An investigation into the monitoring of renal function of patients treated with tenofovir at Odi Hospital in Gauteng Province

A thesis submitted by

Alfreda Nkosinomusa Zitha

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of the

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Department of Pharmacy

Supervisor: Prof. N Schellack

Co-supervisor: Prof. AGS Gous

2015
DECLARATION

I declare that the mini-dissertation hereby submitted to the Sefako Makgatho Health Sciences University, for the degree of Master of Pharmacy, in the Department of Pharmacy has not previously been submitted by me for a degree at this or any other university; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.

__________________________________  __________________
Zitha, A.N (Miss)                      Date
DEDICATION

I dedicate my work to my beautiful daughter, Naledi Sithole for “growing extremely fast” in order to accommodate my busy schedule. She had to learn how to do her own school work with minimal help from me and managed to get recognition (awards) for her efforts.
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<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
</tr>
<tr>
<td>ACR</td>
<td>Albumin creatinine ratio</td>
</tr>
<tr>
<td>ACT</td>
<td>Anatomical Therapeutic Chemical classification</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>AIN</td>
<td>Acute interstitial nephritis</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin receptor blocker</td>
</tr>
<tr>
<td>ARF</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>ARVs</td>
<td>Antiretroviral drugs</td>
</tr>
<tr>
<td>ATN</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>ATV</td>
<td>Atanazavir</td>
</tr>
<tr>
<td>AZT</td>
<td>Zidovudine</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CD&lt;sub&gt;4&lt;/sub&gt; count</td>
<td>T&lt;sub&gt;4&lt;/sub&gt; Lymphocytes</td>
</tr>
<tr>
<td>CEO</td>
<td>Chief executive officer</td>
</tr>
<tr>
<td>C-G</td>
<td>Cockcroft-Gault</td>
</tr>
<tr>
<td>CGA</td>
<td>cause, GFR, albuminuria</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CKF</td>
<td>Chronic kidney failure</td>
</tr>
<tr>
<td>Term</td>
<td>Abbreviation</td>
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<tr>
<td>------</td>
<td>--------------</td>
</tr>
<tr>
<td>Cyclooxygenase</td>
<td>COX</td>
</tr>
<tr>
<td>Cotrimoxazole preventative therapy</td>
<td>CPT</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>CrCl</td>
</tr>
<tr>
<td>Stavudine</td>
<td>d4t</td>
</tr>
<tr>
<td>Defined Daily Dose system methodology</td>
<td>DDD</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>DM</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>EFV</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>EFV</td>
</tr>
<tr>
<td>Estimated Glomerular filtration rate</td>
<td>eGFR</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>ESRD</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>FTC</td>
</tr>
<tr>
<td>Highly Active Antiretroviral Therapy</td>
<td>HAART</td>
</tr>
<tr>
<td>Health care professionals</td>
<td>HCPs</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>HD</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>HIV</td>
</tr>
<tr>
<td>HIV Associated nephropathy</td>
<td>HIVAN</td>
</tr>
<tr>
<td>Organic anion transporter 1</td>
<td>hOAT1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>HT</td>
</tr>
<tr>
<td>International Statistical Classification of Diseases</td>
<td>ICD</td>
</tr>
<tr>
<td>Identification number</td>
<td>ID</td>
</tr>
<tr>
<td>International Diabetes federation</td>
<td>IDF</td>
</tr>
<tr>
<td>Indinavir</td>
<td>IDV</td>
</tr>
<tr>
<td>Kidney disease: Improving global outcomes</td>
<td>KDIGO</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>LPV</td>
</tr>
<tr>
<td>Modification of diet in Renal Disease</td>
<td>MDRD</td>
</tr>
<tr>
<td>Multidrug resistant proteins</td>
<td>MRP</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TDF</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>TMP-SMZ</td>
<td>Trimethoprim- Sulphamethoxazole</td>
</tr>
<tr>
<td>V1</td>
<td>Visit 1 (in relation to baseline)</td>
</tr>
<tr>
<td>V2</td>
<td>Visit 2</td>
</tr>
<tr>
<td>V3</td>
<td>Visit 3</td>
</tr>
<tr>
<td>VL</td>
<td>Viral load</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
ABSTRACT

Abstract

Background:

By the end of 2010 South Africa (SA) had the largest human immunodeficiency virus (HIV) treatment programme in the world, with 1.3 million people receiving antiretroviral therapy (ART). However, burdensome adverse effects, although varying in their impact, have concerned government, health care professionals (HCPs) and patients. The adverse effects include ART renal dysfunction which is often associated with tenofovir disoproxil fumarate (TDF). The National Department of Health of South Africa (NDoHSA) published clinical guidelines in 2010 (ART guidelines, 2010) for the management of HIV and AIDS in adults and adolescents. These guidelines were written to minimize unnecessary drug toxicities and enable primary health care facilities to initiate, manage, monitor and refer patients.

Objectives:

The objectives of the study were to investigate the compliance of health care professionals (HCPs) with the ART guidelines (2010) in monitoring the renal function of patients on tenofovir in the years 2010 and 2012 and to retrospectively investigate the renal function of patients initiated on TDF as part of first line regimen.

Method:

The study was a retrospective observational study where a purposive sampling procedure was used to select the sample of 500 patient cases from an estimated population of 4493, i.e. 11.1% of the population (a 95% confidence interval for the percentage in about 10.2% to 12.1%). These records were reviewed to obtain the necessary data. These records were then audited for compliance by HCPs in monitoring laboratory tests, in particular kidney function tests Scr and CrCl for patients on TDF.

Results:

About 65% of the study participants were female. The median serum creatinine (Scr) remained below 100µmol/l at all visits. Median creatinine clearance (CrCl) remained stable at Kidney Disease: Improving Global Outcomes (KDIGO) stage 2(60-89ml/l) of chronic
kidney function (CKD). Median CD₄ count increased with each visit demonstrating the strengthening immune system while the median viral load (VL) remained unsuppressed at all visits increasing the CKD risk. The mean monitoring intervals were wide at 11 months, 24 months and 34 months from baseline for visit 1, visit 2 and visit 3 respectively.

**Conclusion:**

The renal function of patients that were initiated and remained on tenofovir was poorly monitored by HCPs. CD₄, VL and Scr (CrCl) were not taken at all visits and where it was done the intervals did not correspond to what was prescribed by the guidelines as set out by NDoH (2010).
CHAPTER 1
INTRODUCTION

1.1 INTRODUCTION

In this chapter, the background and rationale for the study will be described. The research question, aim of the study, as well as the objectives of the study are also described. The significance as well as the outline of the dissertation is also explained in this chapter.

1.2 BACKGROUND AND RATIONALE FOR THE STUDY

Khwitshana, Greeff & Hurrel (2014); Fine, Perazella, Lucas & Atta (2008); De Silva, Post, Griffin & Dockrell (2007) cite that advances in the management and treatment of Human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome (AIDS) have transformed HIV into a chronic condition rather than a debilitating terminal illness. Kwhitshana et al. (2014) further cites that, by the end of 2010 South Africa (SA) had the largest HIV treatment programme in the world, with 1.3 million people receiving antiretroviral therapy (ART). However, burdensome adverse effects, although varying in their impact, have concerned government, health care professionals (HCPs) and patients.

The National Department of Health of South Africa (NDoHSA) published clinical guidelines in 2010 (ART guidelines, 2010) for the management of HIV and AIDS in adults and adolescents. These guidelines were written to minimize unnecessary drug toxicities and enable primary health care facilities to initiate, manage, monitor and refer patients.

According to these guidelines, (ART guidelines, 2010) compliance by HCPs to monitoring kidney function will assist in early detection of renal dysfunction which will allow for appropriate and timely intervention (See Table 1.1). This is supported by Katz, Gerntholtz & Naicker (2011) when pointing out that patients with kidney disease should be referred to nephrologists at an early stage so as to institute measures to retard progression and plan timely transplantation and/or dialysis.

The ART guidelines, (2010) also clearly state the level of creatinine clearance (CrCl), [less than 50ml/min] at which urgent up-referral prior to initiation or when on therapy is indicated.
Chapter 1: Introduction

The latest consolidated ART guidelines were published in 2014 and implemented in January 2015. Just like the 2010 and 2013 ART guidelines, the latest guidelines still promote tenofovir (TDF) containing regimen as the first line regimen for all patients needing treatment, including pregnant women. The ART guidelines, (2010, 2013 and 2015), emphasize monitoring the levels of serum creatinine (Scr) in order to identify TDF toxicity (see Table 1.1 below).

Table 1.1: Monitoring tests (2010 ART guidelines versus 2013 guidelines versus 2015 guidelines)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine(Scr)</td>
<td>Month Three, Month Six on ART and then annually</td>
<td>At initial diagnosis of HIV, month three, six, one year and then every 12 months</td>
<td>At initial diagnosis of HIV, month three, six, one year and then every 12 months</td>
</tr>
<tr>
<td>CD4 count</td>
<td>Month six, One year on ART and then every 12 Months thereafter</td>
<td>Only one year on ART</td>
<td>At initial diagnosis of HIV and one year on ART.</td>
</tr>
<tr>
<td>Viral load (VL)</td>
<td>Month six, One year on ART and then every 12 Months</td>
<td>Month six, one year on ART and then every 12 months</td>
<td>Month six, one year on ART and then every 12 months</td>
</tr>
</tbody>
</table>

Source: Adapted from ART guidelines, 2010

Agraval, Ghosh, Barnes & McCullough (2009), also states that late evaluation of patients with chronic kidney disease (CKD) by a nephrologist, especially close to the time of starting dialysis, is associated with sub-optimal pre-end stage renal disease (ESRD) management and mortality risk.

1.3 PROBLEM STATEMENT

According to Ms. Ramasodi (personal communication) a pharmacist working in the Bokamoso HIV clinic, in year 2012, Odi Hospital did not regularly monitor patients initiated on highly active antiretroviral therapy (HAART) as per the recommendations in the guidelines (referred to above). This included patients initiated on TDF. She confirmed that some patients got their blood samples taken for routine monitoring of viral load (VL), CD4
count, Scr and GFR (glomerular filtration rate), but they either never got their results or got their results very late (after several months to over a year).

Zimmermann, Pizzoferato, Bedford, Morris & Hoffman (2006) state that poor monitoring may be contributing to late detection of TDF-associated kidney disease and that earlier recognition of TDF-associated acute changes in renal function will prevent the occurrence of CKD.

According to Agraval, et al. (2009), CKD is an increasingly prevalent health problem with potential for poor outcomes of ESRD and cardiovascular disease. Agraval, et al. (2009), further reports that primary care physicians are less likely than a nephrologist to recognize CKD and differ in their clinical evaluation of CKD. With progression of CKD, primary care physicians tend to refer the patient to a nephrologist later than when the nephrologists would deem appropriate. Mendelssohn, Barret, Brownscombe, Ethier, Greenberg, Kanani, Levin, & Toffelmire (1999) also mention that optimal health outcomes are more likely if a nephrologist physician is involved in caring for these patients from the time creatinine elevation is discovered. Mendelssohn, et al. (1999) further cites that the potential benefits of early referral to a nephrologist include identifying and treating reversible causes of renal failure, slowing the rate of decline associated with progressive renal insufficiency and managing the multiple co-existing conditions associated with CKD.

Late evaluation of patients with CKD by a nephrologist, especially close to the time of starting dialysis, is associated with sub-optimal pre-ESRD management and mortality risk (Agraval et al., 2009).

Patients with CKD stages 1-3 (GFR > 30 ml/min/1.73m2) are generally asymptomatic. (illustrated in Table 1.2 below). It is not until stages 4-5 (GFR < 30 ml/min/1.73M2) that endocrine/metabolic derangements or disturbances in water or electrolyte balance clinically manifest. Therefore, regular screening is important due to the asymptomatic presentation of most kidney disease (Arora, 2015; Fine, 2008; Hudson & Wazny, 2014; Dowling, 2014).
Table 1.2: Presentation of Chronic Kidney Disease

<table>
<thead>
<tr>
<th></th>
<th>Early CKD (Stages 1-2)</th>
<th>Late CKD (Stages 3-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>The patient may not appear in distress</td>
<td>Patient may have edema</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Not likely present</td>
<td>The patient may have fatigue, malaise, pruritus, nausea</td>
</tr>
<tr>
<td>Signs</td>
<td>Not likely present</td>
<td>May present with fluid retention, anemia, dyspnea, reduced urine output</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>Microalbuminuria, mildly elevated serum creatinine and blood urea nitrogen</td>
<td>Persistent proteinuria, reduced glomerular filtration rate or creatinine clearance, abnormal urinalysis</td>
</tr>
<tr>
<td>Other diagnostic tests</td>
<td>Renal ultrasound shows reduced kidney mass</td>
<td></td>
</tr>
</tbody>
</table>


Katz et al. (2011) reports that, in South Africa, many people who develop ESRD are offered neither dialysis nor transplantation (renal replacement therapy-RRT) because of scarce resources and established protocols which accept only patients without significant comorbid disease. Katz et al. (2011) further reports that, following Ghana, Senegal, Kenya and Sudan, South Africa has 50 nephrologists which translates to 1.1 nephrologists per million people of the population (pmp), compared to a country like Egypt, where there are 500 nephrologists (6.5 nephrologists pmp).

In this particular clinic the patients who are initiated on antiretroviral drugs (ARV’s) are seen by nurses/primary care physicians and medical officers. According to Mr. Mathonsi (personal communication), the Human resource manager (2014), there is no nephrologist available at the facility. This was confirmed through the “Doctors allocation 2015”, compiled by Dr. Dlamini (the clinical manager).

For the purpose of this retrospective study, that was initiated in 2012, the 2010 ART guidelines were used since the study participants were initiated on TDF containing
regimen before the ART guidelines of 2013 were implemented. The files studied for the purposes of the study were for those participants initiated on ARV’s for the years between 2010 and 2012.

1.4 RESEARCH QUESTION

The following research questions were posed:

- Did HCPs comply with the ART guidelines, (2010), in monitoring renal function in TDF-naïve patients?
- What was the renal function of patients treated with TDF over the first year for the years between 2010 and 2012?
- How did the compliance of HCPs with the ART guidelines, (2010), affect renal function?

1.5 AIM OF THE STUDY

The aim of the study was to investigate the monitoring of renal function of patients on tenofovir at Odi Hospital, initiated between the years 2010 and 2012.

1.6 OBJECTIVES OF THE STUDY

The objectives of the study were as follows:

- To investigate the compliance of HCPs with the ART guidelines (2010) in monitoring the renal function of patients on tenofovir in the years 2010 and 2012.
- To retrospectively investigate the renal function of patients initiated on TDF as part of first line regimen for the first year.

1.7 IMPORTANCE OR SIGNIFICANCE OF THE STUDY

According to Crum-Cianflone, Ganesan, Teneza-Mora, Riddle, Medina, Barahona, & Brodine (2009), CKD has become an important co-morbidity among HIV-infected persons. The contributing factors to renal disease include the aging of the population, concurrent medical conditions such as diabetes mellitus (DM), hypertension (HT) and uncontrolled viremia (also known as VL). De Silva, et al. (2007) state that CKD is associated with increased progression to AIDS and death, even after HAART was initiated.
Penzak (2005) reports the possibility of multiple drug interactions with the polypharmaceutical drug regimens that is often encountered in the prophylaxis and treatment of infectious diseases. The study aimed to determine if there is compliance with the ART guidelines (2010) in relation to monitoring of kidney function for patients on TDF. The study will also help highlight the need for HCPs to follow the guidelines (where the monitoring intervals are clearly outlined) in order to prevent or detect the kidney failure in its early stages thus allowing early referral to nephrologists/specialists.

1.8 OUTLINE OF THE DISSERTATION

Chapter 1 is an introduction to the study report and it includes the background and the rationale for the study. The problem statement and the research question are also described in this chapter. The purpose of the study (through the aim and objectives, as well as the importance of the study) is explained.

In Chapter 2, the literature is extensively discussed through the following topics: overview of kidney disease, overview of ART related kidney disease in HIV, TDF induced renal side effects, kidney function quantification, ARV regimens in SA and HCPs adherence to ART guidelines.

Chapter 3 covers the methodology of the study. The research design, study site, study population, study period, sample selection, data collection, data entry and analysis, reliability and validity as well as ethical considerations are extensively discussed.

In Chapter 4, the results obtained in the study and the discussion is laid out. The results will be presented in a manuscript format and the prevalence of HCP non-compliance to ART guidelines (2010), in monitoring renal function will be discussed.

The dissertation concludes with Chapter 5, in this Chapter the study limitations; conclusion and the recommendations are described.

1.9 SUMMARY

In Chapter 1, the background and rationale for the study was discussed. The problem statements, the research question, the aim of the study, as well as the objectives of the
study were discussed. Chapter 1 concluded with the discussion on the significance of the study and the outline of the dissertation. Chapter 2 focused on study literature review.
CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

In this chapter, the literature on the study topic and related previous research is laid out. The detailed review of literature is covered under the following headings: kidney disease, overview of ART related kidney disease in HIV, TDF-induced renal side-effects, kidney function quantification, followed by ARV regimens in SA. The chapter is concluded by a description of HCPs adherence to ART guidelines.

2.2 KIDNEY DISEASE

The overall survival improvement of HIV-infected patients receiving ART leads to the accumulation of factors that are harmful to renal function: ageing, co-morbidities such as HT, DM, hyperlipidemia and adverse effects of ARV drugs such as indinavir (IDV) and tenofovir. These factors are likely to increase the frequency of acute or chronic renal impairment (Deti, Thiebaut, Bonnet, Lawson-Ayaayi, Dupon, Neau, et al. 2010).

For this study acute kidney injury (AKI) and CKD is based on the Kidney Disease: Improving Global Outcomes (KDIGO) in Clinical Practice guidelines (Dager & Halilovic, 2014). According to KDIGO AKI is defined as being present if any of the following criteria are met:

1. Increase in Scr by at least 27µmol/L within 48 hours;
2. Increase in Scr by at least 1.5 times from baseline within the prior seven days; or
3. Decrease in urine volume to less than 0.5 ml/kg for 6 hours.

The development of AKI can be divided in the following main pathophysiologic processes (Dager & Halilovic, 2014):

- prerenal AKI,
- intrinsic AKI, and
- post renal AKI

Hudson & Wazny (2014) and Willis, Cheung & Slifer (2013) defined CKD as abnormalities in kidney structure or function, present for three months or longer, with implications for health. Structural abnormalities include albuminuria of more than 3 mg/day, presence of
hematuria or red cells casts in urine sediment, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by imaging or history of kidney transplantation. An abnormality in kidney function is usually indicated by a decrease in GFR.

The etiology of CKD can be classified into: susceptibility factors, initiation factors and progression factors (Hudson & Wazny, 2014).

Susceptibility factors are: advanced age, low income or education and racial/ethnic minority status, reduced kidney mass, low birth weight, family history of CKD, systemic inflammation, and dyslipidemia. Most of these susceptibility factors may not be amenable to pharmacologic or lifestyle interventions, but they may be useful for identifying populations that are at high risk of CKD.

Initiation factors are conditions that directly result in kidney damage and are modifiable by pharmacologic therapy. The conditions include: diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease, Wegener’s granulomatosis, vascular disease and HIV nephropathy.

Progression factors are those factors associated with further decline in kidney function. Persistence of the underlying initiation factors (e.g. DM, HT, glomerulonephritis) themselves may serve as the most important predictor of progressive CKD.

Levey et al. (2011) cite that according to National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI-2002), chronic kidney disease was defined based on the presence of kidney damage or GFR < 60ml/min per 1.73 m² for ≥ 3 months, irrespective of cause, and was classified into five stages based on the level of GFR (see Table 2.1 below).

Table 2.1: Five stages of chronic kidney failure: GFR stages, description and range (ml/min/1.73m²)

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;90</td>
<td>Normal or increased</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severe</td>
</tr>
</tbody>
</table>
CKD is an increasingly alarming worldwide health concern with nearly two million people in the United States of America estimated to require haemodialysis or kidney transplantation by 2030. In response to this widespread problem standardized approaches are now used for the identification of individuals with CKD and their subsequent stratification into the risk categories for end stage renal disease. These efforts have heightened the awareness of the need for early identification of patients with CKD and the importance of monitoring the progression of kidney disease (Dowling, 2014).

Hudson & Wazny (2014) cites that CKD is classified by cause of kidney disease, GFR category and albuminuria levels based on the new recommendations from the Kidney Disease: KDIGO guidelines for evaluation and management of CKD. This is referred to as CGA strategy (cause, GFR, albuminuria). Tables 2.2 and 2.3, outline the GFR and albuminuria category.

**Table 2.2: GFR categories**

<table>
<thead>
<tr>
<th>KDIGO Category</th>
<th>GFR (mL/min/ 1.73 m² [mL/s/m²])</th>
<th>Terms</th>
<th>Corresponding KDOQI Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&gt;90 (&gt;0.87)</td>
<td>Normal or high</td>
<td>Stage 1 CKD</td>
</tr>
<tr>
<td>G2</td>
<td>60–89 (0.58–0.86)</td>
<td>Mildly decreased</td>
<td>Stage 2 CKD</td>
</tr>
<tr>
<td>G3a</td>
<td>45–59 (0.43–0.57)</td>
<td>Mildly to moderately decreased</td>
<td>Stage 3 CKD</td>
</tr>
<tr>
<td>G3b</td>
<td>30–44 (0.29–0.42)</td>
<td>Moderately to severely decreased</td>
<td>Stage 3 CKD</td>
</tr>
<tr>
<td>G4</td>
<td>15–29 (0.14–0.28)</td>
<td>Severely decreased</td>
<td>Stage 4 CKD</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15 (&lt;0.14)</td>
<td>Kidney failure</td>
<td>Stage 5 CKD (ESRD if requiring dialysis)</td>
</tr>
</tbody>
</table>

Source: Adapted from Hudson & Wazny in DiPiro, 2014.

**Table 2.3: Quantification of proteinuria by different methods**

<table>
<thead>
<tr>
<th>Urine Test</th>
<th>Albuminuria Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1: Normal to Mildly Increased</td>
<td>A2: Moderately Increased</td>
</tr>
<tr>
<td>A3: Severely Increased</td>
<td>Other terminology</td>
</tr>
</tbody>
</table>

| Normal to Mildly Increased | Moderately Increased | Severely Increased | Normoalbuminuria | Microalbuminuria |

Source: Adapted from Levy et al. (2011).
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<table>
<thead>
<tr>
<th>AER (mg/24 h)</th>
<th>&lt;30</th>
<th>30–300</th>
<th>&gt;300</th>
</tr>
</thead>
<tbody>
<tr>
<td>PER (mg/24 h)</td>
<td>&lt;150</td>
<td>150–500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>ACR</td>
<td>&lt;3</td>
<td>3–30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>PCR</td>
<td>&lt;15</td>
<td>15–50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Protein reagent strip</td>
<td>Negative to trace</td>
<td>Trace to +</td>
<td>+ or greater</td>
</tr>
</tbody>
</table>

Source: Adapted from Hudson & Wazny in DiPiro, 2014.

**Abbreviations:** AER, albumin excretion rate (24-hour urine collection); PER, protein excretion rate (24-hour urine collection); ACR, albumin-to-creatinine ratio (spot urine sample) (SI units: milligrams of albumin per millimole of creatinine); PCR, protein-to-creatinine ratio (spot urine sample), (SI units: milligrams of protein per millimole of creatinine).

### 2.3 OVERVIEW OF ANTI-RETROVIRAL THERAPY RELATED KIDNEY DISEASE IN HIV

The introduction of HAART prolongs survival and is now providing normal life expectancy in HIV-infected individuals (Dauchy, Lawson-Ayayi, de La Faille, Bonnet, Rigothier, Mehsen, et al., 2011; Fine, et al., 2008) and with improved survival, hence increasing age, these individuals are increasingly likely to experience ailments that affect the general population, including kidney disease.

This report is supported by Crum Cianflone et al., (2010) when they cite that, as a result of the introduction of HAART, the number of deaths due to opportunistic infections (OIs) has significantly declined, while the greater proportion of patients are developing chronic conditions such as cardiovascular, liver, and kidney disease. As the prevalence of HIV infection increases as a result of improved survival, the prevalence of renal dysfunction is also projected to increase.

(Fine et al., 2008; Post, Campbell, Hamzah, Collins, Jones, Siwani, et al. 2008; Overton, Nurutdinova, Freeman, Seyfried, & Mondy, 2009) further state that, even though HIV-associated nephropathy (HIVAN), the most ominous kidney disease related to the direct effects of HIV, may be prevented and treated with ARVs, kidney disease remains an important issue in this population. HIV infected patients also have a high prevalence of other risk factors for renal disease, including hepatitis C, cigarette smoking and injection drug use. Renal survival remains poor even for patients who have attained complete viral suppression (Post, et al., 2008).
Overton et al. (2009), also state that the kidney function has been estimated to be abnormal in up to 30% of HIV infected patients. In addition other metabolic complications such as type 2 DM and HT may also contribute to renal dysfunction over time.

According to De Silva et al. (2007), many drugs used in the treatment or prophylaxis of OIs, including the frequently used trimethoprim-sulphamethoxazole in HIV infection, may cause nephrotoxicity.

According to Peters, Moore, Mermin, Brooks, Downing, Were, Kigozi, Buchacz et al. (2008), HAART may be protective against and therapeutic for HIV-associated renal function. Peters et al. (2008), also acknowledges the fact that renal dysfunction may complicate ART since some medications require dose adjustments and certain ARVs such as TDF and the protease inhibitor IDV can also cause renal dysfunction.

HIV-infected individuals are at increased risk for AKI and CKD (Estrella, Fine, & Atta, 2010; Fine et al. (2008)), and in the HAART era this increase can be largely attributed to non-HIV-related kidney disease. Both AKI and CKD, including microalbuminuria, are associated with increased risk for cardiovascular disease and mortality among HIV-infected individuals versus the general HIV-uninfected population (Estrella et al. 2010).

Estrella et al. (2010) also state that, while the mechanisms by which kidney disease impacts outcomes in HIV-infected persons remain largely unclear, timely detection and accurate diagnosis of kidney disease in HIV-infected individuals are necessary in averting further renal injury and instituting appropriate treatment.

2.4 **Tenofovir Induced Renal Side-effects**

TDF is the first analogue nucleotide reverse transcriptase inhibitor (NtRTI) licensed for the treatment of HIV infection is structurally similar to adefovir and cidovir (Dauchy et al., 2011; Fernandez-Fernandez, Montoya-Ferrer, Sanz, Sanchez-Nino, Izquiredo, Poveda, et al., 2011). TDF is recommended in major guidelines as the first choice nucleoside reverse transcriptase inhibitor (NRTI) that can be administered once daily. The 2010, 2013 and 2015 ART guidelines recommended TDF as part of the first line regimen for all new patients needing treatment.

TDF has been demonstrated to be safe and generally well tolerated for treatment of HIV infection and has not been associated with significant renal toxicity or changes in GFRs in randomised placebo-controlled clinical trials of patients with normal baseline renal
function, even though cases of severe renal dysfunction and population level reductions in (CrCl) among TDF-treated patients have been reported in observational studies after licensure (Young, Buchacz, Baker, Moorman, Wood, Chmiel, et al., 2007; Young, Buchacz, Moorman, Wood, Brooks & the HIV Outpatient Study (HOPS) Investigators, 2009).

However, TDF-containing regimens were associated with mild, and at times a significantly greater loss of kidney function than were ART regimens not containing TDF. (Cooper, Wiebe, Smith, Keiser, Naicker & Tonelli, 2010; Yoshino, et al., 2012). Renal impairment caused by TDF is reversible after discontinuation of TDF, but there are reported cases where the renal function does not recover even after discontinuation of TDF (Yoshino et al., 2012).

The exact intracellular targets of TDF toxicity are not clear but evidence is mounting that TDF is specifically toxic to the mitochondria in the renal proximal tubule. TDF is eliminated unchanged in the urine by a combination of glomerular filtration and proximal tubular secretion. About 20-30% of the drug is actively transported into the renal proximal tubule cells by organic anion transporters (hOAT1) and to a lesser extent OAT3 in the basolateral membrane. The drug is subsequently secreted to the tubular lumen by apical membrane transporters MRP-4 and MRP-2 (multi-drug resistance proteins, encoded by ABCC4 and ABCC2 genes, respectively (Hall, Hendry, Nitsch, DConnolly, 2011; Fernandez-Fernandez et al., 2011; Goicoechea, Liu, Best, Sun, Jain, Kemper et al., 2008; Young, Schafer, FuxFurrer, Bernasconi, Vernazza, et al., 2012).

A number of drugs interact with these transporters and may cause excessive entry or reduced outflow of the drug, favouring accumulation and increasing toxicity. These include lopinavir/ritonavir (LPV/r) and atazanavir/ritonavir (ATV/r), which are known to increase plasma levels of TDF by 20 to 30 % (Reid, Stohr, Walker, Williams, Kityo, Hughes, et al., 2008; Young et al., 2012). Some studies cite the following as the possible explanations for the increase in plasma TDF (Reid, Stohr, Walker, Williams, Kityo, Hughes, P. et al., 2008; Young, et al. 2012):

• Higher absorption of the prodrug TDF by a protease inhibitor (PI)-related inhibition of P-glycoprotein; or

• Reduced renal clearance of TDF due to protease inhibitor-induced drug interaction.
MRP2 is postulated to possibly mediate the efflux (i.e. cellular exit) from proximal tubules. Competitive inhibition of MRP2 in renal cells may result in decreased efflux and increased intracellular accumulation and nephrotoxicity with drugs such as nucleoside phosphonates, for example: acidofovir, TDF and adefovir. Despite minimal expression in the kidney, data suggests that MRP2 play a significant role in the renal excretion of some drugs. It is hypothesised that inhibition of MRP2 by a low dose of r may increase tubular concentrations of TDF by decreasing its apical efflux; this in turn may lead to TDF mediated nephrotoxicity (Penzak, 2005).

Several studies recommend a more frequent kidney function monitoring where drug regimens containing low dose r (a potent inhibitor of MRP2) in combination with TDF are used. The increased frequency of kidney function monitoring also applies to high risk patients such as those concomitant diseases such as DM, HT, or chronic hepatitis or liver failure, older patients, patients with baseline CD4 counts less than 200 cells/µL, sepsis or septicaemia, diarrhoea, malaria and nephrotoxic co-medication (Goicoechea et al., 2008; Gallant & Moore 2009; Horberg, Tang, Towner, Silverberg, Bersoff-Matcha, Hurley, et al., 2010; Reid et al., 2010).

2.5 KIDNEY FUNCTION QUANTIFICATION

The Gold standard quantitative index of kidney function is a measured GFR. Measurement of GFR is important for early recognition and monitoring of patients with chronic kidney disease and as a guide for drug dose adjustments (Dowling, 2014).

According to Fine et al. (2008), accurate and rapid identification and subsequent diagnosis of kidney disease are essential to improve outcomes, as they support early and focused intervention. Screening tools are limited and predominantly centre on GFR estimation and proteinuria assessment. The Cockcroft-Gault (C-G) equation is the most commonly used CrCl estimating formula, even though the simplified Modification of Diet in Renal Disease (MDRD) formula has gained wider acceptance. Proteinuria is the hallmark of glomerular disease and may be the earliest indicator of kidney disease in some patients (Fine, et al., 2008).

According to Hall et al. (2011), many studies have examined the relationship between TDF exposure and kidney function by measuring serum creatinine and in most cases
calculating CrCl or estimated GFR, using either C-G or MDRD study equation, respectively.

Hall et al., (2011) mention that, whereas both formulas are widely used, they have acknowledged weaknesses as estimates of true kidney function, e.g. the C-G calculation does not correct for body surface area and tends to overestimate GFR, whereas the MDRD equation underestimates GFR at higher levels.

According to van Deventer, George, Paiker & Becker, 2008), MDRD equation was derived in the United States of America by analysis of data from African Americans with known kidney disease. Van Deventer et al. (2008) reported that high Scr levels and urinary creatinine rates for a given GFR in African Americans compared with non-African Americans may not be true for black South Africans as the two populations have different origins. Creatinine is derived from skeletal muscle and HIV-infected patients can have abnormal mass and in patients with low muscle mass, low Scr values may more likely reflect reduced creatinine generation even in the face of renal function impairment. This is an important consideration when interpreting results (Gupta, Ongoor, Shen, Musick, Goldman & Woolf-Kaloustian, 2011; Hall et al., 2011).

According to (Mendelssohn, Barret, Brownscombe, Ethier, Greenberg, Kanani, Levin, Toffelmire, 1999) all newly discovered renal insufficiency as evidenced by Scr elevated to a level above the upper of the normal range of the laboratory must undergo investigations to determine the potential reversibility of disease to evaluate the prognosis and to optimize planning of care.

Most patients with even mildly elevated Scr levels have lost about 50% of their renal filtration and already have mild to moderate renal insufficiency and these patients must undergo a variety of investigations to determine if reversible factors can be identified (Mendelssohn et al., 1999). This is depicted by figure 2.1 below:
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Figure 2.1: Approaches to diagnosis and treatment of patients with elevated levels of Scr, at 3 stages of disease: Newly discovered elevations of creatinine level (A), progressive chronic renal failure (B) and just before end-stage renal disease (C).

- **A. Newly discovered elevation of creatinine**
  1. Identify reversible factors
  2. Consider kidney biopsy

  Work up includes CBC, determination of electrolytes, bicarbonate, urea, creatinine, calcium, phosphorus, glucose, total protein and albumin, serum protein electrophoresis, urinalysis; 24-h urine collection for protein and creatinine clearance, and ultrasonography

- **B. Progressive chronic renal failure**
  1. Reduce rate of progression.
  2. Treat co-morbid diseases.

  Treatment includes control of BP, consideration of ACE inhibition and other protective strategies, modification of diet, evaluation of lipid levels, control of calcium/phosphate, management of anaemia with erythropoietin, and for children, administration of rhGH

- **C. Pre-ESRD**
  1. Begin patient education
  2. Choose treatment modality
  3. Consider transplantation
  4. Create access for dialysis
  5. Enter patient into ESRD treatment program on an elective basis.

  NB: Adequate preparation requires at least 1 year.

**CBC**, complete blood count; **BP**, blood pressure; **ACE**, angiotensin-converting enzyme; **rhGH**, recombinant human growth hormone; **ESRD**, end stage renal disease.

Source: Adapted from Mendelssohn *et al.*, (1999)

According to the 2010, 2013 and 2015 ART guidelines, Scr should be routinely monitored at month three, six and subsequently every 12 months to identify TDF toxicity.
Fine et al. (2008) stated that a retrospective analysis of a large cohort of patients, who received either TDF or an alternative NRTI as part of HAART regimen, showed that the use of TDF was associated with a greater decline in renal function compared with the use of other NRTIs. Patients who received TDF had a significantly greater decrease in CrCl, also referred to as GFR, which was identifiable within 90 days (three months) of initiating TDF treatment and persisted over the one year follow-up period.

According to Dowling (2014), GFR is the single best indicator of kidney function, but a single equation may not be suitable for all populations and a choice of equation has been shown to impact CKD prevalence estimates. This has led to revitalized interest in the development of new equations (see Tables 2.4 and 2.5 below) to estimate GFR. Dowling (2014) further cites that some practitioners are advocating the use of the four-variable Modification of Diet in Renal Disease Study equation (MDRD4) in patients without CKD, although it appears to have a weaker correlation with GFR than the C-G equation. Recent evidence suggests that the MDRD4 equation should be reserved for patients with a GFR <60 ml/min/1.73 m² (<1.0 ml/s/m²). The use of newer equations, such as the CKD-EPI, has improved accuracy in patients with GFR >60 ml/min/1.73 m² (<1.0 ml/s/m²); however, further studies incorporating additional biomarkers such as cystatin C are underway. The units used for Scr in all equations referred to in Tables 2.4 and 2.5 are mg/dl.
Table 2.4: Equations for the Estimation of Creatinine Clearance in Adults with Stable Renal Function

<table>
<thead>
<tr>
<th>Author</th>
<th>Equation-Men</th>
<th>Equation-Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockroft and Gault</td>
<td>( CLcr = (140 - age) \times ABW/(Scr \times 72) )</td>
<td>( CLcr \times 0.85 )</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>( CLcr = (100/Scr) - 12 )</td>
<td>( CLcr = (80/Scr) - 7 )</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>( CLcr = 98 - [0.8 \times (age - 20)]/Scr )</td>
<td>( CLcr \times 0.9 )</td>
</tr>
<tr>
<td>Mawer et al.</td>
<td>( CLcr = [(145 - age)/Scr] - 3 )</td>
<td>( CLcr \times 0.85 )</td>
</tr>
<tr>
<td>Hull et al.</td>
<td>( CLcr = [(29.3 - (0.203 \times age)] [1 - (0.03 \times Scr)]/(14.4 \times Scr) )</td>
<td>( CLcr = [(25.3 - (0.175 \times age)] [1 - (0.03 \times Scr)]/(14.4 \times Scr) )</td>
</tr>
</tbody>
</table>

Source: Adapted from Dowling (2014)
Table 2.5: Formulae and respective equations used for estimation of CrCl in Adults with Stable Renal Function

<table>
<thead>
<tr>
<th>Author(s) and Methodology</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levey et al. (MDRD6)</td>
<td>GFR = 170 × (Scr)−0.999 × [age]−0.176 × [0.762 if patient is female] × [1.180 if patient is black] × [BUN]−0.170 × [Alb]0.318</td>
</tr>
<tr>
<td>Levey et al. (MDRD4)</td>
<td>GFR = 186 × (Scr)−1.154 × (age)−0.203 × (0.742 if patient is female) × (1.210 if patient is black)</td>
</tr>
<tr>
<td>Levey et al. (MDRD4-IDMS)</td>
<td>GFR = 175 × (Scr)−1.154 × (age)−0.203 × (0.742 if patient is female) × (1.210 if patient is black)</td>
</tr>
<tr>
<td>Levey et al. (CKD-EPI)</td>
<td>GFR = 141 × min(Scr/k, 1)α × max(Scr/k, 1)-1.209 × 0.993age × 1.018 [if female] × 1.159 [if black]</td>
</tr>
<tr>
<td>Rule et al. (MCQ)</td>
<td>GFR = \exp[1.911 + \frac{5.249}{S_{cr}} - \frac{2.114}{S_{cr}^2} - 0.00686 \times \text{Age} - 0.205 \text{ (if female)}]</td>
</tr>
<tr>
<td>Larsson et al.</td>
<td>GFR = 77.24 × (CysC in mg/L)−1.2623</td>
</tr>
<tr>
<td>Macdonald et al.</td>
<td>\log_{10}eGFR = 2.222 + \left(-0.802 \times \sqrt{\text{CysC in mg/L}}\right) + (0.009876 \times \text{LM})</td>
</tr>
<tr>
<td>CKD-EPI Equation 8112</td>
<td>eGFR = 127.7 × (CysC in mg/L)−1.17 × (age in years)−0.13 × 0.91 (if female) × 1.06 (if black)</td>
</tr>
<tr>
<td></td>
<td>*eGFR = 127.7 × (−0.105 + 1.13 × \text{standardized SCysC})−1.17 × \text{age}−0.13 × (0.91 if female) × (1.06 if black)</td>
</tr>
<tr>
<td>CKD-EPI Equation 9112</td>
<td>eGFR (mL/min/1.73 m2) = 76.7 × (CysC in mg/L)−1.19</td>
</tr>
<tr>
<td></td>
<td>*eGFR (mL/min/1.73 m2) = 76.7 × (−0.105 + 1.13 × CysC in mg/L)−1.19</td>
</tr>
<tr>
<td>CKD-EPI Equation 10112</td>
<td>eGFR (mL/min/1.73 m2) = 177.6 × (Scr in mg/dL)−0.65 × (CysC in mg/L)−0.57 × (age in years)−0.20 × 0.82 [if female] × 1.11 [if black]</td>
</tr>
<tr>
<td></td>
<td>*eGFR (mL/min/1.73 m2) = 177.6 × (Scr in mg/dL)−0.65 × (−0.105 + 1.13 × CysC in mg/L)−0.57 × (age in years)−0.20 × 0.82 [if female] × 1.11 [if black]</td>
</tr>
</tbody>
</table>

Source: Adapted from Dowling (2014)
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2.6 ANTI-RETROVIRAL REGIMENS IN SOUTH AFRICA

According to ART guidelines (2010), the standard ART consists of at least three ARVs (HAART) to maximally suppress HIV and stop the progression of HIV disease. These guidelines also stipulate that treatment-naïve patients should be initiated on triple therapy, which consists of one non-nucleoside reverse transcriptase inhibitor [NNRTI such as nevirapine(NVP) or efavirenz(EFV)], and two NRTIs, TDF and lamivudine (3TC)/emtricitabine (FTC).

ART guidelines, (2010), recommend TDF as the drug of choice for all new patients needing treatment (treatment-naïve patients) unless there is a contraindication.

According to the ART guidelines, (2010, 2011 and 2015), TDF is contraindicated when CrCl is <50ml/min, and in that case zidovudine (AZT) is the replacement drug.

2.7 HEALTH CARE PROFESSIONAL COMPLIANCE TO ART GUIDELINES

The ART guidelines (2010), (same as ART guidelines, 2013 and ART guidelines, 2015) promote TDF containing regimen as the first line regimen for all new patients needing treatment. Renal disease or the use of other nephrotoxic drugs such as aminoglycosides was cited as the contraindication to TDF.

According to Dowling (2014) accurate measurement of GFR in clinical practice is a critical variable for individualization of the dosage regimens of renally excreted medications so that one can maximize their therapeutic efficacy and avoid potential toxicity.

Renal function monitoring also presents HCPs a chance to adjust drug dosages where necessary, for example, Rossiter (2014) recommends the following dosage regimen for 3TC when GFR is below or equal to 50ml/min:

- GRF 10-50ml/min: 150mg first dose then 50 to 150mg 24 hourly
- GFR<10ml/min, 50mg first dose then 25-50mg 24 hourly

According to Rossiter (2014) TDF is contraindicated when CrCl is <50ml/min, but Moosa, van der Walt, Naicker & Meyers (2015) and the guidelines for the use of antiretroviral Agents in HIV-1-Infected Adults and Adolescents (2015) recommend the following:

- CrCl 30-49ml/min, 300 mg 48 hourly
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- **CrCl 10-29 ml/min**, 300mg twice weekly (every 72-96 hours)
- **CrCl<10** and not on haemodialysis (HD), no recommendation/has not been studied
- **On HD**, 300mg every 7th day

It is important to note that, once a patient has a CrCl below 50 ml/min they need to be urgently referred and if that is not possible they need to be treated in consultation with a specialist, preferably a nephrologist.

Vawda & Variawa (2012) report that the HIV/AIDS epidemic represents a major public health crisis in our country and, in as much as various critical policies and programmes have been devised in response, the key to a successful outcome lies in the hands of the HCPs tasked with implementing such strategies. Vawda & Variawa (2012) further report that the National Strategic Plan (NSP) on HIV, sexually transmitted infections (STIs) and tuberculosis (TB) (2007-2011) advocated ‘task shifting’ in order to alleviate the burden on the HCPs and thus improve the level of care they provided. Task shifting entails the training of lesser qualified HCPs to perform tasks which they were previously not trained to do or tasks that were beyond their practice such as allowing trained nurses to initiate ART.

In the very same report Vawda & Variawa (2012) cite that South Africa has implemented task shifting since 2010 but to date, no large scale objective study has been undertaken with regard to the success, efficacy and or shortcomings of this approach.

Mbilinyi, Daniel & Lie (2011), reported that HCPs especially the nurse midwives felt that they lacked the right skills to attend to people living with HIV (PLWHIV). Mbilinyi *et al.* (2011) further cited that the quality of staff and service provision significantly affects ARV treatment.

To the best of our knowledge, literature on HCP compliance to ART guidelines in South Africa (SA) is limited and this was confirmed by Kwhitshana *et al.* (2014) by citing that there are limited published data, both locally and internationally, for assessing adherence to these guidelines, using objective evidence based approaches such as assessing prescriptions and the choice of laboratory tests associated with specific drug regimens, as delineated in the guidelines. The above mentioned underscores the need for and importance of this study.
2.8 SUMMARY

The literature discussed in this chapter highlights the need and the importance of closely monitoring kidney function of HIV patients, especially those at risk of developing kidney disease, those on tenofovir based ART, the elderly and co-morbid conditions such as HT and DM. The need for HCPs to follow the ART guidelines in monitoring kidney function is illustrated. The patients that require close monitoring (high risk patients) are described.

In the next chapter the study methodology is described.
3.1 INTRODUCTION

This chapter presents the methodology. The chapter starts with a discussion of study site and the study design. This is followed by the study population and sample used in the study. The data collection process is explained and the data collection instruments are described in detail in subsequent sections. Data entry and analysis are described as well as methods put in place to ensure the reliability and validity of the data. The chapter ends with a discussion of the ethical considerations for this study.

3.2 STUDY DESIGN

The study was a retrospective observational study, where patient records (files) were reviewed to obtain the necessary data.

3.3 STUDY SITE

The study was conducted in Bokamoso Clinic, an ART clinic, at Odi District Hospital located in Mabopane, South Africa. According to Odi hospital information (2014), the hospital is a level one facility serving a catchment population of 524 632 in Gauteng Province and 324 183 from Northwest Province. The approved number of beds is 227, whilst the usable number is 198 (one ward was converted into the consulting rooms for Allied HCPs) (Odi Hospital Statistical information 2014).

The statistical information reveals that an average of 3 564 patients remained on ART at the end of each month (Odi Hospital Statistical information 2014).

The general staff establishment at Bokamoso Clinic as per information extracted from the register (April 2015) is: one pharmacist, two pharmacist assistants, seven professional nurses, four enrolled nurses, six enrolled nursing assistants, one dietician, one social worker, one data capturing clerk, two administration clerks, and eight counsellors. There are two permanent medical officers and one registrar allocated to Bokamoso clinic.
Chapter 3: Method

3.4 STUDY POPULATION

The study population was estimated based on the August 2012 statistics. The cumulative number of patients (including active patients, those transferred out, lost to follow up, deceased or stopped treatment) for the month of August 2012 was 10,724 (personal communication). The total number of patients that received a TDF containing regimen in the month of August 2012 was 4,493 (see Table 3.1 below):

Table 3.1: Number of patients per month on TDF containing regimen

<table>
<thead>
<tr>
<th>Cumulative number of patients</th>
<th>Patients on Therapy (n=10724)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ART</td>
</tr>
<tr>
<td>Active patients</td>
<td>4,640</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>3,455</td>
</tr>
<tr>
<td>Deceased</td>
<td>536</td>
</tr>
<tr>
<td>Transferred out</td>
<td>1,881</td>
</tr>
<tr>
<td>Stopped</td>
<td>212</td>
</tr>
</tbody>
</table>

Source: adapted from August statistics, using the SOZO data management system (Bokamoso clinic: 2012)

From Table 3.1 (information from the clinic statistics), it is evident that 4,493 patients received TDF containing regimen in August 2012. According to the Pharmacy statistics 2,244 patients received treatment during this period. An average of 1,173 patients received TDF containing regimen each month in 2012.
Table 3.2 denotes the number of patients that received a TDF containing regimen from January 2012 to December 2012.

## Table 3.2: Gauteng ARV Patient Monitoring statistics 2012: Odi Hospital

<table>
<thead>
<tr>
<th>Regimens (Adults)</th>
<th>Jan-12</th>
<th>Feb-12</th>
<th>Mar-12</th>
<th>Apr-12</th>
<th>May-12</th>
<th>Jun-12</th>
<th>Jul-12</th>
<th>Aug-12</th>
<th>Sep-12</th>
<th>Oct-12</th>
<th>Nov-12</th>
<th>Dec-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF,3TC,NVP</td>
<td>208</td>
<td>137</td>
<td>151</td>
<td>183</td>
<td>232</td>
<td>107</td>
<td>255</td>
<td>371</td>
<td>136</td>
<td>245</td>
<td>225</td>
<td>7</td>
</tr>
<tr>
<td>TDF,3TC,EFV</td>
<td>373</td>
<td>831</td>
<td>756</td>
<td>955</td>
<td>1277</td>
<td>562</td>
<td>1259</td>
<td>1756</td>
<td>1063</td>
<td>946</td>
<td>839</td>
<td>444</td>
</tr>
<tr>
<td>TDF,3TC,LPV/r</td>
<td>60</td>
<td>63</td>
<td>54</td>
<td>62</td>
<td>91</td>
<td>27</td>
<td>63</td>
<td>117</td>
<td>38</td>
<td>51</td>
<td>98</td>
<td>39</td>
</tr>
<tr>
<td>TOTAL</td>
<td>641</td>
<td>1 031</td>
<td>961</td>
<td>1 200</td>
<td>1 600</td>
<td>696</td>
<td>1 577</td>
<td>2 244</td>
<td>1 237</td>
<td>1 242</td>
<td>1 162</td>
<td>490</td>
</tr>
</tbody>
</table>

Source: Adapted from Odi Pharmacy Statistics, 2012
3.5 SAMPLE SELECTION

Files were chosen using systematic random sampling techniques, where every tenth file was chosen until the statistically calculated sample size of 500 evaluable cases could be reached.

Inclusion criteria

- Patients who had been on TDF-based regimen for more than twelve months
- Adult patients (over 18 years of age)
- No previous kidney injury (GFR > 60 ml/min/1.73 m²)

Exclusion criteria

- Pre-existing kidney disease at initiation of TDF containing HAART as denoted by decreased GFR (<60 ml/min/1.73 m²) and raised serum creatinine, Scr (>100 µmol/L)
- Patients who were exposed to ART before they were switched to a TDF containing HAART
- Patients who were previously exposed to ART through prevention-of-mother-to-child (PMTCT) programme or post exposure prophylaxis (PEP)

3.6 DATA COLLECTION AND DATA COLLECTION INSTRUMENTS

The data collected included patient demographics, disease condition(s), specialists(s) seen, Scr and GFR and list of medications.

The data collection process was carried out as outlined in the following diagrammatic expression presented in Figure 3.1.
Figure 3.1: Data Collection Procedure

Similar to an American study conducted by Gupta et al. (2011), the study was a retrospective analysis of data within the medical records and the individuals included in the study were those who were at least 18 years of age, had not previously received ART, had complete enrolment data available for estimation of renal function (age, sex, serum creatinine, weight) and other variables of interest included: CD$_4$ cell count, viral load, height body mass index (BMI) and world health organisation (WHO) disease stage.

The study excluded those previously exposed to ART and those with pre ART kidney disease (Gupta et al. 2011).

The study collection procedure also mimicked that by Young et al. (2007) where diagnoses, treatments and laboratory values were also collected.
3.6.1 Data collection Instrument

The instrument used was a data collection form (Appendix A) adapted from (ART guidelines, 2010; Gupta et al., 2011; Young et al., 2007), in accordance with the objectives of the study. The form was divided into four sections:

Section A was largely used to collect data on demographics of participants, co-morbid condition(s) and other medicines the participant was taking during the study period.

Section B explored data on HCWs adherence to ART guidelines (2010), e.g. whether or not health care professionals monitored the kidney function at initiation of TDF as recommended in the ART guidelines.

Section C was used to record the ART regimen the participant was taking at stipulated intervals. Where there was a change in the regimen, the reasons for change were also recorded in this section.

Section D was used to record data collected on whether or not HCPs monitored CD4 count, VL and Scr (CrCl) at follow-up visits as per ART guidelines (2010).

3.7 PILOT STUDY

The pilot study was conducted after the ethical clearance was received from Sefako Makgatho Health Sciences University Research Ethics Committee (SMUREC) (Appendix B) and the letter of approval received from the Chief Executive Officer of Odi District hospital (Appendix C). According to van Teijlingen and Hundley (2002), the pilot study aids in developing and testing the adequacy of research instruments and in identifying logistical problems which might occur using proposed methods. The first five files were used to evaluate the feasibility of the study and to understand the work flow at Bokamoso ART clinic. Through this mini study the researcher learned that the clerks were not always available to hand over the files but had to personally find the files from the shelves.

3.8 DATA COLLECTION

3.8.1 Data collection period

The study was conducted over a 21 months period from November 2013 to July 2015.
3.8.2 Enrolment and data collection

Data collection only commenced after ethical approval for the study was obtained from the Sefako Makgatho Health Sciences University Research Ethics Committee (SMUREC) (Appendix B) and permission to conduct the study was granted by the hospital chief executive officer (CEO) (Appendix C). All data was collected by the researcher, who is a pharmacist.

3.9 DATA ENTRY AND ANALYSIS

All the available data (data necessary to address all objectives) was captured as per the data collection form described above (see Appendix A).

Microsoft Excel™ software was used as the tool for data analysis.

Once the research was completed, the researcher descriptively analysed the data with the help of a statistician. The statistical analysis was done on Statistical Analysis System (SAS) [(SAS Institute Inc, Carey, NC, USA), Release 9.3, running under Microsoft Windows for a personal computer. All the data was summarised, described and organized in accordance with the objectives. The analysis was supported by figures and graphs.

Data was entered by the researcher on six different Excel™ spreadsheets. The spreadsheets were designed with the help of a statistician. These spreadsheets were designed and labelled (Sections A1, A2, A3, B, C and D) in accordance with the tools used to collect data.

Section A1 was used to enter the participant's identification number (ID), the demographic data and the world health organisation (WHO) staging. Section A2 was used to enter co-morbid conditions and the ICD codes. Section A3 was used to enter the current medicine regimen (drug name, strength, DDD and ACT). Section B was used to enter the following variables: Scr, CrCl, VL, CD₄ count and ART regimen initiated. Section C was used to enter the ART regimen followed for one year (three, six and twelve months) from the date of initiation. The reason for any change in regimen at the above mentioned intervals was entered in this section. Section D was used to enter the variables specified in section B (Scr, CrCl, VL, CD₄ count) at three, six and twelve months into therapy. In this section, a tick (√) in the Y (Yes) or N (No) box was used to indicate if Scr, CrCl, VL, CD₄ count was done or not at month three, six and at month 12. This information aided in determining the compliance of the HCPs with the guidelines.
Chapter 3: Method

The entries were double checked by the supervisor to ensure accuracy before the captured data was sent to the statistician for analysis.

3.10 RELIABILITY AND VALIDITY

Data was collected only by the researcher and cross-checked by the supervisor. File numbers were recorded to serve as reference and proof of data collected. Files were selected based on the inclusion criteria. An independent pharmacist was recruited (for the purposes of the study and was independent to the researcher and the supervisor) to evaluate the files and the recordings made on the data collection form.

Results obtained were analysed as comprehensively as possible with the assistance of a statistician and compared to available literature so that the results could be placed in a realistic content.

According to Kimberlin & Winterstein (2008) reliability (consistency) and validity (accuracy) of the measures are the key indicators of the quality of a measuring instrument.

Kimberlin & Winterstein (2008) also state that reliability estimates evaluate the stability of measures, internal consistency of measurement instruments, and interrater reliability of instrument scores. Suresh, Thomas & Suresh (2011) describes reliability as the extent to which a measuring technique consistently provides the same results if the measurement is repeated.

Validity is often defined as the extent to which an instrument measures what it purports to measure. Suresh et al. (2011) describes validity as the degree to which the investigative goals are measured accurately. Suresh et al. (2011) further cite that validity and reliability together determine the accuracy of the measurement, which is essential to make valid statistical inference from medical research.

That is, where necessary, the researcher shall attempt to communicate and seek clarity about particular ARV prescriptions which may not be clearly defined according the ART guidelines (2010). Disagreements between the researcher and other related health officials were resolved through discussion and review of the ART guidelines (2010). The renal impairment assessed was discussed with the treating physician and research supervisors to determine if there was causality between the renal failure and other diseases.
According to this criterion, the following categories were used to classify, analyze data, and describe TDF and renal failure:

- Development of kidney disease where none was observed at baseline
- Worsening kidney disease after the introduction of TDF containing regimen

According to literature reviewed by De Coster, McLaughlin & Noseworthy (2010), the most common criterion for referral to nephrologists is either GFR or Scr. For the purpose of this study, the development and worsening of kidney disease was marked by a decreasing calculated CrCl or eGFR and increasing Scr.

3.11 ETHICAL CONSIDERATIONS

In order to ensure research integrity, the researcher in this study had an obligation to ensure that the research was conducted in an environment which reflected the code of ethics for the profession of a pharmacist as guided by the South African Pharmacy Council (SAPC). In other words, all patient-related information, which was accessed as a part of the data collection for the proposed study, was handled according to the stipulations of the privacy rule as per the professional code of ethics for pharmacists and health care professionals.

Data collection was conducted after approval had been received from SMUREC, (SMUREC number: MREC/H/182/2013: PG) (refer to Appendix B for the ethics certificate) as well as approved consent from the CEO of ODI Hospital (see Appendix C).

Prior to the commencement of the study, the researcher ensured that an information session was conducted for all relevant stakeholders (for instance: All Bokamoso staff members, including the head of the department, the clerks, the medical officers, nurses and pharmacists (see Appendices E, F and G: Study Summary, List of signatures for members who attended the information session and PowerPoint presentation, respectively). The Executive Committee (EXCO) of the Hospital each received a copy of the protocol for perusal. Only data relevant to the objectives of this study were documented. A coding system was used to protect the identity of the patients thus ensuring confidentiality.

This research was a retrospective study and only involved the recording of previously collected data. Therefore no consent of any patient was required.
3.12 SUMMARY

This chapter provides a comprehensive discussion of the method used in the study. The study was a retrospective observational study and it was conducted at Odi District Hospital (ART clinic named Bokamoso) located in Mabopane (Pretoria), South Africa.

Evaluable patient records were selected; they all had to meet the inclusion criteria as described in this chapter.

The study was conducted over a period of 2 years (2013 to 2015). Data collection tools, reliability and validity as well as the method to ensure ethical clearance have been described. The SREC and SMUREC both approved the study and issued an ethical clearance. The hospital CEO gave permission to conduct the study. There was no need to obtain consent from patients as this study was a retrospective study.

The results of the data collected, will be presented and discussed as a manuscript in Chapter 4.
CHAPTER 4
MANUSCRIPT

4.1 INTRODUCTION

This chapter will present the study findings and discussion in a manuscript format and will be submitted to a peer reviewed journal. The journal selected is the South African Journal of HIV Medicine (SAJHIVMED). The guidelines for authors are attached as Appendix D.

MANUSCRIPT

An investigation into the compliance of Health Care Workers to monitoring of renal function of patients treated with tenofovir at Odi Hospital in Gauteng Province

Abstract

Background:

By the end of 2010 South Africa (SA) had the largest human immunodeficiency virus (HIV) treatment programme in the world, with 1.3 million people receiving antiretroviral therapy (ART). However, burdensome adverse effects, although varying in their impact, have concerned government, health care professionals (HCPs) and patients. The adverse effects include ART renal dysfunction which is often associated with tenofovir disoproxil fumarate (TDF). The National Department of Health of South Africa (NDoHSA) published clinical guidelines in 2010 (ART guidelines, 2010) for the management of HIV and AIDS in adults and adolescents. These guidelines were written to minimize unnecessary drug toxicities and enable primary health care facilities to initiate, manage, monitor and refer patients.

Objectives:

The objectives of the study were to investigate the compliance of health care professionals (HCPs) with the ART guidelines (2010) in monitoring the renal function of patients on tenofovir in the years 2010 and 2012, to retrospectively investigate the renal function of patients initiated on TDF as part of first line regimen.
Method:

The study was a retrospective observational study where a purposive sampling procedure was used to select the sample of 500 patient cases from an estimated population of 4,493, i.e. 11.1% of the population (a 95% confidence interval for the percentage in about 10.2% to 12.1%). These records were reviewed to obtain the necessary data and then audited for compliance by HCPs in monitoring laboratory tests, in particular kidney function tests (Scr and CrCl) for patients on TDF.

Results:

About 65% of the study participants were female. The median serum creatinine (Scr) remained below 100µmol/l at all visits. Median creatinine clearance (CrCl) remained stable at Kidney Disease: Improving Global Outcomes (KDIGO) stage 2(60-89ml/l) of chronic kidney function (CKD). Median CD$_4$ count increased with each visit demonstrating the strengthening immune system while the median viral load (VL) remained unsuppressed at all visits increasing the CKD risk. The mean monitoring intervals were wide at 11 months, 24 months and 34 months from baseline for visit 1, visit 2 and visit 3 respectively.

Conclusion:

The renal function of patients that were initiated and remained on tenofovir was poorly monitored by HCPs. CD$_4$, VL and Scr (CrCl) were not taken at all visits and where it was done the intervals did not correspond to what was prescribed by the guidelines as set out by the NDoH (2010).

Introduction

Background

Chronic kidney disease (CKD) has become an important comorbidity among human immunodeficiency virus (HIV)-infected persons. $^{(1)}$ The use of antiretroviral therapy (ART) has contributed to the lower incidence of HIV associated nephropathy (HIVAN), one of the common findings among patients with acute renal failure (ARF) in the pre-HAART era. $^{(2)}$ HIV has been shown to be directly involved in renal damage. Primary tubular abnormalities may be missed until they affect the glomerular function; a specific and early screening is thus necessary to prevent them. $^{(3)}$

Since the introduction of highly active antiretroviral therapy (HAART), the number of deaths due to opportunistic infections (OIs) has significantly declined, with a greater proportion of patients
developing chronic conditions not traditionally related to HIV, such as liver, and kidney disease.\(^1,3\)

The effects of HAART leads to the accumulation of factors that are harmful for renal function: ageing, comorbidities such as hypertension (HT), diabetes (DM), hyperlipidemia and adverse effects of antiretroviral drugs (ARVs) such as indinavir (IDV) and tenofovir disoproxil fumarate (TDF). These factors are likely to increase the frequency of acute renal failure (ARF) or CKD.\(^4,5\) Low CD\(_4\) count and high plasma viral load (VL) are also counted among the risk factors for renal diseases in persons living with HIV.\(^1,5,6,7\) Viral load>4000 copies/ml is a risk factor for CKD.\(^8,9\)

The number of patients diagnosed with end stage renal disease (ESRD) continues to grow around the world.\(^10\) By 2030 more than 70% of patients with ESRD are estimated to be living in low income countries, such as sub-Saharan Africa.\(^11\) Advances in the management and treatment of the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) have transformed HIV into a chronic condition rather than a debilitating terminal illness.\(^12,13\) By the end of 2010 South Africa (SA) had the largest HIV treatment programme in the world, with 1.3 million people receiving ART.\(^12\) However, burdensome adverse effects, although varying in their impact, have concerned government, health care professionals (HCPs) and patients.\(^12,14\)

HIV-CKD is compounded by the nephrotoxic potential of long term ART,\(^15,16\) for example, TDF, an oral prodrug of tenofovir. TDF is a nucleotide reverse transcriptase inhibitor, indicated for use in ART–naive patients which has been associated with renal failure and renal tubular dysfunction.\(^17\) Patients with HIV are also at an increased risk of non-ART drug induced renal toxicity; most commonly associated with trimethoprim-sulphamethoxazole (TMP-SMZ), also known as co-trimoxazole.\(^18\)

The National Department of Health of South Africa (NDoHSA) published their first clinical guidelines for the management of HIV infection in 2010 (ART guidelines, 2010).\(^14\) These guidelines were written to minimize unnecessary drug toxicities and enable primary health care facilities to initiate, manage, monitor and refer patients. These guidelines stipulate intervals for monitoring of renal function. Serum creatinine and creatinine clearance (CrCl) have to be monitored at baseline, three months, six months and then every twelve months for patients on TDF in order to identify early toxicity. According to these guidelines, compliance by HCPs to monitoring kidney function will assist in early detection of renal dysfunction which will allow for
appropriate (timely) intervention. Patients with kidney disease should be referred at an early stage so as to institute measures to retard progression and plan timely adequate treatment.\(^{(19)}\)

The latest consolidated ART guidelines were published in 2014 and implemented in January 2015.\(^{(20)}\) Just like the 2010 and 2013 ART guidelines,\(^{(21)}\) the latest guidelines still promote the TDF containing regimen as the first line regimen for all patients, including pregnant women,\(^{(14, 20, 21)}\) but emphasize monitoring the levels of Scr in order to identify TDF toxicity.

Late evaluation of patients with CKD, especially close to the time of starting dialysis, is associated with sub-optimal pre-end stage renal disease (ESRD) management and mortality risk.\(^{(22)}\) Optimal health outcomes are more likely if caring for these patients from the time creatinine elevation is discovered.\(^{(23)}\) Potential benefits of early referral include identifying and treating reversible causes of renal failure, slowing the rate of decline associated with progressive renal insufficiency and managing the multiple co-existing conditions associated with CKD.\(^{(24)}\) Kidney function has been estimated to be abnormal in up to 30% of HIV infected patients. Other metabolic complications such as type 2 diabetes and hypertension may also contribute to the renal dysfunction over time.\(^{(24)}\) Gupta et al found that CrCl<60ml/min or estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m\(^2\) at enrollment (initiation) was independently associated with an increased risk of HIV disease progression.\(^{(8)}\)

To the best of our knowledge, literature on HCP compliance to ART guidelines in South Africa (SA) is limited and this was confirmed by Kwhitshana et al (2014), by citing that there are limited published data, both locally and internationally, for assessing adherence to these guideline using objective evidence based approaches such as assessing prescriptions and the choice of laboratory tests associated with specific drug regimens, as delineated in the guidelines. The above mentioned underscores the need for and importance of this study.

**Research method**

**Study design and Setting**

The study was a retrospective observational study, where patient records (files) were analysed. The study was conducted in an ART clinic, Bokamoso Clinic at Odi District Hospital located in Mabopane, South Africa. The hospital is a level one facility serving a catchment population of 52 4632 in Gauteng Province and 32 4183 in Northwest Province.

**Study Population and Sample Selection**
The medical records of 500 adult patients (> 18 years of age) who had been on TDF-based regimen (ART naive at initiation) for more than twelve months and had no previous kidney injury, i.e. CrCl > 60 ml/min were eligible for inclusion into the study. The purposive sampling procedure was used to select the study sample of 500 patient cases from an estimated population of 4,493, i.e. 11.1% of the population (a 95% confidence interval for the percentage in about 10.2% to 12.1%).

The medical records of those with pre-existing kidney disease at initiation of TDF containing ART as denoted by decreased CrCl (<60 ml/min/1.73 m2) and raised serum creatinine, Scr (>100 µmol/l) were excluded from the study.¹⁴, ²⁵

The general staff establishment at Bokamoso Clinic as per information extracted from the register: one pharmacist, two pharmacist assistants, seven professional nurses, four enrolled nurses, six enrolled nursing assistants, one dietician, and one social worker, one data capturing clerk, two administration clerks, and eight counsellors. There are two permanent medical officers and one registrar allocated to Bokamoso clinic.

The study population was estimated based on the August 2012 statistics. The cumulative number of patients (including active patients, those transferred out, lost to follow up, deceased or stopped treatment) for the month of August 2012 was 10,724. The total number of patients that received a TDF containing regimen in the month of August 2012 was 4,493.

**Data Collection and analysis**

CrCl was calculated using the Cockroft–Gault (C-G) equation adapted for the SI unit for Scr.²⁶

Male: CrCl = (140-age) ×weight/ (0.82×serum creatinine µmol/L)

Female: CrCl = (140-age) ×weight× 0.85/ (0.82×serum creatinine µmol/L)

A data collection instrument that was adapted from ART guidelines (2010); Gupta et al. (2011); Young et al. (2007), in accordance with the objectives of the study, was used to retrospectively collect patient demographics, co-morbid conditions and other medicines, laboratory tests (CD4 cell count, viral load, Scr and CrCl). Adherence to ART guidelines (2010), e.g. whether or not health care professionals monitored the kidney function at initiation of TDF as recommended in the ART guidelines, record the ART regimen and where there was a change in the regimen and the reasons for change were also recorded.
Once the research was completed, the researcher descriptively analysed the data. The statistical analysis was done on Statistical Analysis System (SAS) [(SAS Institute Inc, Carey, NC, USA)], Release 9.3, running under Microsoft Windows for a personal computer. All the data was summarised, described and organised in accordance with the objectives. The analysis was supported by figures and graphs.

**Ethical consideration:** Ethical approval for the study was obtained from the Sefako Makgatho Health Sciences University Research Ethics Committee (SMUMREC): MREC/H/182/2013: PG., as well as permission and consent from the Odi Hospital management respectively. An information session was held with all stakeholders of the various hospital sections (Clinic, pharmacy department and administrative clerks) prior to securing their approval and consent. The research was retrospective and only involved the records of prescriptions received by patients. For that reason no consent from any patient was required.

**Results**

From the total population of this study which comprised of 500 (100%) evaluable cases, the sample size for CD4 count reduced by 0.6%, 5.8% and 30.2% at first visit (V1), second visit (V2) and third visit (V3) respectively and is illustrated by Figure 1. This was true for both Scr and CrCl markers (Figure 1). The similar trend was observed with CD4 count and VL marker. Of note is the relatively low sample size for VL (five at baseline, 88 at V1, 85, and 59 in relation to the sample for other markers) which makes it difficult to report reliable trends.
Figure 1: Sample size for count at baseline, V1, V2 and V3

Note: *Lost to follow up, no further records could be found in the file
V=visit

Demographics of the study population

As seen in Table 1, the sample comprised of a study sample with 65.4% female and 34.6% male. The median age was 37 (IQR: 32-44) years. All participants were of black ethnicity group. The majority of the participants (37%) were at World Health Organisation (WHO) stage 3, at baseline. The vast majority of participants were initiated on regimen 1.

Co-trimoxazole and non-steroidal anti-inflammatory drugs (NSAIDs) were the most co-prescribed nephrotoxic agents at 97.6% and 57.42% respectively. Angiotensin converting enzyme (ACE) inhibitors were the least prescribed nephrotoxic agents at 1.5%.

About 74% of participants had a CD4 cell count of $\leq 200$ cells/$\mu$L. This included 21.8% who had a CD4 cell count of $\leq 50$ cells/$\mu$L. VL was only performed in five of 500 participants. Approximately 42% of participants had CrCl $\leq 60$ ml/min at initiation indicating the need for close kidney function monitoring. Body mass index (BMI) was not calculated for all participants since the height was not routinely recorded.
Table 1: Demographic and treatment detail at baseline (n=500)

<table>
<thead>
<tr>
<th>Age in years, median(IQR)</th>
<th></th>
<th>37(32-44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, n (%)</td>
<td>18-30</td>
<td>96(19.2)</td>
</tr>
<tr>
<td></td>
<td>31-40</td>
<td>215(43.0)</td>
</tr>
<tr>
<td></td>
<td>41-50</td>
<td>139(27.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>50(10.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender, n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>327</td>
<td>65.4</td>
</tr>
<tr>
<td>Male</td>
<td>173</td>
<td>34.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity, n (%)</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>500</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO Staging, n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>2(10.4)</td>
</tr>
<tr>
<td>2</td>
<td>91</td>
<td>18.2</td>
</tr>
<tr>
<td>3</td>
<td>185</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>11.4</td>
</tr>
<tr>
<td>Unknown</td>
<td>157</td>
<td>31.4</td>
</tr>
</tbody>
</table>

| Weight(kg), median(IQR)    |          | 58.05(51.65-66.85) |

| Co-morbid conditions, n (%)|          | Hypertension 52(10.4) |
|                           |          | Diabetes 2(0.4)       |
|                           |          | Co-trimoxazole 488(97.6) |
|                           |          | NSAIDS 287(57.42)     |
|                           |          | ACE Inhibitors 6(1.5) |

| Nephrotoxic drugs, n (%)  |          | Regimen 1 434(86.8) |
|---------------------------|----------| Regimen 2 62(12.4)  |
|                           |          | Regimen 3 4(0.8)    |

| ART regimen, n (%)        |          | n = 5, 394224(79033-547598) |

| VL(copies/ml), median(IQR)|          |           |

|                            |          | n = 5, 394224(79033-547598) |
### CD$_4$(cells/µL), Median(IQR)

<table>
<thead>
<tr>
<th>CD$_4$(cells/µL)</th>
<th>Median(IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50</td>
<td>112(56 – 177)</td>
</tr>
<tr>
<td>51-200</td>
<td>209(62.2)</td>
</tr>
<tr>
<td>201-350</td>
<td>61(12.2)</td>
</tr>
<tr>
<td>351-500</td>
<td>4(0.8)</td>
</tr>
</tbody>
</table>

### Scr(µmol/L)

<table>
<thead>
<tr>
<th>Scr(µmol/L)</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>73.43±34.60</td>
<td>Normal range: 49-90 µmol/L for females and 60-104 µmol/L for males</td>
</tr>
</tbody>
</table>

### CrCl(ml/min)(mean±SD) [CKD Staging]

<table>
<thead>
<tr>
<th>CrCl(ml/min)</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>* CrCl&gt;90(CKD stage 1)</td>
<td>67(13.40)</td>
</tr>
<tr>
<td>CrCl 60-89(CKD stage 2)</td>
<td>214(42.80)</td>
</tr>
<tr>
<td>CrCl 30-59(CKD stage 3)</td>
<td>207(40.40)</td>
</tr>
<tr>
<td>CrCl 15-29(CKD stage 4)</td>
<td>10(2)</td>
</tr>
<tr>
<td>CrCl&lt;15(CKD stage 5)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Adapted from Hudson & Wazny in DiPiro, 2014.

Note: height measurement was never recorded in the participant records.

**WHO**, World Health Organisation; **NSAIDS**, non-steroidal anti-inflammatory drugs; **ACE**, Angiotensin converting enzyme; **ART**, antiretroviral therapy; **VL**, viral load; **Scr**, serum creatinine; **CrCl**, creatinine clearance; **CKD**, chronic kidney disease

### Laboratory results

The laboratory results are summarised in Table 2. Of note is the declining sample size with each visit for all markers: CD$_4$ count, VL and Scr. The median CD4 count demonstrated an increase with each visit (<200 cells/µL at baseline and > 200 cells/µL at all successive visits). The sample size for VL was notably low at all visits in relation to other markers (CD$_4$ count and Scr/CrCl).

The median Scr remained within a normal range at all visits. CrCl remained stable at CKD stage 2 as illustrated in Table 2 below.
### Table 2: CD4, Viral Load (VL), Serum Creatinine (Scr) and Creatinine Clearance (CrCl) at baseline, 1st, 2nd and 3rd visit.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Baseline</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4 (cells/μL)</strong></td>
<td>n= 500</td>
<td>n=499</td>
<td>n=459</td>
<td>n=281</td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td>112(56-177)</td>
<td>283(183-394)</td>
<td>364(253-478)</td>
<td>408(289-552)</td>
</tr>
<tr>
<td><strong>VL (copies/ml)</strong></td>
<td>*n= 5</td>
<td>n=88</td>
<td>n=85</td>
<td>n=59</td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td>394224(79033-547598)</td>
<td>531(103-29134.5)</td>
<td>500(115-28721)</td>
<td>2683(125-50413)</td>
</tr>
<tr>
<td><strong>Scr(μmol/L)</strong></td>
<td>n= 500</td>
<td>n=497</td>
<td>n=471</td>
<td>n=349</td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td>69(59-82)</td>
<td>70(57-83)</td>
<td>72(58-85)</td>
<td>62.9(50.46-77.6)</td>
</tr>
<tr>
<td><strong>CrCl(ml/min)</strong></td>
<td>n= 500</td>
<td>n=497</td>
<td>n=471</td>
<td>n=349</td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td>62.9(50.46-77.6)</td>
<td>68.8(54.85-85.76)</td>
<td>66.4(52.45-88.54)</td>
<td>69.18(53.53-88.08)</td>
</tr>
<tr>
<td></td>
<td>[CKD stage 2]</td>
<td>[CKD stage 2]</td>
<td>[CKD stage 2]</td>
<td>[CKD stage 2]</td>
</tr>
</tbody>
</table>

*Sample size too small for meaningful analysis

### Monitoring intervals in the first twelve months of ART initiation (HCP Compliance to ART guidelines, 2010)

The mean monitoring intervals and ranges at all three visits were similar (Table 3) for CD4 and VL. In general (on average), the monitoring was done at baseline, nine months(V1), 21 months(V2) and 31 months(V3) instead of the intervals as recommended by the ART guidelines (2010), baseline, six months (V2) and 12 months(V3) monitoring intervals. On average, the Scr/CrCl was monitored at 11, 24 and 34 months instead of the intervals as recommended by the National Department of Health, ART guidelines (2010), baseline, three months (V2), six months (V2) and 12 months (V3) monitoring intervals.
The intervals between visits ranged from 0 to 46 for both Scr and CrCl. There were participants who were monitored within a month of initiating ART and those who were monitored at 46 months for V1. As seen in Table 3, a similar pattern applies to other markers (CD4 and VL).

Table 3: Monitoring intervals (months) for markers: CD4, VL, Scr and CrCl

<table>
<thead>
<tr>
<th>Marker</th>
<th>Baseline</th>
<th>V1(Mean interval)</th>
<th>V1(Range)</th>
<th>V2(Mean interval)</th>
<th>V2(Range)</th>
<th>V3(Mean interval)</th>
<th>V3(Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>9</td>
<td>1-36</td>
<td>21</td>
<td>4-41</td>
<td>31</td>
<td>10-51</td>
<td></td>
</tr>
<tr>
<td>VL</td>
<td>9</td>
<td>1-38</td>
<td>21</td>
<td>4-47</td>
<td>32</td>
<td>1-52</td>
<td></td>
</tr>
</tbody>
</table>

Should be monitored at baseline, 6 months(V2) and 12 months(V3)

| Scr    | 11       | 0-46              | 24        | 2-45              | 34        | 2-53              |
| CrCl   | 11       | 0-46              | 24        | 2-45              | 34        | 2-53              |

Renal function of the study population

Table 4 indicates that 24 % (124, n=500) of the participants were initiated on TDF containing ART at CrCl<50 ml/min despite the contraindication as stipulated in the National Department of Health ART guideline. This percentage slightly decreased and was reported at 21.7% by V3. The percentage of those participants that were initiated at CrCl between 50 to 60 ml/min also decreased from 19.2% to 11.7% by V3. The percentage of those initiated at CrCl>60ml/min increased from 56.6 to 67.34 by V3 (Illustrated by Table 4).
<table>
<thead>
<tr>
<th>Marker</th>
<th>Visits</th>
<th>N</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl&lt;50(ml/min): TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>contraindicated</td>
<td>Baseline</td>
<td>500</td>
<td>121</td>
<td>24.2</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>497</td>
<td>93</td>
<td>18.71</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>471</td>
<td>94</td>
<td>19.96</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>349</td>
<td>76</td>
<td>21.78</td>
</tr>
<tr>
<td>CrCl : 50-60(ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>Baseline</td>
<td>500</td>
<td>96</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>497</td>
<td>73</td>
<td>14.69</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>471</td>
<td>79</td>
<td>16.77</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>349</td>
<td>39</td>
<td>11.7</td>
</tr>
<tr>
<td>CrCl ≥ 60ml/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF indicated</td>
<td>Baseline</td>
<td>500</td>
<td>283</td>
<td>56.6</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>497</td>
<td>331</td>
<td>66.60</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>471</td>
<td>298</td>
<td>63.27</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>349</td>
<td>235</td>
<td>67.34</td>
</tr>
</tbody>
</table>

Note: CrCl, creatinine clearance; N, sample size; f, frequency; %, percentage; V1, visit 1; V2, visit 2; V3, visit 3
Chapter 4: Manuscript

The CrCl results for participants at CKD stages 1-2 (CrCl ≥ 60ml/min) and 3-5 (CrCl < 60ml/min) are presented in more detail in Table 5a and Table 5b respectively. Those participants with CrCl < 60ml/min require close monitoring (25, 28, 29, 30 and 31) and/or referral (management in consultation with a specialist). At all visits (baseline to V3), the percentage of participants at each stage remained relatively stable.

Table 5(a): (Chronic kidney failure stages 1-2) at baseline 1st visit, 2nd visit and 3rd visit

<table>
<thead>
<tr>
<th>CrCl ≥ 60ml/min (in detail)</th>
<th>Visit</th>
<th>N</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 90ml/min</td>
<td>Baseline</td>
<td>500</td>
<td>67</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>497</td>
<td>102</td>
<td>20.52</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>471</td>
<td>111</td>
<td>23.57</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>349</td>
<td>81</td>
<td>23.21</td>
</tr>
<tr>
<td>60-89ml/min</td>
<td>Baseline</td>
<td>500</td>
<td>216</td>
<td>43.2</td>
</tr>
</tbody>
</table>
Table 5(b): (Chronic kidney failure stages 3-5) at baseline 1st visit, 2nd visit and 3rd visit

<table>
<thead>
<tr>
<th>CrCl&lt; 60ml/min (in detail)</th>
<th>Visit</th>
<th>N</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-59ml/min (CKD, stage 3)</td>
<td>Baseline</td>
<td>500</td>
<td>205</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>497</td>
<td>155</td>
<td>31.19</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>471</td>
<td>159</td>
<td>33.76</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>349</td>
<td>108</td>
<td>30.95</td>
</tr>
<tr>
<td>15-29ml/min (CKD, stage 4)</td>
<td>Baseline</td>
<td>500</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>497</td>
<td>11</td>
<td>2.21</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>471</td>
<td>12</td>
<td>2.55</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>349</td>
<td>5</td>
<td>1.43</td>
</tr>
<tr>
<td>&lt;15ml/min</td>
<td>Baseline</td>
<td>500</td>
<td>2</td>
<td>0.4%</td>
</tr>
<tr>
<td>(CKD, stage 5)</td>
<td>V1</td>
<td>497</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>---------------</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>V2</td>
<td>471</td>
<td>2</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>V3</td>
<td>349</td>
<td>2</td>
<td>0.57</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

In our study the majority of patients were females and all participants were of black ethnicity group. Among other risk factors (older age, hypertension, diabetes mellitus, low CD\textsubscript{4} cell count and high plasma VL) for renal disease, black race is cited in some studies as one of the risk factors for renal disease amongst persons living with HIV\textsuperscript{(1, 5, 6, 7)}. About 37\% of the participants were categorised at baseline as WHO-stage 3. Contrary to the DoH recommendation through the ART guidelines (2010), in this study WHO clinical HIV staging was not recorded at follow up visits. At stage 3 and stage 4, CD\textsubscript{4} count were <200 cells/µL, with the resultant increased risk for CKD\textsuperscript{(1, 8, 9, 32)}.

There are an estimated 5.8 million people living with HIV (PLWHIV) in South Africa. The co-existence of HIV with HT and DM is increasing and patients should be screened for associated glomerulonephritis. HIV patients with renal dysfunction (defined as eGFR<60ml/min/1.73m\textsuperscript{2}) are most likely to be older (for the purpose of this study, defined as >50 years of age\textsuperscript{33}), have DM, HT and lower baseline CD\textsubscript{4} (<200cells/µL).\textsuperscript{(1)} Our study (as illustrated in Table 5b) found that 43.4\% of participants had a baseline CrCl<60ml/min. Figure 2, indicates that of 217 participants with CrCl<60ml/min at baseline, about 17\% were older than 50 years of age, 10\% had HT and 73\% had CD\textsubscript{4} (<200cells/µL).

Seedat et al. through the South African hypertension practice guideline (2014) reports that 30.4\% of the adult population have HT,\textsuperscript{(34)} contrary to our study findings where only 10.4\% of the study population were reported to be having HT. According to the International Diabetes Federation (IDF), the prevalence of DM in SA is estimated at 6.46\%. In this study only 0.4\% had DM as a co-morbid condition.\textsuperscript{(35)} There are other studies that reported results that were similar/comparable to our findings,\textsuperscript{(3, 36)} while others were in disagreement with our findings.\textsuperscript{(5)}

Since the Bokamoso clinic focuses largely on ART and patients are treated at other clinics for other chronic conditions, there is a high chance that in this study there was underreporting of co-morbid conditions, including HT and DM.

About 97.6\% of study participants were exposed to co-trimoxazole during the study period. Lower rates of use were reported in other studies, done in France and in the United States of America, ranging from 8.4\% to 44.7\%.\textsuperscript{(1, 3, 27)}

Co-trimoxazole preventative therapy (CPT) is highly effective in preventing \textit{Pneumocystis jirovecii} pneumonia, toxoplasmosis, isosporiasis, and other bacterial pneumonias.\textsuperscript{(37)} For patients on ART,
CPT can be stopped once the CD4 count is $>200 \text{cells} / \mu\text{L}$. Co-trimoxazole preventative therapy has also been shown to decrease hospitalisation and mortality in HIV infected TB patients. As a result, CPT is recommended as part of a minimum package of care for HIV positive adults and children. \(^{(37)}\) Acute interstitial nephritis (AIN) is said to be the usual mechanism of renal toxicity associated with co-trimoxazole. \(^{(38, 39)}\) Co-trimoxazole has also been associated with acute tubular necrosis (ATN) and may interfere with renal excretion of creatinine. \(^{(39)}\) Trimethoprim (TMP) inhibits proximal tubular secretion of creatinine and can result in elevation of measured creatinine. Trimethoprim can also result in hyperkalemia by inhibiting the epithelial sodium channel at the distal convoluted tubule, which provides the driving force for potassium excretion. \(^{(39)}\)

NSAIDs usage in this study was reported at 57.42%; contrary to 27% reported by Roe et al. \(^{(2)}\) NSAIDS are widely used to relieve pain and signs of inflammation. The widespread use makes NSAIDs among the most common causes of drug induced renal injury. \(^{(39)}\) Prostaglandin (PG) inhibition mediated by NSAIDs explains many of its renal complications. AKI can occur with either non-selective NSAIDs or selective (cyclooxygenase, COX-2 specific) NSAIDs. PGs have also been shown to play a role in stimulating renin and angiotensin mediated aldosterone release. Thus NSAIDs mediated PG inhibition can result in hyperkalaemia and metabolic acidosis (hyporeninemic hypoaldosteronism). \(^{(39)}\)

Hyponatremia induced by NSAIDs is possibly related to the inhibitory effect of PGs on antidiuretic hormone (ADH) facilitated water absorption at the distal collecting tubules. \(^{(39)}\) NSAID-mediated PG inhibition is also responsible for sodium retention, which can lead to HT and oedema. \(^{(39)}\)

ACE inhibitors are widely used in the treatment of HT, congestive heart failure (CHF) and for delaying the progression of diabetic nephropathy. Angiotensin II constricts both the afferent and the efferent arterioles, but the effect is more pronounced on the efferent arteriole. \(^{(39)}\) The net effect of Angiotensin II is an increased intraglomerular pressure. This mechanism is critical in renal autoregulation, i.e., maintaining a stable GFR across a wide range of renal perfusion pressures. \(^{(39)}\) ACE inhibitors and angiotensin II receptor blockers (ARBs) antagonise the activity of angiotensin II, thereby interfering with the renal autoregulation of GFR. The loss of autoregulation could precipitate or potentiate AKI.

The co administration of NSAIDs along with ACE inhibitors or ARBs should be avoided, especially in the setting of pre-existing CKD or volume depletion (prerenal acute renal failure) due to increased risk of nephrotoxicity. \(^{(39)}\)
Even though BMI was not calculated in this study (height not recorded), the increase in weight over time may have resulted in or worsened obesity. Obesity is known to contribute directly to the risk of diabetes and hypertension, some of the frequently cited risk factors for renal disease.\(^1,4,16,24,40\)

This evaluation demonstrates that the median CD\(_4\) count increased with each visit indicating the improving immune system following ART initiation. Even though the sample size for VL marker was relatively low, unlike in the study by Gale et al.\(^{13}\) where participants attained striking improvements in VL, the trend observed in our study is that, the median VL remained detectable and high. VL is expected to be at an undetectable level at six months following ART initiation.\(^{14}\)

The mean CrCl remained stable at stage 2 CKD at all visits (baseline to V3).

Of note is that the percentage of participants with CrCl<60ml/min generally declined with each visit (baseline to V3) and the percentage of those with CrCl≥60 ml/min increased (illustrated in Table 4) indicating renal improvement. This finding could be demonstrating the contribution of HAART in reducing HIVAN.\(^{24}\)

In our study the mean CrCl at all visits (baseline, V1, V2 and V3) revealed a high prevalence of CKD stage 2. This study demonstrated stable mean CrCl (kidney function) at CKD stage 2 despite persistent viremia (similar to findings in the study by Post et al.\(^{6}\)) as demonstrated by mean VL values at V1, V2 and V3 respectively.

Of note is that, at all visits, there were cases of CKD (stages 1-3) that qualify for up referral to tertiary institutions for specialist consultation according to the NDoH.

Ayokunle at al. reported an observation of CKD, (which they defined as estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m\(^2\) and/or albumin creatinine ratio (ACR) ≥30mg/g) in 47.6% of newly diagnosed participants.\(^{41}\) This finding was comparable to our study where 43.4% was reported at baseline. Other studies also reported a prevalence ranging from 6% to 27 % which is a bit low compared to this study.\(^{11,42}\)

Contrary to the recommendations in the ART guidelines (2010), where monitoring for Scr/CrCl should be done at three months, six months and 12 months then yearly, the intervals for monitoring were irregular and did not follow the recommended intervals. On average, the Scr/CrCl was monitored at eleven months, 24 months and 34 months in relation to baseline.
Practical implications:

Several studies, \(^{(7, 8, 9, 41)}\) recommend early detection of CKD as the most important measure to halt or delay progression to ESRD. Screening urinalysis for proteinuria and estimation of renal function is recommended by Moosa et al.\(^{(15)}\). Those with a GFR (CrCl) <60ml/min should therefore be referred to an institution where they can be evaluated by a specialist.\(^{(14)}\)

Screening tools such as proteinuria and microalbuminuria were not routinely measured but may help identify early renal dysfunction when Scr and/or CrCl are normal.\(^{(8)}\)

Limitations of the study:

The sampling, non-random (convenience) method made it difficult to generalise the findings to the total population and other institutions.

Estimated glomerular filtration rate was not well documented as such only CrCl was used in this study.

Screening for albuminuria and proteinuria, another most important marker/screening tool of renal disease was not studied, since it was not routinely performed/recorded.

The information on the risk factors such as hypertension and diabetes mellitus could have been underreported in the Bokamoso clinic file but in the out-patient, hospital file and/or files at primary health care clinics, local to the patients’ place of residence (local clinics). This applies to other nephrotoxic drugs (including over the counter medicines and herbal medicines) and which might have been collected from other points of service. The information on TB medication was not available because patients were down referred to the local clinics.

Recommendations:

We recommend CKD screening (including proteinuria) and management of modifiable risk factors (e.g. HT and DM) at all service points.

A well designed, prospective study (including a control group) might yield a better picture on the kidney function monitoring by HCPs.

Special attention and follow up for those with stages CKD stages 3 to 4 is also recommended.
Long term: Hiring of resident HIV specialist and/or nephrologists. Nephrology outreach programs may also be of benefit

Conclusion

The overall aim of the study was to assess the compliance of HCPs with the ART 2010 guidelines in monitoring the kidney function of patients initiated on HAART.

The study revealed that the renal function of patients treated with tenofovir was not closely monitored as per the recommendation in the NDoH ART guidelines, 2010. The CrCl results demonstrate that there were cases where TDF was contraindicated (CrCl<50ml/min) at initiation i.e. these patients were not supposed to be initiated on TDF containing regimen. Similarly there were cases of TDF contraindication at all successive visits, V1, V2 and V3.

CD4, VL and Scr (CrCl) were not taken at all visits and where it was done the intervals were too wide compared to the NDoH ART guidelines, 2010. These findings demonstrate that the renal function of patients that were initiated and remained on TDF was poorly monitored by HCPs.

According to the results, the renal function of the study population demonstrated improvement and it remained stable at CKD stage 2. However there were cases were patients presented with CKD stages 3 to 5 at all of the visits. These findings highlight the importance of baseline and routine renal function monitoring (as per the recommendation in the NDoH ART guidelines) to allow for prompt diagnosis and appropriate management.

Our study is one of the few studies in SA to assess the compliance with ART guidelines (2010) by HCPs. Further studies are indicated to look into other risk factors for kidney disease and to look into individual cases that demonstrated a declining kidney function from V1, V2 and V3 in relation to baseline.

Acknowledgements: We thank Professor, Herman Schoeman, the statistician, for his patience and insight in analysing the data and all the clerks at Bokamoso clinic for making the process of finding records easier.

Competing interests: The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article

References


9. Lucas, G.M.; Ross, M.J; Stock, P.G.; Shlipak, M.G; Wyatt, C.M & Gupta S.K et al. Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients


Receiving Highly Active Antiretroviral Therapy in the HIV Outpatient Study. INT ASSOC PHYSICIANS AIDS CARE 6(3); 2007 pp. 178-187


CHAPTER 5

SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1 INTRODUCTION

The results presented in chapter 4 are summarised in the first section of this chapter. Conclusions according to the objectives formulated for this study and recommendations offered based on the results of the study are presented. This chapter is concluded with the limitations of the study and closure.

5.2 SUMMARY

Five hundred evaluable patient files were selected for this study. The aim of this study was to investigate the monitoring of renal function of patients on TDF at Odi Hospital, initiated between the years 2010 and 2012.

The two objectives for this study were as follows:

1. To investigate the compliance of HCPs with the ART guidelines (2010) in monitoring the renal function of patients on TDF in the years 2010 and 2012

2. To retrospectively investigate the renal function of patients on TDF in the years 2010 and 2012

5.2.1 Method

The study was conducted in Bokamoso clinic, an ART clinic, at Odi Hospital located in Mabopane in the Gauteng Province of South Africa. The data was extracted from patient files using a data collection form adapted from ART guidelines (2010), Gupta et al (2011) and Young et al (2007). The form was divided into four sections as follows:
• Section A was largely used to collect data on demographics of participants, co-morbid condition(s) and other medicines the participant was taking during the study period.

• Section B explored data on HCPs adherence to ART guidelines (2010), e.g. whether or not health care professionals monitored the kidney function at initiation of TDF as recommended in the ART guidelines.

• Section C was used to record the ART regimen the participant was taking at stipulated intervals. Where there was a change in the regimen, the reasons for change were also recorded in this section.

• Section D was used to record data collected on whether or not HCPs monitored CD4 count, VL, Scr and CrCl at follow-up visits as per ART guidelines, 2010.

All the available data (data necessary to address all objectives) was captured as per the data collection form described above. Data was entered by the researcher on six different Excel™ spreadsheets. The spreadsheets were designed with the help of a statistician. These spreadsheets were designed and labelled (Sections A1, A2, A3, B, C and D) in accordance with the tools used to collect data.

• Section A1 was used to enter the participant’s identification number (ID), the demographic data and the WHO staging.

• Section A2 was used to enter co-morbid conditions and ICD codes.

• Section A3 was used to enter the current medicine regimen (drug name, strength, DDD and ACT).

• Section B was used to enter the following variables: Scr, CrCl, VL, CD4 count and ART regimen initiated.

• Section C was used to enter the ART regimen followed for year (at three, six and twelve months) from the date of initiation. The reason for any change in regimen (if recorded) at the above mentioned intervals was entered in this section.

• Section D was used to enter the variables specified in section B (Scr, CrCl, VL, CD4 count) at three, six and twelve months into therapy. In this section, a tick (✓) in the Y
Chapter 5: Summary, Conclusion and Recommendations

(Yes) or N (No) box was used to indicate if Scr, CrCl, VL, CD\textsubscript{4} count was done or not at month three, six and at month 12. This information aided in determining the compliance of the HCPs with the guidelines.

Only data relevant to the objectives of this study were documented. A coding system was used to protect the identity of the patients thus ensuring confidentiality.

Once the research was completed, the researcher descriptively analysed the data with the help of a statistician. The statistical analysis was on Statistical Analysis System (SAS)\cite{SAS Institute Inc, Carey, NC, USA}, Release 9.3, running under Microsoft Windows for a personal computer. All the data was summarised, described and organized in accordance with the objectives.

5.2.2 Results

The study sample comprised of 65.4\% female and 34.6\% male. From the total population of this study which comprised of 500 (100\%) evaluable cases, the sample size reduced by 0.6\%, 5.8\% and 30.2\% at first visit (V1), second visit (V2) and third visit (V3) respectively. This was true for both Scr and CrCl markers. The similar trend was observed with CD\textsubscript{4} count and VL marker. Of note is the relatively low sample size for VL (five at baseline, 88 at V1, 85, and 59 in relation to the sample for other markers) which makes it difficult to report reliable trends.

The vast majority of participants were initiated on regimen 1. Co-trimoxazole and NSAIDs were the most co prescribed nephrotoxic agents at 97.6\% and 57.42\% respectively.

About 74\% of participants had a CD\textsubscript{4} cell count of ≤ 200 cells/\mu L and this included 21.8\% who had a CD\textsubscript{4} cell count of ≤ 50 cells/\mu L. VL was only performed in six of 500 participants. Approximately 42\% of participants had CrCl ≤ 60 ml/min at initiation indicating the need for close kidney function monitoring. Body mass index (BMI) was not calculated for all participants since the height was not recorded.
5.2.2.1. Laboratory results

The median CD$_4$ count demonstrated an increase with each visit (<200 cells/µL at baseline and > 200 cells/µL at all successive visits). The sample size for VL was notably low at all visits in relation to other markers (CD$_4$ count and Scr/CrCl). The median Scr remained within a normal range at all visits. CrCl remained stable at stage 2 CKD failure.

5.2.2.2. Monitoring intervals in the first twelve months of ART initiation (HCP compliance to ART guidelines, 2010)

The mean monitoring intervals and ranges at all three visits were similar for CD$_4$ and VL. In general (on average), the monitoring was done at baseline, nine months(V1), 21 months(V2) and 31 months(V3) instead of the intervals as recommended by the NDoH, ART guidelines (2010) baseline, six months (V2)and 12 months(V3) monitoring intervals. On average, the Scr/CrCl was monitored at 11 months, 24months and 34 months instead of the intervals as recommended by the National Department of Health, ART guidelines (2010), baseline, three months (V2), six months (V2) and twelve months (V3) monitoring intervals.

The ranges between visits ranged from 0 to 46 for both Scr and CrCl. There were participants who were monitored within a month of initiating ART and those who were monitored at 46 months for V1. The similar pattern applied to other markers (CD$_4$ and VL).

5.2.2.3. Renal function of the study population

About 24% (124, n=500) of the participants were initiated on TDF containing ART at CrCl<50 ml/min despite the contraindication as stipulated in the NDoH ART guideline, 2010. This percentage slightly decreased and was reported at 21.7 % (76, n=349) by V3. The percentage of those participants that were initiated at CrCl between 50 to 60 ml/min also decreased from 19.2% to 11.7% (39, n= 349) by V3. The percentage of those initiated at CrCl>60ml/min increased from 56.6 to 67.34 (235, n= 239) by V3. (Illustrated by table 5.1)
### Table 5.1: CrCl levels at baseline, V1, V2 and V3

<table>
<thead>
<tr>
<th>Marker</th>
<th>Visits</th>
<th>N</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl&lt;50(ml/min): TDF contraindicated</td>
<td>Baseline</td>
<td>500</td>
<td>121</td>
<td>24.2</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>497</td>
<td>93</td>
<td>18.71</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>471</td>
<td>94</td>
<td>19.96</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>349</td>
<td>76</td>
<td>21.78</td>
</tr>
<tr>
<td>CrCl : 50-60(ml/min) Borderline</td>
<td>Baseline</td>
<td>500</td>
<td>96</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>497</td>
<td>73</td>
<td>14.69</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>471</td>
<td>79</td>
<td>16.77</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>349</td>
<td>39</td>
<td>11.7</td>
</tr>
<tr>
<td>CrCl ≥ 60ml/min TDF indicated</td>
<td>Baseline</td>
<td>500</td>
<td>283</td>
<td>56.6</td>
</tr>
<tr>
<td></td>
<td>V1</td>
<td>497</td>
<td>331</td>
<td>66.60</td>
</tr>
<tr>
<td></td>
<td>V2</td>
<td>471</td>
<td>298</td>
<td>63.27</td>
</tr>
<tr>
<td></td>
<td>V3</td>
<td>349</td>
<td>235</td>
<td>67.34</td>
</tr>
</tbody>
</table>
5.3 CONCLUSION

The overall aim of the study was to assess the compliance of HCPs with the ART 2010 guidelines in monitoring the kidney function of patients initiated on HAART.

The study revealed that the renal function of patients treated with tenofovir was not closely monitored as per the recommendation in the NDoH ART guidelines (2010). The CrCl results demonstrate that there were cases where TDF was contraindicated (CrCl<50ml/min) at initiation i.e. these patients were not supposed to be initiated of TDF containing regimen. Similarly there were cases of TDF contraindication at all successive visits, V1, V2 and V3.

CD4, VL and Scr (CrCl) were not taken at all visits and where it was done the intervals were too wide compared to the NDoH ART guidelines, 2010. These findings demonstrate that the renal function of patients that were initiated and remained on TDF was poorly monitored by HCPs.

According to the results, the renal function of the study population demonstrated improvement and it remained stable at CKD stage 2. However there were cases in CKD stages 3 to 5 at all visits. These findings highlight the importance of baseline and routine renal function monitoring (as per the recommendation in the NDoH ART guidelines) to allow for prompt diagnosis and appropriate management.

Our study is one of the few studies in SA to assess the compliance with ART guidelines (2010) by HCPs. Further studies are indicated to look into other risk factors for kidney disease and to look into individual cases that demonstrated a declining kidney function from V1, V2 and V3 in relation to baseline.

5.4 RECOMMENDATIONS

- Continuous training of HCPs on the ART guidelines especially because some are not full time employees of Bokamoso clinic but they rotate to other units at stipulates intervals.

- The HCPs should be sensitized on an ongoing basis of the recommendations in the ART guidelines and the consequences of deviating from them. (Note: The CrCl was calculated by the researcher, never by the HCPs), the initiation of ART was mainly
based on the Scr. Most laboratory results were without the GFR (not requested) which made it difficult to tell when GFR was less than 50ml/ml (TDF contraindicated).

- **Active Identification of those with CrCl<60ml/min** (CKD stages, 3 to 5) and develop protocol(s) of the interventions with the help of HIV specialists and/or nephrologists. Where there is kidney function deterioration with TDF still indicated (CrCl between 50-60 mil/min), the monitoring intervals should be reduced and tailored to the individual patient (instead of the recommended intervals).

- **CKD Screening** (including proteinuria) and management of modifiable risk factors (e.g. HT, DM, CD4, VL and obesity) at all service points. Patients should be educated/sensitised of these risk factors including adverse effects of nephrotoxic drugs such as NSAIDs on an ongoing basis (at every encounter with the HCP, individually and/or as a group).

Ensure ease of access to the results. The majority of the results were not in the participants file and were retrieved by the researcher on line. If the prescriber does not get the results in the file it makes it difficult to make any interventions where needed. Therefore assigning someone who has knowledge/who can read results to collect and assess results before filing and report abnormal results (thus allowing for timely intervention in case of abnormal results) on time instead of waiting for the next patient consultation date, which may happen three or six months later.

- **All HCPs** (including pharmacists) should be given permission to access laboratory results anytime the need arises in order to avoid delay in interventions due to non-availability of results from the laboratory because of logistical problems like malfunctioning printer(s) or unavailability of printing paper. A computer system that allows HCWs to access all information about the patient, including medical information from local clinics is also recommended.

- **Height measurement** should be taken to help in the calculation of the BMI. The fact that the BMI was not calculated made it difficult to intervene when the patient was underweight or overweight. Underweight leads to low muscle mass which may result to low Scr which may lead to overestimation of CrCl and mask the underlying renal function
insufficiency. Overweight is associated with HT, DM (the well documented contributors to renal disease) and may also result to increased muscle mass.

- The ART clinic mainly focuses on management of HIV infection and its common complications and conditions are managed at a local clinic next to where the patient resides or at Odi Hospital Outpatient department (OPD). This practice complicates the ART since some complications such as kidney disease may be solely attributed to ART while conditions such as uncontrolled HPT and DM and other nephrotoxic drugs (including over the counter medicines and herbal medicines) may also be contributing to the kidney dysfunction. We therefore recommend a “consolidated approach” in the management of PLWHIV where all the information about the patient is kept in one file.

- Hiring of resident HIV specialist and/or nephrology outreach programs may also be of benefit

- Further studies that consider all the patient information (consolidated file) to get a more accurate picture of other co morbid conditions and medicines that could be contributing to kidney insufficiency are recommended.

5.5 LIMITATIONS OF THE STUDY

The sampling, non-random (purposive) method made it difficult to generalise the findings to the total population and other institutions.

eGFR was not well documented as such only CrCl was used in this study.

Screening for albuminuria and proteinuria, other more important markers/screening tools of renal disease was not studied, since it was not routinely performed/recorded.

The information on the risk factors such as HT and DM could have been underreported in the Bokamoso clinic file but in the Out-patient, hospital file and/or files at primary health care clinics, local to the patients’ place of residence (local clinics). This applies to other nephrotoxic drugs (including over the counter medicines and herbal medicines) and which might have been
collected from other points of service. The information on TB medication was not available because patients were down referred to the local clinics.

5.6 CLOSURE

The ART guidelines (2010) [newer versions: ART guidelines 2013 and 2015] serve as a guide to HCPs with regard to comprehensive management of HIV infected adults and adolescents. The ART regimens are described, as well as laboratory and clinical monitoring at diagnosis, at initiation of ART and whilst on treatment are (NDoHSA, 2010).

Tenofovir is recommended in the guidelines as the part of first line HAART for all eligible patients where there is no contraindication (2013 and 2015 ART guidelines recommend TDF for all eligible patients, including pregnant women). According to the ART guidelines, the purpose of the clinical and laboratory monitoring of patients on TDF is to identify its toxicity to the kidney.

Halving the number of new HIV infections as well as ensuring that at least 80% of people who are eligible for treatment for HIV are receiving it and at least 70% of these people should be alive and still on treatment after five years after initiation, is one of the goals the NSP (2012-2016) aims to achieve. The NSP is guided by the targets of the Millennium Development goals (MDGs). The MDGs present specific development and health targets for 2015 (and beyond) towards which SA and other countries are striving. [SANAC, South African National AIDS Council].

For this goal to be achieved, effective HIV/AIDS management (including monitoring and management of ARVs side effects) requires team work and involvement of all stakeholders such as hospital management, HCPs and patients. ART trained HCPs, including medical officers, nurses, pharmacists and social workers are essential for successful implementation and compliance with ART guidelines.

The life expectancy of PLWHIV who are able to maintain suppressive ARV regimens now approaches those without infection (Gale, 1999). However, renal disease is increasingly recognised as a cause of morbidity among them (Young, 2009). Our findings highlight the importance of assessing baseline renal function and routine monitoring of Scr and CrCl in PLWHIV on HAART, so that those who develop renal disease may be timeously diagnosed and appropriately managed.
References

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References


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Young, B., Buchacz, K., Moorman, B.S.N., Wood, K.C., Brooks, M.D. & the HIV Outpatient Study (HOPS) Investigators. 2009. Renal Function in Patients with Pre-existing Renal Disease Receiving Tenofovir-Containing Highly Active Antiretroviral Therapy in the Outpatient Study. AIDS Patient Care and STDs; 23(8):589-592.


Appendices

APPENDICES

Appendix A: Data Collection Form

Section A

Participant’s File Number: ____________________________

Demographics

Gender:  
M  F

Age: ____________________________

Ethnicity:  
W  B  I  C  A

Nationality: ____________________________

Weight (kg): ____________________________

Height (cm): ____________________________

BMI (kg/m²): ____________________________

WHO staging:  
1  2  3  4
## Appendices

### Co morbid conditions

<table>
<thead>
<tr>
<th>Co morbid conditions</th>
<th>ICD Code*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
<td>3.</td>
</tr>
<tr>
<td>4.</td>
<td>4.</td>
</tr>
<tr>
<td>5.</td>
<td>5.</td>
</tr>
<tr>
<td>6.</td>
<td>6.</td>
</tr>
</tbody>
</table>

*ICD-10 = International Statistical Classification of Diseases

### Current Medicine regimen

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Strength</th>
<th>DDD*</th>
<th>ATC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.</td>
<td>1.</td>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
<td>2.</td>
<td>2.</td>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
<td>3.</td>
<td>3.</td>
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</tr>
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<td>4.</td>
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</tr>
<tr>
<td>5.</td>
<td>5.</td>
<td>5.</td>
<td>5.</td>
</tr>
<tr>
<td>6.</td>
<td>6.</td>
<td>6.</td>
<td>6.</td>
</tr>
</tbody>
</table>

* DDD - Defined Daily Dose system methodology  
  ATC - Anatomical Therapeutic Chemical classification

### Section B

**Newly admitted/initiated patients on regimen 1 - TDF containing**

<table>
<thead>
<tr>
<th>Scr level done</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>If yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr level</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CrCl /eGFR done</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VL done</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen initiated</th>
<th></th>
</tr>
</thead>
</table>

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Appendices

**Section C**

**ART regimen followed for one year**

<table>
<thead>
<tr>
<th>Regimen 1, 2, 3 or 4*</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>If change of regimen specify reason</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Regimen 1 = TDF, lamivudine (3TC)/emtricitabine (FTC) and Efavirenz (EFV)
  Regimen 2 = TDF, 3TC and Nevirapine (NVP)
  Regimen 3 = TDF, 3TC and Lopinavir/ritonavir (LPV/r)
  Regimen 4 = Other

**Section D**

**HCW adherence to monitoring of CD₄ count, VL & Cr as per NDoHSA ART guidelines (2010)**

<table>
<thead>
<tr>
<th></th>
<th>MONITORED AT:</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD₄ Value</strong></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>VL Value</strong></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CrCl or eGFR Value</strong></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Appendix B: SMUREC Clearance certificate

MEDUNSA RESEARCH & ETHICS COMMITTEE
CLEARANCE CERTIFICATE

MEETING: 16/2013
PROJECT NUMBER: MREC/H/182/2013: PG
PROJECT:
Title: An investigation of the monitoring of kidney function of patients on tenofovir at Odi Hospital
Researcher: Miss A Zitha
Supervisor: Dr N Schelack
Co-supervisor: Prof A Gous
Hospital Superintendent: Dr TP Dlamini (Odi Hospital)
Other involved HODs: Ms MD Mekgoe (Odi Hospital) Ms SJ Boshoman (Odi Hospital)
Department: Pharmacy
School: Health Care Sciences
Degree: MSc (Med) in Pharmacy

DECISION OF THE COMMITTEE:
MREC approved the project.
DATE: 01 August 2013

PROF GA OGUNBANJO
CHAIRPERSON MREC

The Medunsa Research Ethics Committee (MREC) for Health Research is registered with the US Department of Health and Human Services as an Institution Review Board (IRB00004219) and functions under a Federal Wide Assurance (FWA00009419).
Expiry date: 11 October 2016

Note:

i) Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the Committee.

ii) The budget for the research will be considered separately from the protocol. PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.
Appendices

Appendix C: Approval by the Hospital CEO

APPROVAL OF THE STUDY BY THE HOSPITAL CEO

CLINICAL RESEARCH POLICY

Readers are hereby informed of the following:

1. The study involves human subjects.
2. The study has been approved by the Institutional Review Board (IRB).
3. Participants have given informed consent.
4. The study complies with all ethical guidelines.

INFORMATION FOR PARTICIPANTS

1. The study involves the collection of personal data.
2. Participants are free to withdraw from the study at any time.
3. Confidentiality will be maintained.
4. Participants have the right to request access to their records.

INFORMATION FOR THE PUBLIC

1. This study has been approved by the hospital administration.
2. The study is conducted in accordance with all relevant laws and regulations.
3. Participants are protected by the hospital’s policies and procedures.
4. Participants are not required to pay any fees for their participation.

APPROVED BY:

[Signature]

DATE: [Date]

[Institutional Logo]
Appendix D: Guidelines for Authors for the South African Journal of HIV Medicine (SAJHIVMED)

Structure and style of your original research article

The page provides an overview of the structure and style of your original research article to be submitted to the Southern African Journal of HIV Medicine. The original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal presented according to a clear and well-structured format (between 3500 and 5500 words with a maximum of 60 references).

Please use British English, that is, according to the Oxford English Dictionary. Avoid Americanisms (e.g. use 's' and not 'z'). Consult the Oxford English Dictionary when in doubt and remember to set your version of Microsoft Word to UK English.

- **Language**: Manuscripts must be written in British English.
- **Font**:
  - **Font type**: Palatino
  - **Symbols font type**: Times New Roman
  - **General font size**: 12pt
- **Line spacing**: 1.5
- **Headings**: Ensure that formatting for headings is consistent in the manuscript.
  - First headings: normal case, bold and 14pt
  - Second headings: normal case, underlined and 14pt
  - Third headings: normal case, bold and 12pt
  - Fourth headings: normal case, bold, running-in text and separated by a colon.

Our publication system supports a limited range of formats for text and graphics. Text files can be submitted in the following formats only:

- **Microsoft Word (.doc)**: We cannot accept Word 2007 DOCX files. If you have created your manuscript using Word 2007, you must save the document as a Word 2003 file before submission.
- **Rich Text Format (RTF)** documents uploaded during Step 2 of the submission process. Users of other word processing packages should save or convert their files to RTF before uploading. Many free tools are available that will make this process easier.

The structure and style of your original article

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Appendices

The format of the compulsory cover letter forms part of your submission and is on the first page of your manuscript and should always be presented in English. You should provide all of the following elements:

- **Article title**: Provide a short title of 50 characters or less.
- **Significance of work**: Briefly state the significance of the work being reported on.
- **Full author details**: Provide title(s), full name(s), position(s), affiliation(s) and contact details (postal address, email, telephone and cellular number) of each author.
- **Corresponding author**: Identify to whom all correspondence should be addressed to.
- **Authors’ contributions**: Briefly summarise the nature of the contribution made by each of the authors listed.
- **Summary**: Lastly, a list containing the number of words, pages, tables, figures and/or other supplementary material should accompany the submission.

**Page 2 and onwards**

**Title**: The article’s full title should contain a maximum of 95 characters (including spaces).

**Abstract**: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an original research article should consist of five paragraphs that are labelled. These labelled paragraphs should deal with the background, objectives, method, results and conclusion.

- **Background**: Why do we care about the problem? State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)
- **Objectives**: What problem are you trying to solve? What is the scope of your work (e.g. is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.
- **Method**: How did you go about solving or making progress on the problem? State how the study was performed and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- **Results**: What is the answer? Present the main findings (that are, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative change or differences on answers to questions.
- **Conclusion**: What are the implications of your answer? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)
Do not cite references in the abstract and do not use abbreviations excessively in the abstract.

The following headings serve as a guide for presenting your research in a well-structure format. As an author you should include all first level headings but subsequent headings (second and third level headings) can be changed.

**Introduction (first-level heading)**

The introduction contains two subsections, namely the background section and the literature review. The introduction section should be written from the standpoint of readers that is without specialist knowledge in that area and must clearly state the introduction to the research and its aims in the context of previous work bearing directly on the subject. The introduction section to the article normally contains the following five elements:

- **Key focus (third-level heading):** A thought-provoking introductory statement on the broad theme or topic of the research.
- **Background (third-level heading):** Providing the background or the context to the study (explaining the role of other relevant key variables in this study).
- **Trends (third-level heading):** Cite the most important published studies previously conducted on this topic or that has any relevance to this study (provide a high-level synopsis of the research literature on this topic).
- **Objectives (third-level heading):** Indicate the most important controversies, gaps and inconsistencies in the literature that will be addressed by this study. In view of the above trends, state the core research problem and specific research objectives that will be addressed in this study and provide the reader with an outline of what to expect in the rest of the article.
- **Contribution to field (third-level heading):** Explanation of the study’s academic (theoretical and methodological) or practical merit and/or importance (provide the value-add and/or rationale for the study).

**Research design (first-level heading)**

- **Research approach (second-level heading)**
- **Research method (second-level heading)**
  - **Materials (third-level heading):** Describe the type of organism(s) or material(s) involved in the study.
  - **Setting (third-level heading):** Describe the site and setting where your field study was conducted.
  - **Design (third-level heading):** Describe your experimental design clearly, including a power calculation if appropriate. Note: Additional details can be placed in the online supplementary location.
Appendices

- **Procedure (third-level heading):** Describe the protocol for your study in sufficient detail (clear description of all interventions and comparisons) that other scientists could repeat your work to verify your findings.

- **Statistical analysing (third-level heading):** Describe how the data were summarised and analysed, additional details can be placed in the online supplementary information.

- **Reliability (third-level heading):** Reliability is the extent to which an experiment, test, or any measuring procedure yields the same result on repeated trials. Without the agreement of independent observers able to replicate research procedures, or the ability to use research tools and procedures that yield consistent measurements, researchers would be unable to satisfactorily draw conclusions, formulate theories, or make claims about the generalisability of their research.

- **Validity (third-level heading):** Validity refers to the degree to which a study accurately reflects or assesses the specific concept that the researcher is attempting to measure. While reliability is concerned with the accuracy of the actual measuring instrument or procedure, validity is concerned with the study's success at measuring what the researchers set out to measure. Researchers should be concerned with both external and internal validity. External validity refers to the extent to which the results of a study are generalisable or transferable. Internal validity refers to (1) the rigor with which the study was conducted (e.g. the study's design, the care taken to conduct measurements, and decisions concerning what was and wasn't measured) and (2) the extent to which the designers of a study have taken into account alternative explanations for any causal relationships they explore. In studies that do not explore causal relationships, only the first of these definitions should be considered when assessing internal validity.

- **Ethical considerations (third-level heading):** Articles based on the involvement of people must have been conducted in accordance with relevant national and international guidelines. Approval must have been obtained for all protocols from the author's institutional or other relevant ethics committee and the institution name and permit numbers provided at submission.

- **Potential benefits and hazards (fourth-level heading):** What risks to the subject are entailed in involvement in the research? Are there any potential physical, psychological or disclosure dangers that can be anticipated? What is the possible benefit or harm to the subject or society from their participation or from the project as a whole? What procedures have been established for the care and
Appendices

protection of subjects (e.g. insurance, medical cover) and the control of any information gained from them or about them?

- **Recruitment procedures** (fourth-level heading): Was there any sense in which subjects might be ‘obliged’ to participate – as in the case of students, prisoners, learners or patients – or were volunteers being recruited? If participation was compulsory, the potential consequences of non-compliance must be indicated to subjects; if voluntary, entitlement to withdraw consent must be indicated and when that entitlement lapses.

- **Informed consent** (fourth-level heading): Authors must include how informed consent was handled.

- **Data protection** (fourth-level heading): Authors must include in detail the way in which data protection was handled.

## Results (first-level heading)

This section provides a synthesis of the obtained literature grouped or categorised according to some organising or analysis principle. Tables may be used and models may be drafted to indicate key components of the results of the study.

- Organise the results based on the sequence of Tables and Figures you will include in the manuscript.

- The body of the Results section is a text presentation of the key findings which includes references to each of the Tables and Figures.

- Statistical test summaries (test name, p-value) are usually reported parenthetically in conjunction with the biological results they support.

- Present the results of your experiment(s)/research data in a sequence that will logically support (or provide evidence against) the hypothesis, or answer the question, stated in the Introduction.

All units should conform to the **SI convention** and should be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

## Discussion (first-level heading)

This section normally contains the following elements (it is strongly suggested that sub-headings are used in this section):

- **Outline of the results** (second-level heading): Restate the main objective of the study and reaffirm the importance of the study by restating its main contributions; summarise the results in relation to each stated research objective or research
Appendices

hypothesis; link the findings back to the literature and to the results reported by other researchers; provide explanations for unexpected results.

- **Practical implications (second-level heading):** Reaffirm the importance of the study by restating its main contributions and provide the implications for the practical implementation your research.

- **Limitations of the study (second-level heading):** Point out the possible limitations of the study and provide suggestions for future research.

- **Recommendations (second-level heading):** Provide the recommendations emerging out of the current research.

**Conclusion**

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance, with a recommendation for future research (implications for practice). Provide a brief conclusion that restates the objectives, the research design, the results and their meaning.

**Acknowledgements**

If, through your study, you received any significant help in conceiving, designing, or carrying out the work, or received materials from someone who did you a favour by supplying them, you must acknowledge their assistance and the service or material provided. **Authors should always acknowledge outside reviewers of their drafts and any sources of funding that supported the research.**

- **Competing interests (second-level heading):** A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organisations that can potentially prevent you from executing and publishing unbiased research. Authors should disclose any financial competing interests but also any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript. **Where an author gives no competing interests, the listing will read 'The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this article.'**

- **Authors' contributions (second-level heading)*:** This section is necessary to give appropriate credit to each author, and to the authors' applicable institution. The individual contributions of authors should be specified with their affiliation at the time of the study and completion of the work. An ‘author’ is generally considered to be someone who has made substantive intellectual contributions to a published study. Contributions made by each of the authors listed, along the lines of the following (please note the use of author initials):
Appendices

J.K. (University of Pretoria) was the project leader, L.M.N. (University of KwaZulu-Natal) and A.B. (University of Stellenbosch) were responsible for experimental and project design. L.M.N. performed most of the experiments. P.R. made conceptual contributions and S.T. (University of Cape Town), U.V. (University of Cape Town) and C.D. (University of Cape Town) performed some of the experiments. S.M. (Cape Peninsula University of Technology) and V.C. (Cape Peninsula University of Technology) prepared the samples and calculations were performed by C.S., J.K. (Cape Peninsula University of Technology) and U.V. wrote the manuscript.

References (first-level heading)
Begin the reference list on a separate page with no more than 60 references. Southern African Journal of HIV Medicine uses the Vancouver referencing style, details of which can be downloaded from the journal website. Note: No other style will be permitted.
Appendix E: Study Summary

An investigation of the monitoring of patients treated with tenofovir (TFD)
Project number: MREC/H/182/2012:PG
Pharmacist/Research: A.N. Zitha (0723693811 or 0127252328)
Supervisor: Professor N. Schellack and Professor A.G.S. Gous

The study will focus on assessing the Health care professionals (HCPs) adherence to NDoHSAART guidelines, 2010 in monitoring the kidney function of patients initiated on TDF containing HAART.

- Which patients will be included in the study?
  - Patients who had been on TDF-based regimen for more than twelve months
  - Adult patients (over 18 years of age)
  - No previous kidney injury (GFR > 60 ml/min/1.73 m²)

- Which patients will be excluded from the study?
  - Pre-existing kidney disease at initiation of TDF containing HAART as denoted by decreased GFR (<60 ml/min/1.73 m²) and raised serum creatinine, Scr (>100 µmol/L).
  - Patients who were exposed to ART before they were switched to a TDF containing HAART.
  - Patients who were previously exposed to ART through prevention of mother to child (PMTCT) programme or post exposure prophylaxis (PEP)

- Thank you for your time

Figure 1: Study flow diagram
Appendix F: Attendance register for the pre study presentation

<table>
<thead>
<tr>
<th>NAMES</th>
<th>DESIGNATION</th>
<th>TIME</th>
<th>MD NUMBER</th>
<th>SIGNATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. F. D.</td>
<td>Pharmacist</td>
<td>10:00</td>
<td>123456789</td>
<td>Signature</td>
</tr>
<tr>
<td>T. M. R.</td>
<td>Doctor</td>
<td>10:30</td>
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</tr>
<tr>
<td>V. A. K.</td>
<td>Nurse</td>
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<td>876543210</td>
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</tr>
<tr>
<td>E. M. G.</td>
<td>Technician</td>
<td>11:30</td>
<td>765432109</td>
<td>Signature</td>
</tr>
<tr>
<td>S. F. L.</td>
<td>Medical Assistant</td>
<td>12:00</td>
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</tr>
<tr>
<td>J. A. B.</td>
<td>Lab Technician</td>
<td>12:30</td>
<td>543210987</td>
<td>Signature</td>
</tr>
<tr>
<td>A. K. S.</td>
<td>Director</td>
<td>13:00</td>
<td>432109876</td>
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</tbody>
</table>

... (continued)
AN INVESTIGATION OF THE MONITORING OF RENAL FUNCTION OF PATIENTS TREATED WITH TENOFOVIR AT ODI HOSPITAL IN GAUTENG PROVINCE

Researcher: Alfreda Nkosinomusa Zitha
Supervisors: Dr Natalie Schellack
            Professor AGS Gous
Date: 25 October 2013
Department of Pharmacy
University of Limpopo
Medunsa Campus

RATIONALE FOR THE STUDY (1)

- The introduction of HAART (highly active antiretroviral therapy) prolongs survival and is now providing normal life expectancy in HIV infected individuals.
- With improved survival hence increasing age, these individuals are increasingly likely to experience ailments that affect the general population including the kidney disease.
- HIV infected patients also have a high prevalence of other risk factors for renal disease, including, hepatitis C, cigarette smoking and injection drug use.
RATIONALE FOR THE STUDY (2)

- **Timely detection** and accurate diagnosis of kidney disease in HIV infected individuals are necessary in averting further renal injury and institute appropriate treatment (Fernandez-Fernandez *et al*., 2011)
- TDF is associated with a **greater decline** in renal function compared with the use of other NRTIs. Patients who received TDF had a significant decrease in CrCl (GFR) [Fine *et al*., 2008]
- **Acute renal failure (ARF)** and **Fanconi syndrome** associated with TDF has been reported (Hall *et al*., 2011)

RATIONALE FOR THE STUDY (3)

- **NB!** Not all Fanconi syndrome patients experience full recovery of renal function after discontinuation of TDF
- This lack of full recovery highlights the need for early and accurate diagnosis of this toxicity
AIM OF THE STUDY

- To investigate the **monitoring of renal function** of patients on tenofovir at Odi Hospital.

STUDY SITE

- The study will be conducted in an ARV clinic (Bokamoso Clinic) at Odi District Hospital located in Mabopane (Pretoria), South Africa.
- The hospital is a level one facility serving a population of about 880537, including the population from the North West Province (NWP). The approved number of beds is 227, whilst the usable number is 198.
OBJECTIVES

- To investigate the compliance of health care workers with the NDoHSA ART guidelines (2010) in monitoring the renal function of patients on tenofovir.
- To retrospectively investigate the renal function of patients initiated on TDF as part of first line regimen for the first year.
- To determine if there is an association between the compliance with the NDoHSA ART guidelines and the renal function of patients on tenofovir.

STUDY SITE

- The study will be conducted in an ARV clinic (Bokamoso Clinic) at Odi District Hospital located in Mabopane (Pretoria), South Africa.
- The hospital is a level one facility serving a population of about 880537, including the population from the North West Province (NWP). The approved number of beds is 227, whilst the usable number is 198.
STUDY DESIGN

A retrospective observational study will be conducted, where patient records (files) will be analyzed. Information for the purpose of this research will be retrieved from the files of patients treated during the study period.

STUDY POPULATION AND SAMPLE (1)

- **Sample selection**
  - **Inclusion criteria**
  - Patients should have been on TDF-based regimen for more than twelve months
  - Adult patients (over 18 years of age)
  - No previous kidney injury (GFR > 60 ml/min/1.73 m²)
STUDY POPULATION AND SAMPLE (2)

- **Exclusion criteria**

- **Pre-existing kidney** disease at initiation of TDF containing HAART as denoted by decreased GFR (<60 ml/min/1.73 m²) and raised serum creatinine, Scr (>120 µmol/L).
- Patients who were exposed to ART before they were switched to a TDF containing HAART.
- Patients who were previously exposed to ART through prevention of mother to child (PMTCT) programme or post exposure prophylaxis (PEP).

STUDY POPULATION AND SAMPLE

- The population will consist of all files of patients who were initiated on TDF containing HAART. These patients must have been on treatment for over a year.

- In line with cross-sectional research design, the sample will be a census of all files of patients who were initiated (and remained) on TDF during the period specified.

- It is thus anticipated that approximately four hundred (400) evaluable cases will be obtained in the period understudy.
DATA COLLECTION PROCESS

Selection of patient files as per the inclusion criteria.

Fill out the data collection form with information from patient files

All statistical procedures will be performed on SAS Release 9.2 running under Microsoft Windows for a personal computer. The data will be analyzed with the help of a statistician.

Data Collection Form

Section A
Participant's File Number: [Blank]
Demographics

<table>
<thead>
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<th>M</th>
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<td></td>
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<td>B</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO staging</td>
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<td></td>
</tr>
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</table>

Co-morbid conditions

<table>
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<tr>
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</tr>
<tr>
<td>2: 3</td>
</tr>
<tr>
<td>4: 5</td>
</tr>
<tr>
<td>5: 6</td>
</tr>
</tbody>
</table>

*ICD-10: International Statistical Classification of Diseases
Appendices

Section B
Newly admitted patients on regimen 1 - TDF containing

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Strength</th>
<th>DDD*</th>
<th>ATC*</th>
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<tbody>
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</tr>
<tr>
<td>6</td>
<td>6</td>
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</tbody>
</table>

DDD*: Defined Daily Dose system methodology
ATC*: Anatomical Therapeutic Chemical classification

Section C
ART regimen followed for one year

<table>
<thead>
<tr>
<th>Regimen option</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen 1, 2, 3 or 4*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen 5 = TDF + Lamivudine (3TC) + Emtricitabine (FTC) and Efavirenz (EFV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen 6 = TDF, 3TC and Nevirapine (NVP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen 7 = TDF, 3TC and Lapatinib (LPVc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen 8 = Other</td>
<td></td>
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</tbody>
</table>

Section D
MCW monitoring adherence to monitoring of CD4 count, VL & Cr as per NDoHSA
ART guidelines (2016)

<table>
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<th>Parameter</th>
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<tr>
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<td>No</td>
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<tr>
<td>VL Value</td>
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</tr>
<tr>
<td>Cr or eGFR Value</td>
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</tr>
</tbody>
</table>
**ETHICAL CONSIDERATION**

- This research is a *retrospective* study and only involves the recording of previously collected data. Therefore no consent of any patient is required.
# Appendices

## UNIVERSITY OF LIMPOPO

### MEDUNSA RESEARCH & ETHICS COMMITTEE

**CLEARANCE CERTIFICATE**

**MEETING:** 09/2013  
**PROJECT NUMBER:** MREC2013/02/0415-PO  
**PROJECT:**  
**Title:** An investigation of the monitoring of kidney function of patients on haemodialysis at Clinic C  
**Researcher:**  
**Supervisor:** Dr R Schlebusch  
**President:** Prof D. Schlebusch  
**Hospita l Superintendent:** Prof D. Schlebusch  
**Ethics involved:**  
**Department:** Biochemistry  
**Degree:**  
**Decision:** MREC approved the project  
**DATE:** 01 August 2013  
**MREC CHAIRPERSON:** Dr R Schlebusch

## PROTOCOL

**Decision of the Committee**

The Medunsa Research Ethics Committee (MREC) is Health Research is regulated with the U.S. Department of Health and Human Services and the Department of Health and Human Services under 45 CFR 46.121(a), as an Institutional Review Board (IRB). This study was approved on 01 August 2013.

### PROTOCOL:

**Note:**

1. Should any departure be contemplated from the research procedures as approved, the researchers must contact the committee and the hospital CEO.
2. The budget for this research will be considered separately from the protocol. Please quote the Protocol Numbers in all quotes.

### APPROVAL OF THE STUDY BY THE HOSPITAL CEO

**CONSENT FOR THE STUDY**

**Clinical Research Policy**

- **Informed Consent:**
  - Signed and witnessed by the researcher and the study participant.
  - Signed by the study participant and witnessed.
  - Signed by the study participant and witnessed by the hospital CEO.
  - Signed and witnessed by the research assistant.
  - Signed and witnessed by the medical doctor.

**Appendix A:**

- **Ethics Committee:**
  - Signed by the research assistant.
  - Signed by the medical doctor.
  - Signed by the hospital CEO.

**Chief Executive Officer:**

**DATE:** 01/08/2013
Appendices

BIBLIOGRAPHY


AKNOWLEDGEMENTS

- My Supervisors: Dr N Schellack & Prof AGS Gous
- The University Statistician: Prof Schoeman
- The University Research Assistant : Amma
- The CEO of Odi Hospital: Ms Megoe
- The Clinical Manager: Dr Dlamini
- The Nursing Manager: Sr Boshomane
- Training officer: Ms D. Pooe
- The Bokamoso clinic Manager: Sr. Kodisang
- The Pharmacy Team
THANK YOU

QUESTIONS???