

The study reviewed tenofovir and lamivudine dosing errors as a component of the drug regimen in patients on HAART with renal impairment at the University Teaching Hospital in Lusaka, Zambia. The study will gather information on dosing of tenofovir and lamivudine in clients on HAART with renal impairment and will guide effective implementation of treatment guidelines for HAART in Zambia and improve pharmaceutical care services provided by pharmacy personnel at the University Teaching Hospital.

1.1. RATIONALE OF STUDY

The prevalence of renal dysfunction among HIV sero-positive participants was 42% at the University Teaching Hospital in Lusaka (Banda, 2010). The prevalence of dosing errors have not been documented here at University Teaching Hospital and in Zambia despite quantification of the burden of renal impairment in patients before initiation of antiretroviral therapy. The prevalence of renal dysfunction is common in patients who are HIV infected and those taking antiretroviral drugs. This study gathered information on how tenofovir and lamivudine were dosed in patients with renal impairment at the University Teaching Hospital.

The first line antiretroviral drugs include tenofovir a nucleotide reverse transcriptase inhibitor which has been associated with development of renal dysfunction. Therefore the majority (55 %; 2039 out of 3658 in 2012) of patients were on the tenofovir based regimen, hence highlighting the importance of this study.

Patients on a tenofovir based regimen who have confirmed renal impairment are switched to an abacavir based regimen which needs dose adjustments for the lamivudine component based on the calculated creatinine clearance for the patient (MoH, 2010). However it has been observed that patients are switched to abacavir based regimen without dose adjustments for the lamivudine component of their HAART regimen (AIDC Self Report).

The study reviewed the dosing of tenofovir and lamivudine in patients with renal dysfunction and provided data on whether these drugs were under dosed, overdosed or dosed appropriately. The study findings were envisaged to facilitate the introduction of measures to reduce dosing errors or to uphold good clinical practices hence reducing morbidity and mortality. The study results would provide information for other researchers in the field and contribute to the knowledge base in managing renal patients.
The study was only undertaken at UTH which is the national referral facility involved in managing patients developing renal failure and has a hemodialysis unit for patients that may require renal replacement therapy.

1.2. RESEARCH QUESTION

What is the prevalence of dosing errors related to use of tenofovir and lamivudine in patients on HAART with renal impairment at UTH?

1.3. STUDY JUSTIFICATION

Studies conducted in US hospitals suggest that antiretroviral therapy medication errors are on the rise. Yehia, et al., (2012) identified the most common errors associated with antiretroviral therapy as incomplete regimen and incorrect dosage or schedule with a prevalence of 29 %. Tourret, *et.al.,* (2007) noted that 59% of patients' antiretroviral drugs were improperly prescribed. The dosing was too low for 18% of the patients and too high for 39% of the patients. Twenty-eight patients (26%) did not receive any of their ARV drugs at the recommended dose. Lamivudine was the most frequently prescribed ARV drug (administered to 74% of the treated patients). It was overprescribed in 62% of the cases.

The dosing errors related to the use of tenofovir and lamivudine in Zambia have not been quantified and no literature was published at the time this study was conducted. Pharmacists at AIDC pharmacy have observed considerable medication errors related to the dosage of both tenofovir and lamivudine in patients on HAART with renal impairment. Anecdotal data involving review of AIDC pharmacy records on dosing errors related to tenofovir and lamivudine use in patients on HAART with renal impairment showed a percentage dosing error of about 30 percent.

Banda, *et al.,* (2010) reported that the prevalence of renal dysfunction among HIV sero-positive participants in their study undertaken at the University Teaching Hospital was 42%. Antiretroviral therapy (ART) medication errors may lead to drug resistance, treatment failure, and death.

1.4. AIM

The overall aim of the study was to review appropriateness of tenofovir and lamivudine dosing in study patients on HAART with renal impairment at the University Teaching Hospital in Lusaka Zambia

1.5. SPECIFIC OBJECTIVES

1. To determine the prevalence of tenofovir dosing errors in patients on HAART with renal impairment at UTH.
2. To determine the prevalence of lamivudine dosing errors in patients on HAART with renal impairment at UTH.

CHAPTER TWO

2.0. LITERATURE REVIEW

The study within this review of literature focused on objectives 1 and 2 as set out in sub-section 1.5 of the chapter on aims and objectives. The objects were met through collection and analysis of data from the patient medical records.

1. To determine the prevalence of tenofovir dosing errors in patients on HAART with renal impairment at UTH.
2. To determine the prevalence of lamivudine dosing errors in patients on HAART with renal impairment at UTH.

Chronic kidney disease affects renal drug elimination and other pharmacokinetic processes involved in drug disposition such as, absorption, drug distribution, and nonrenal clearance (metabolism). Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes. Dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate. Recommended methods for maintenance dosing adjustments are dose reductions, lengthening the dosing interval, or both. (Munar and Singh, 2007)

Kidney disease is more common among patients with HIV. In the USA an estimated 10% of HIV-infected outpatients experience acute kidney injury at least once over a 2-year period, and approximately 10% have chronic kidney disease, with a glomerular filtration rate (GFR) < 60 mL/min. Several nucleoside and nucleotide analogue reverse transcriptase inhibitors are excreted primarily through the kidney and must be dose adjusted for patients with chronic kidney disease, and for those who are on hemodialysis (McNicholl and Rodriguez. 2012).

The definition and classification for chronic kidney disease was proposed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) in 2002 and endorsed by the Kidney Disease: Improving Global Outcomes (KDIGO) in 2004. Chronic kidney disease can be classified according to the US K/DOQI group. The classification is based on estimated GFR, and recognizes five stages of kidney disease, as follows:

Table 3.0 Staging of Kidney Disease

Stage	*Description*	*GFR (mL/ minute per 1.73 m2)*
1.	Kidney damage with normal or increased GFR	≥ 90
2.	Kidney damage with a mild decrease in GFR	60 to 89
3.	Moderate decrease in GFR	30 to 59
4.	Severe decrease in GFR	15 to 29
5.	Kidney failure	< 15 (or dialysis)

Evaluation of renal function using both qualitative and quantitative methods is an important part of the evaluation of patients. Estimation of creatinine clearance has been considered the clinical standard for assessment of renal function (Dipiri, et al. 2008). Quantitative indices, such as the assessment or estimation of glomerular filtration rate (GFR), are now considered the most useful diagnostic tool for the identification of the presence of chronic kidney disease (Levey, et al. 2005 and Stevens, et al. 2006).

The measurement or estimation of creatinine clearance remains the most commonly used index for individualizing medication dosage regimens for patients with acute or chronic kidney disease. GFR can be calculated in the clinical setting using one of the following three equations:

- *Chronic Kidney Disease Epidemiology Consortium (CKD-EPI):* Estimates GFR based on age, race, and serum creatinine. A CKD-EPI calculator can be found at http://mdrd.com
- *Modification of Diet in Renal Disease (MDRD)*: Estimates GFR based on age, race, sex, and serum creatinine. An MDRD calculator can be accessed at http://mdrd.com
- *Cockcroft-Gault*: Calculates creatinine clearance based on serum creatinine, age, weight, and sex. A Cockcroft-Gault calculator can be accessed at http://nephron.com/cgi-bin/CGSI.cgi

Any of these equations may be used to follow trends in creatinine as part of determining GFR. If creatinine is rising (normal range), GFR will be falling by any of these equations; if creatinine is stable, then GFR is stable by any of these equations. The MDRD or CKD-

EPI equations are used by clinical laboratories when reporting estimated GFR from serum creatinine, while the drug manufacturers' recommended dose adjustments for kidney function are based on the Cockcroft-Gault equation, not the MDRD (Justman, 2012).

According to the 2010 Adult and Adolescent ART protocol for Zambia the kidney function should be assessed at baseline(two weeks before HAAART initiation), 12 weeks after HAART initiation, 6 months post initiation and on a yearly basis. The protocol further advices for collection of patients' age, sex, height and weight for all serum creatinine laboratory requests to allow for adequate assessment for creatinine clearance. The 2010 Adult and Adolescent ART protocol for Zambia recommend the use of the Cockcroft–Gault equation for estimating creatinine clearance in patients. The equation requires knowledge of the patient's gender, weight, age and serum creatinine. The equation is:

Creatinine clearance (mL/min) = $\frac{F \times (140 - age) \times weight\ (kg)}{Serum\ creatinine\ (micromol/L)}$

Where; F = 1.04 for females and 1.23 for males. (Dhillon and Raymond, 2009)

Inappropriate dosing in patients with renal dysfunction can cause toxicity or ineffective therapy. Therefore, the normal dosage regimen of a drug may have to be adjusted in a patient with renal dysfunction. Dosage adjustment is based on the remaining kidney function, most often estimated on the basis of the patient's glomerular filtration rate (GFR) estimated by the Cockcroft–Gault equation (Verbeeck and Musuamba, 2009).

Hu, *et. al.,* (2001) conducted a study in the USA which involved retrospective chart review of 1044 patients older than 80 years admitted to the University of California Davis Medical Center between January and December 1997 with a diagnosis of infection. Administered dosages of each study drug were compared with the appropriate adjusted doses. They examined the variables of age, weight, serum creatinine, and sex to determine whether any were individually predictive of dosing errors.

Hu, *et. al.,* (2001) concluded that widespread errors in medication dosing were made in elderly hospitalized patients. The Cockcroft-Gault equation revealed significant renal insufficiency requiring dose adjustments in most elderly patients studied, especially those

older than 85 years of age and with low body weight. They proposed that estimation of glomerular filtration rate should be performed routinely on all admitted patients older than 80 and in any patient with low lean body mass. Dosing errors were identified in all of the antibiotics studied, and the overall dosing error rate was 34%. The factors that were predictive of dosage errors were advanced age and low body weight. Serum creatinine and sex were not statistically significant factors.

A prospective observational, study conducted over a one year period in a in a 750-bed tertiary-care teaching hospital in 2011 in the United Kingdom by pharmacists trained in HIV pharmacotherapy reviewed prescriptions for 247 admissions (189 patients). Interactions with antiretrovirals were checked for contraindicated combinations. Inpatient antiretroviral prescriptions were compared with outpatient dispensing records for reconciliation. Renal and hepatic function was monitored to determine the need for dose adjustments. Sixty antiretroviral-related problems were identified in 41 patients (21.7%). The most common problem was contraindicated combinations (*n*=20; 33.3%), followed by incorrect dose (*n*=10; 16.7%), dose omission (*n*=9; 15%), lack of dosage reduction in patients with renal or hepatic impairment (*n*=6; 10% and *n*=1; 1.7%, respectively), omission of an antiretroviral (*n*=6; 10%), addition of an alternative antiretroviral (*n*=5; 8.3%) and incorrect schedule according to outpatient treatment (*n*=3; 5%). Fifteen out of 20 errors were made during admission. A multivariate analysis showed that factors associated with an increased risk of antiretroviral-related problems included renal impairment [odds ratio (OR) 3.95; 95% confidence interval (CI) 1.39–11.23], treatment with Atazanavir (OR 3.53; 95% CI 1.61–7.76) and admission to a unit other than an infectious diseases unit (OR 2.50; 95% CI 1.28–4.88). Use of a nonnucleoside reverse transcriptase inhibitor was a protective factor (OR 0.33; 95% CI 0.13–0.81). Ninety-two per cent of the pharmacist's interventions were accepted. (Carcelero *et al.*, 2011).
The study concluded that Antiretroviral-related errors affected more than one-in-five patients. The most common causes of error were contraindicated or not recommended drug–drug combinations and dose-related errors. The study concluded that a clinical pharmacist trained in HIV pharmacotherapy could help to detect errors and reduce the duration of their effect. (Carcelero et al. 2011)

Purdy, Raymond and Lesar (2000) undertook a study that looked at antiretroviral prescribing errors in hospitalized patients. They detected a total of 108 clinically

significant prescribing errors involving antiretrovirals during the 34-month study period. The most common errors were overdosing and underdosing. Overall, errors occurred in 5.8% of admitted patients prescribed antiretroviral medications. The rate of error increased from 2% of admissions in 1996 to 12% of admissions in 1998. The most common likely related factors associated with errors were confusion/lack of familiarity regarding appropriate dosing frequency (30.3%) or dosage (25.5%), and confusion due to need for multiple dosage units per dose (13%).

In the USA, Rastgar, et.al. (2006) reviewed a total of 209 admissions during a 1-year period in which HIV-infected patients received antiretroviral therapy. After review of the medical records for 77 admissions with a potential error, 61 (25.8%) uncorrected errors from 54 admissions were identified.
The most common type of error was an error with respect to the amount or frequency of dosage, which occurred in 34 (16.3%) of the admissions; 18 of these errors were attributed to failure of prescribers to appropriately adjust dosage for renal insufficiency.

In France Taurret, et.al (2007) conducted a study which reviewed antiretroviral drug dosing in HIV-infected patients undergoing hemodialysis. The study found that 107 of the 129 patients received a total of 317 ARV drugs, 59% of which were improperly prescribed. The dosing was too low for 18% of the patients and too high in 39% of the patients. Twenty-eight patients (26%) did not receive any of their ARV drugs at the recommended dose. The study showed that the highest prescribed dose was 10-times higher than recommended. Lamivudine was the most frequently prescribed ARV drug (administered to 74% of the treated patients). It was overprescribed in 62% of the cases. This shows the relevance of reviewing dosing of tenofovir and lamivudine in patients with renal impairment in settings like ours at the University Teaching Hospital.

Shavadia (2009) in a study done in Kenya found that none of the study subjects had a calculated creatinine clearance in their medical records. Fifteen of the 93 patients (16.1%) had no serum creatinine performed in the twelve months preceding the last clinic visit. Nine of the remaining 78 patients (11.5%) had evidence of renal insufficiency (CrCI <60mls/min) as estimated by the Cockcroft Gault method, with six patients (7.7%) requiring dose adjustments to one or more drugs in their antiretroviral therapy (ART) regimen (CrCI <50mls/min). This highlights the need for regular monitoring of renal

function in patients receiving antiretroviral drugs and dose adjustments in the individual component of the regimen.

In a study by Mulenga et.al, (2008) which was done in Lusaka, Zambia among adults initiating ART creatinine clearance was calculated by the Cockcroft-Gault method, 8,456 (33.5%) had renal insufficiency: 73.5% were mild (60-89 mL/min), 23.4% moderate (30-59 mL/min), and 3.1% severe (<30 mL/min). Risk for mortality at or before 90 days was elevated for those with mildly, moderately and severely reduced creatinine clearance. Mild, moderate and severe renal insufficiency was also associated with increased mortality after 90 days, when compared to those with normal renal function.

Mulenga et.al, (2008) concluded that renal insufficiency at time of ART initiation was prevalent and associated with increased mortality risk among adults. These results have particular relevance for settings like Zambia, where tenofovir - a drug with known nephrotoxicity - has been adopted as part of first-line therapy. This emphasizes the need for resource-appropriate screening algorithms for renal disease, both as part of ART eligibility and pre-treatment assessment.
However, Mulenga *et al*. (2008) did not review the dosing of tenofovir or lamivudine in the study subjects.

CHAPTER THREE

3.0. METHODOLOGY

This chapter provides details of the study design adopted to address objectives 1 and 2 which required collection of empirical data from study patient files. The chapter also contains details for the study setting, study population, inclusion/exclusion criteria, sample size, variables, data collection tools, data analysis and ethical considerations. Renal dysfunction for the purpose of the study has been defined as creatinine clearance less than 50ml/minute and requiring dosage adjustments for antiretroviral therapy.

3.1. STUDY DESIGN

A retrospective cross sectional study using patient file review was conducted over a period of four months. The study design was selected as it was the cheapest and easiest method to provide useful information over a short period of time on the prevalence of tenofovir and lamivudine dosing errors in patients with renal impairment on HAART. A retrospective cross sectional study was the appropriate research strategy to determine the prevalence of dosing errors and association with prescribed doses.

3.2. STUDY SITE

This retrospective cross sectional study was conducted in ART Clinic at the Adult Infectious Diseases Centre (AIDC) located at University Teaching Hospital, a national referral and tertiary-care hospital with approximately 80,400 admissions per year.

3.3. STUDY POPULATION

The study population included all patients on tenofovir and lamivudine as a component of their HAART regimen meeting the inclusion criteria of the study, at Adult Infectious Diseases Center (AIDC) at the University Teaching Hospital

3.4. INCLUSION CRITERIA

Study patients who met the following criteria were included in the study

- Adult patients aged 18 years and above
- Patients with renal impairment (CrCl less than or equal to 50 mL per minute) who were on HAART at Adult Infectious Diseases Center (AIDC) at UTH
- Patient files with at least one documented laboratory test for kidney function

3.5. EXCLUSION CRITERIA

Study patients who met the following criteria were excluded from the study

- Patients under the age of 18 years
- Patients without documented laboratory test for kidney function
- Patients who are in transit and without files (not on the data base for electronic medical records).

3.6. SAMPLE SIZE DETERMINATION

The study was designed to tolerate an absolute standard error of up to 5 percent, with the power of the study at 95 percent. The following formula was used to calculate the sample size as; $n = \underline{Z^2 P(100-P)}/ d^2$

Where;

Z = 1.96, factor from normal distribution,

P = Expected prevalence of 30%,

d = Absolute sampling error and

n = Sample size

Therefore,

$n = \underline{(1.96)^2 x\ 30(100-30)} = \mathbf{323}$

5^2

The electronic medical records at Adult Infectious Diseases Center (AIDC) were reviewed to ascertain the number of patients who had documented renal dysfunction for the period between January 2011 to December 2012 and a total of 132 patients were found in the

electronic records (AIDC records, 2013). A total of 76 files (57.6%) were reviewed in the study out of 132 files identified through the electronic records.

3.7. VARIABLES

Table 4.0 OPERATIONAL VARIABLES

OBJECTIVE	Variable(S)	STUDY INDICATOR
To determine the dosing errors of tenofovir in patients on HAART with renal impairment.	• Dose of tenofovir	• Percentage of patients receiving correct doses of tenofovir • Percentage of patients receiving incorrect doses of tenofovir
To determine the dosing errors of lamivudine in patients on HAART with renal impairment	• Dose of lamivudine	• Percentage of patients receiving correct doses of lamivudine • Percentage of patients receiving incorrect doses of lamivudine

3.8. DATA COLLECTION TOOLS

Structured data collection forms (Appendices Table 6) were employed to collect patient specific data from study patient files stored at the AIDC registry with the aid of study assistants. The files sampled were collected using a purposive sampling. The electronic records were reviewed to indicate participants who had documented renal impairment and these were transferred to excel datasheet and this was used to collect the files for study patients at the registry. All the files (76) which were found at the registry from the 132 identified were included in the study.

3.9. DATA ANALYSIS

Data were analysed using Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA).

Dosing errors were categorised as either underdose or overdose based on the estimated creatinine clearance for the patients. Categorical variables for categorical data such as age, weight, marital status, glomerular filtration rate, drug regimens and tenofovir and lamivudine doses were expressed as , frequencies and percentages, and presented graphically using histograms, pie charts and bar charts.

Nominal variables were presented by measures of central tendency and standard deviation. Data were expressed as mean+ or – standard deviation for continuous variables.

Inferential analysis was used to analyze the association of dosing errors and prescribed dose. The association between dosing errors and prescribed dose were executed using Pearson Chi-square tests and all statistical tests were two-tailed. A p value < 0.05 was considered statistically significant in the study.

3.10. ETHICAL CONSIDERATIONS

Permission to conduct the study at the University Teaching Hospital (UTH) was obtained from UTH Management. Formal ethical approval was obtained from The University of Zambia Biomedical Research Ethics Committee (UNZABREC) before data collection commenced.

The study involved review of patient's medical records (files) and Electronic Medical Records (EMR). The medical records which were used for data collection purposes were not taken away from the hospital premises. Patients confidentiality was maintained as the files used during data collection were allocated codes designed by the researcher. The patients' records and any other relevant documents were handled as regulated by the hospital authorities.

Double entry was used during data collection to ensure validity and precision of the information which was collected. This involved verification of data that had been collected and entered for analysis for correctness and accuracy as obtained from the data sources.

Results of this study would be released to the designated authorities and published in journals as prescribed by UNZA for the award of a Master's degree in Clinical Pharmacy.

The data collected did not include any material which infringed on the confidentiality and dignity of the participants as codes were used.

CHAPTER FOUR

4.0. RESULTS

This chapter gives the results for the following objectives of the study

1. Tenofovir dosing errors in patients on HAART with renal impairment
2. Lamivudine dosing errors in patients on HAART with renal impairment
3. Association between dosing errors and the prescribed doses

In this study 76 participants were included and met the inclusion criteria. The number of male study patients was higher than that of female study patients. Of the total participants in the study 40 (52.6%) were male and 36 (47.4%) were female.

4.1. Tenofovir Dose Error Type

In this study tenofovir dosing errors were not found. It was dosed correctly (100%) in study patients with renal impairment.

4.2. Lamivudine Dose Error Type

In this study lamivudine dosing errors were found to be 40% (30/75) in patients on HAART with renal impairment. Lamivudine dose was under dosed in 8% (6/75) of the patients and overdosed in 32% (24/75) of the patients on HAART with renal impairment (Figure 2).

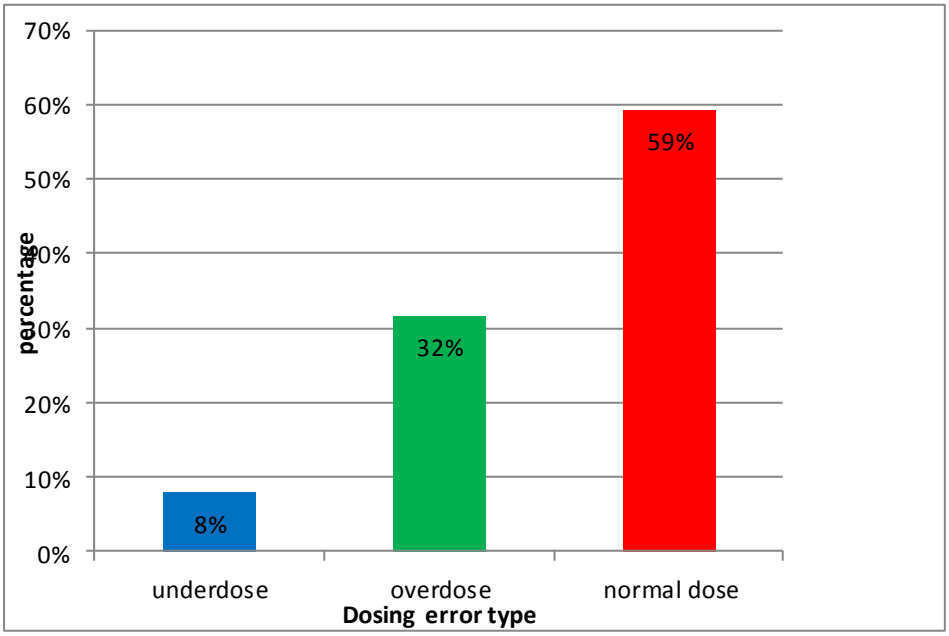

Figure 1 Lamivudine Dosing errors for patients with renal impairment

The figure shows that lamivudine was overdosed (32.0%) in patients on HAART with renal impairment.

4.2.1 Dose of lamivudine Prescribed by Prescriber

Table 5 Lamivudine dose prescribed for patients with renal impairment

Dose of Lamivudine Prescribed	Frequency	Percent
150mg once daily	35	46.1
150mg, then 100mg once daily	8	10.5
150 mg, then 50mg once daily	12	15.8
50 mg, then 25mg once daily	3	3.9
150mg twice daily	17	22.4

In this study the dose of Lamivudine in patients with renal impairment was adjusted. It was most prescribed at dose of 150mg once daily (46.1%, 25/75) and the least dose was prescribed at a dose of 50mg stat, then 25mg once daily (3.9%, 3/75), (Table 2).

4.2.2. Association dose of lamivudine prescribed and dosing error type.

In this study a statistical significance was observed (CI 95, $p < 0.001$) between the dose of lamivudine prescribed and dosing error type by Pearson Chi square test.

CHAPTER FIVE

5.0. DISCUSSION

The discussion section focusses on the results of the two objectives in section 1.5 which looked at tenofovir and lamivudine dosing errors in study patients on HAART with renal impairment. The dosing errors for tenofovir and lamivudine were reviewed in 76 patients on Highly Active Antiretroviral Therapy with renal impairment at the Adult Center for Infectious Diseases at the University Teaching Hospital in Lusaka.

5.1. Tenofovir dose error type

Our results indicate that tenofovir dosing errors were not detected. There was no error (Figure 1) in study patients with renal impairment. Only 3.9% (3/76) study patients received tenofovir as part of their HAART regimen. The findings of the study reflect the recommendations of the Zambian HIV consolidated guidelines (2014) to avoid tenofovir when creatinine clearance was less than 50 millilitres per minute (MoH, 2014). The dose of tenofovir should only be adjusted when renal impairment is independent of the drug. The study patients who received tenofovir had the doses adjusted according to their creatinine clearance. The findings could also be associated with the practice to substitute tenofovir with other nucleoside reverse transcriptase inhibitors such as abacavir which do not need adjustment of dose in the presence of renal impairment. The other reason could be the non-availability of tenofovir single formulation, which made it difficult to dose the drug.

5.2. Lamivudine dose error type

This study shows that lamivudine dosing errors were prevalent (40.0%, 30/76) for those patients who received lamivudine as part of their HAART regimen of which 8.0% (6/76) were under dosed and 32.0% (24/76) were over dosed (figure 2). The findings of the current study are similar to those in a study by Tourret, et.al. (2007) found that lamivudine was under dosed in 6.0%, overdosed in 62.0% of the cases and dosed correctly in 32.0% of the patients who received lamivudine as part of their HAART regimen.

The findings of the current study are supported by the findings of the study by Gray *et. al.*, (2005) which involved a review of electronic medical records which identified wrong dose (37.5%) as the most frequent type of error. Lamivudine was the most commonly identified antiretroviral drug to be involved in the errors

The dosing errors for lamivudine could be associated with the commonest HAART drug regimen (73.7%) of abacavir, lamivudine and efavirenz. The dosing of abacavir and efavirenz do not need to be adjusted in patients with renal impairment, hence the likelihood of the three drugs being prescribed as standard adult doses.

The findings of the current study are similar to what Tourret, *et. al*, (2007) found in France. Tourret, *et. al*, (2007) found that 74% of the patients were prescribed lamivudine, and 62% of the treated patients received an over prescription. Among these over treated patients, 44% received 300 mg of lamivudine per day, which is the regular dose for patients who do not have CKD, instead of the recommended dosage of 25–50 mg/day for patients undergoing hemodialysis.

The use of preprinted prescriptions in the management of patients on HAART could have contributed to the dosing errors which were observed as the prescribers are only required to tick the appropriate regimen with its associated standard (unadjusted) dosage. However, when dosage adjustment is necessary the prescriber is required to cancel the preprinted dose and write the adjusted dose in ink or in some cases request pharmacists to adjust the dose and document the dosage recommendations in the patient's clinical record.

5.2.1 Dose of Lamivudine Prescribed by Prescriber

This study shows that the most prescribed dose for lamivudine in study patients with renal impairment was 150mg once daily (46.1%, 25/75) and the least dose was prescribed at a dose of 50mg at once, then 25mg once daily (3.9%, 3/75). The dose prescribed by the prescribers was influenced by the availability of suitable dosage forms for patients with renal impairment. At certain periods dosage formulations allowing for administration of doses less than or equal to 100mg were not available. This could have affected the manner in which lamivudine was prescribed.

5.2.2 Association of dose of lamivudine prescribed and dosing error type

The study shows that there is an association between the dose of lamivudine prescribed and dosing error type. The Pearson Chi-Square was performed to determine the association between the dose of lamivudine prescribed and dosing error type. This study shows a statistical significance (CI 95, $p < 0.001$) between the dose of lamivudine

prescribed and dosing error type by Pearson Chi square test. This shows the influence of the dose of lamivudine prescribed influencing the dosing errors

5.3. LIMITATIONS

The following limitations to the study were identified

- The findings of our research cannot be generalized because of the setting of the research which only looked at adult patients at the University Teaching Hospital. The errors may be higher if pediatric patients were included in the research where most of the antiretroviral drugs are dosed according to body weight. Also the sample size was not large enough to allow for generalization. The study did not include all the antiretroviral drugs such as the protease inhibitors
- The exclusion of inpatients and paediatric patients which could have an influence on the outcome.
- There was no contact with patients to include actual administration errors (if any) by the patients or caregivers for the medicines prescribed.
- The study only included patients who had files and are followed up (reviewed) at the AIDC at the University Teaching Hospital.

CHAPTER SIX

6.0. CONCLUSION

The results indicate that tenofovir dosing errors were not detected. This study shows that lamivudine dosing errors were prevalent (40.0%, 30/75) for those patients who received lamivudine as part of their HAART regimen of which 8.0% (6/75) were under dosed and 32.0% (24/75) were over dosed.

Tenofovir dosing errors were not found because it was not prescribed widely in patients with renal impairment and it was not available as a single drug formulation at Adult Infectious Diseases Center at University Teaching Hospital. Lamivudine dosing errors could be associated with the commonest HAART regimen of abacavir, lamivudine and efavirenz (73.7%) for study patients with renal impairment. The dosing of abacavir and efavirenz do not need to be adjusted in patients with renal impairment, hence the likelihood of the three drugs being prescribed as standard adult doses.

6.1. RECOMMENDATIONS

In view of the findings of this retrospective cross sectional study, the following recommendations were made;

1. Pharmacists and prescribers should collaborate to avoid dosing errors and all patients accessing HAART with elevated serum creatinine should have their creatinine clearance /estimated glomerular filtration rate calculated to reduce dosing errors.
2. The research can be extended to other hospital in the province and country to obtain more robust findings which can be generalized
3. The study should be extended to in patients where dosing errors are more likely to be higher.

REFERENCES

Banda, J., Mweemba, A., Siziya, S., Mweene, M., Andrews, B., and Lakhi, S., (2010) Prevalence and Factors associated with Renal Dysfunction in HIV Positive and Negative Adults at The University Teaching Hospital in Lusaka, Medical Journal of Zambia. Vol 37; 3

Behar, D. M., Rosset, S., Tzur, S., Selig, S., Yudkovsky, G., Bercovici, S., Kopp, J. B, Winkler, C. A., Nelson, G. W., Wasser, W. G., and Skorecki, K. African ancestry allelic variation at the MYH9 gene contributes to increased susceptibility to non-diabetic end-stage kidney disease in Hispanic Americans. *Hum Mol Genet.* 2010; 19:1816-1827.

Berns, J. S. and Kasbekar, N, (2006) Highly Active Antiretroviral Therapy and the Kidney: An Update on Antiretroviral Medications for Nephrologists, *Clin J Am Soc Nephrol* 1: 117–129, 2006. doi: 10.2215/CJN.00370705

Brunton, L. L., Lazo, J. S., and Parker, K. (2006) Goodman and Gilman's The Pharmacological Basis of Therapeutics, Eleventh Edition. McGraw-Hill publishers

Carcelero, E., Tuset, M., Martin, M., De Lazzari, E., Codina, C., Miró, J. and Gatell, J.M. (2011) 'Evaluation of antiretroviral-related errors and interventions by the clinical pharmacist in hospitalized HIV-infected patients' *British Journal of HIV Medicine*, 2011; 12(8), pages 494–499

Coca, S. and Perazella, M. A. Rapid Communication: acute renal failure associated with tenofovir: evidence of drug-induced nephrotoxicity. *Am J Med Sci* 2002; 324: 342–4.
Creput, C., Gonzalez-Canali, G., Hill, G., Piketty, C., Kazatchkine, M. and Nochy, D. Renal lesions in HIV-1-positive patient treated with tenofovir. AIDS 2003; 17: 935–7.

Dhillon, S. and Raymond, R. 2009. *Pharmacy Case Studies,* Great Britain, Pharmaceutical press.

Dipiro, J. T., Talbert, R. L., Yee, G. C., Matzke, G. R., Wells, B. G., and L. Michael Posey, L. M., (2008), Pharmacotherapy a pathophysiologic approach, The McGraw-Hill Companies Inc., The United States of America .

Gaspar, G., Monereo, A., Garcia-Reyne, A. and de Guzmán, M. Fanconi syndrome and acute renal failure in a patient treated with tenofovir: a call for caution. AIDS 2004; 18: 351–2.

Gray, J., Hicks, R.W. and Hutchings, C. Antiretroviral medication errors in a national medication error database, *AIDS Patient Care STDS*. 2005 Dec; 19(12):803-12.

Gupta, S. K., Eustace, J. A., Winston, J. A., Ivy, I., Boydstun, I. I., Ahuja, T. S., Rodriguez, R. A., Tashima, K. T., Roland, M., Franceschini, N., Palella, F. J., Lennox, J. L., Klotman, P. E., Nachman, S. A., Hall, S. D., and Szczech, L. A. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2005; 40:1559-1585.

Hu, K. T., Matayoshi, A. and Stevenson, F. Calculation of the Estimated Creatinine Clearance in Avoiding Drug Dosing Errors in the Older Patient, *American Journal of the Medical Sciences* (2001) 322 (3): 133-136

Justman J. E, (2012) Kidney Disease in HIV-Infected Patients: Guideline and Commentary. HIV Clinical Guidelines: NYS Department of Health AIDS Institute. Accessed on 07 October 2014 at http//.www.medscape.com/hiv

K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Disease 2002; 39(2 Suppl 2):S1-246.

Kalyesubula, R. and Perazella, M. A.2011 Nephrotoxicity of HAART, Academic Editor: Martine Peeters Copyright © 2011

Karras, A., Lafaurie, M., Furco, A., Bourgarit, A., Droz, D., Sereni, D., Legendre, C., Martinez, F. and Molina, J. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis 2003; 36: 1070–3.

Kearney, B. P., Flaherty, J. F. and Shah, J. Tenofovir disoproxil fumarate: Clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet* 43: 595–612, 2004

Kearney, B.P., Flaherty, J. F. and Shah, J., Tenofovir disoproxil fumarate clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet.* 2004; 43(9):595-612.

Lesar, T. S., Briceland, L. and Stein, D. S., *JAMA.* 1997;277(4):312-317. doi:10.1001/jama.1997.03540280050033.

Levey, A. S., de Jong, P. E., Coresh, J., Nahas, M. E., Brad C Astor, B. C., Matsushita, K., Gansevoort, R. T., Kasiske, B. L. and Eckardtet, K. U., Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; 67(6):2089–2100.

Lyseng-Williamson, K. A., Reynolds, N. A. and Plosker, G. L. Tenofovir disoproxil fumarate: A review of its use in the management of HIV infection. *Drugs* 65: 413–432, 2005

McNicholl, I.R. and Rodriguez, R. A. Dosing of Antiretroviral Drugs in Adults with Chronic Kidney Disease and Hemodialysis, San Francisco: University of California San Francisco, Center for HIV Information; 2010. Accessed April 1, 2011.

Ministry of Health, Adult and adolescent Antiretroviral Therapy protocols 2010. Ministry of Health, 2011.

Mulenga, L.B., Kruse, G., Lakhi, S., Cantrell, R. A., Reid, S.E., Zulu, I., Stringer, E.M., Krishnasami, Z., Mwinga, A., Saag, M.S., Stringer, J. S. A., and Chi, B. H. Baseline renal insufficiency and risk of death among HIV infected HIV adults on antiretroviral therapy in Lusaka, Zambia. AIDS 2008, 22:1-7.

Munar, M.Y. and Singh, A. 2007 Drug Dosing Adjustments in Patients with Chronic Kidney Disease, *American Family Physician.* 2007 15; 75(10):1487-1496

Peyriere, H., Reynes, J., Rouanet, I., Daniel, N., de Boever, C. M., Mauboussin, J., Leray, H., Moachon, L., Vincent, D. and Salmon-Céron, D. Renal tubular dysfunction associated

with Tenofovir therapy: report of 7 cases. Journal of Acquired Immune Deficiency Syndrome 2004; 35: 269–73.

Rastegar, D.A., Knight, A. M. and Monolakis, J. S. Antiretroviral medication errors among hospitalized patients with HIV infection. Clin. Infect. Dis. 2006; 43: 933-938

Schaaf, B., Ariesa, S. P., Kramme, E., Steinhoff, J. and Dalhoff, K. Acute renal failure associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome. Clin Infect Dis 2003; 37: e41–3.

Shavadia, J. Antiretroviral Therapy Dose Adjustments Based On Calculated Creatinine Clearance. East African Medical Journal Vol. 86 No. 4 April 2009

Stevens, L. A., Coresh, J., Greene, T., and Levey, A. S., Assessing kidney function - Measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 354(23):2473–2483.

Tourret, J., Tostivint, I., Du Montcel, S., Karie, S., Launay-Vacher, V., Vigneau, C., Bessette, C., Deray, G. and Bagnis, C. I. Antiretroviral Drug Dosing Errors in HIV-Infected Patients Undergoing Hemodialysis. Clinical Infectious Diseases 2007; 45:779–84

Verbeeck, R. K. and Musuamba, F. T. 2009, Pharmacokinetics and dosage adjustment in patients with renal dysfunction, *European Journal of Clinical Pharmacology* (2009) 65:757–773

Verhelst, D., Monge, M., Meynard, J. L., Fouqueray, B., Mougenot, B., Girard, P., Ronco, P., and Rossert, J. Fanconi syndrome and renal failure induced by tenofovir: a first case report. *Am J Kidney Dis 2002*; 40: 1331–3.

Williams DJP (2007), 'Medication Errors' *R Coll Physicians Edinb*; **37:**343–346 © 2007 Royal College of Physicians of Edinburgh

Wyatt, C. M., Winston, J. A., Malvestutto, C. D. and Fishbeinet, D. A. Chronic kidney disease in HIV infection: an urban epidemic. AIDS. 2007; 21:2101-2113.

Yehia, B. R., Mehta, J. M., Ciuffetelli, D., Moore, R. D., Pham, P. A., Metlay, J. P., and Gebo, K. A. Antiretroviral Medication Errors Remain High but Are Quickly Corrected Among Hospitalized HIV-Infected Adults. *Clin Infect Dis. (2012) 55 (4): 593-599. doi: 10.1093/cid/cis491 3.*

Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection (2014), Ministry of Health and Ministry of Community Development Mother and Child Health, 2014

Zimmermann, A. E., Pizzoferrato, T., and Bedford, J., Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis.* 2006; 42(2):283-290.

APPENDICES

Table 6 Data collection form

Variables	Definition	Measurement	SPSS CODE
I.D (Code)	Number given to participant as files are sampled	Continuous	Scale
Age (Years)	Age is grouped	Categorical	18 – 27 :1 28 – 37 : 2 38 – 47 :3 48 – 57: 4 58 – 67 : 5 68 – 77 : 6
Weight (Kg)	Weight is grouped in averages of 10 kg	Categorical	35 – 44 :1 45 – 54 :2 55 - 64 :3 65 – 74 :4 75 – 84 :5 Above 85 : 6
Sex	Sex is defined as gender and divided as Female and Male	Nominal	Female: 1 Male: 2
Marital Status	Marital status is the condition of being married or unmarried	Categorical	Single :1 Married :2 Divorced :3 Widowed :4
Serum Creatinine	Serum Creatinine is the amount of creatinine in blood	Continuous	Scale
eGFR	Baseline	Categorical	≥50 :1 30-49 :2 15-29 :3 5-14 :4 <5 :5

eGFR	6 Months	Categorical	≥50 :1 30-49 :2 15-29 :3 5-14 :4 <5 :5
eGFR	12 Months	Categorical	≥50 :1 30-49 :2 15-29 :3 5-14 :4 <5 :5
Duration on HAART	Number of months on Highly Active Anti-Retroviral Therapy	Continuous	Scale
Drug Regimen	Drug regimen as described by the National HIV/AIDS treatment Guidelines for Adults and adolescents in Zambia 2010	Categorical	TDF/FTC/EFV:1 AZT/3TC/EFV:2 ABC/3TC/EFV :3 TDF/FTC/NVP :4 AZT/3TC/NVP :5 ABC/3TC/NVP :6 TDF/FTC/LPV/r:7 AZT/3TC/LPV/r:8 ABC/3TC/LPV/r :9
Dose Prescribed (Tenofovir)	Dose of Tenofovir prescribed by the medical doctor	Categorical	300 mg OD :1 300 mg every 48 hrs :2 300 mg twice weekly :3 300 mg weekly :4
Dose errors	Wrong Dose of Tenofovir prescribed	Categorical	under dose : 1 Overdose : 2 Correct dose : 3
Dose Prescribed (Lamivudine)	Dose of Lamivudine prescribed by the medical doctor	Categorical	150 mg OD :1 150 mg, then 100 mg OD :2 150 mg, then 50 mg OD

			:3 50 mg , then 25 mg OD :4 150 mg BD : 5
Dose errors	Wrong Dose of lamivudine prescribed	Continuous	Under dose : 1 Overdose : 2 Correct dose : 3

BUDGET

Table 7 Budget for the Research

ITEM	QUANTITY	UNIT COST	TOTAL COST
Computer	01	5,000.00	5,000.00
Printer	01	2,000.00	2,000.00
stationary	01	3,000.00	3,000.00
Ethics approval	01	250.00	250.00
Transport	01	2,000.00	2,000.00
Study Assistants	02	1,000.00	2,000.00
Miscellaneous	01	2,000.00	2,000.00
Total			16,250.00

TIME FRAME

Table 8 Ghant Chart for the study

ACTIVITY	FEB	MAR	APRI	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Idea Submission											
Proposal writing											
Proposal presentation to the department											
Proposal presentation to the graduation forum											
Proposal submission to the UNZA biomedical ethics committee											
Data collection											
Data analysis and report writing											
Defending the thesis											