INCIDENCE AND RISK FACTORS OF RENAL DYSFUNCTION AMONG HIV POSITIVE PATIENTS ON NEVIRAPINE BASED REGIMENS AT KENYATTA NATIONAL HOSPITAL

A thesis submitted in partial fulfillment of the requirements for the award of the degree of Master of Pharmacy (Pharmacoepidemiology and Pharmacovigilance) Degree of the University of Nairobi.

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November 2014

DECLARATION

I declare that this Thesis is my original work and has not been submitted for evaluation for research and examination in any other institutions of higher learning.

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DEDICATION

I fondly dedicate this work to my loving husband Jimmy Larry and my beautiful children Jayden, Jayson and Natalie for their immense moral support and patience during my studies.

ACKNOWLEGEMENT

My appreciation first and foremost goes to the Almighty God for giving me strength, attitude and zeal to pursue this course.

Special thanks my family, husband and children, for giving me moral support throughout this time I was writing my thesis.

My special gratitude goes to my supervisors Prof C.K. Maitai, Dr Faith Okalebo and Dr Margaret Oluka and lecturers for their guidance, mentorship, encouragement, invaluable time, support and advice towards the preparation of this thesis.

I am highly indebted to Dr Faith Okalebo for her immense support, encouragement and guidance in the preparation of this thesis. Her patience with me is noteworthy.

I am grateful to the Comprehensive Care Clinic at the Kenyatta National Hospital. The pharmacy staff especially John Mugambi and Jude Odhiambo, I owe you special appreciation for your unreserved cooperation and assistance during data collection and entry, as well as the records department for availing the patient files in time. To the study subjects I appreciate you for accepting to participate in the study.

My gratitude to the EPIVIGIL class of 2012 especially Makori Jones, Christabel Khaemba and Ndwiga Albert, for their moral support and time spent sharpening each other and the team work.

Last but not least, this study was made possible by the support of MEPI through Partnership for Improved Medical Education in Kenya (PRIME-K) grant number NIH-5R24TW008889-02.

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LIST OF ABBREVIATIONS AND ACRONYMS

AKD	Acute Kidney Disease
ARF	Acute Renal Failure
ACE	Angiotensin Converting Enzyme
ART	Anti-Retroviral Therapy
ARV	Antiretroviral drug
BP	Blood Pressure
BMI	Body Mass Index
CCC	Comprehensive Care Centre
CD4	Subgroup of T-lymphocyte carrying CD4 antigens
CKD	Chronic Kidney Disease
DART	Disease development of antiretroviral therapy in Africa
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
ESRD	End Stage Renal Disease
eGFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
KNH	Kenyatta National Hospital
MDRD	Modified Diet in Renal Disease
NVP	Nevirapine
PCR	Polymerase Chain Reaction
PUD	Peptic Ulcer Disease
RIFLE	Risk, Injury, Failure, Loss, End stage kidney disease
SNP	Single Nucleotide Polymorphism
SBP	Systolic Blood Pressure
UoN	University of Nairobi
UO	Urine Output

OPERATIONAL DEFINITIONS

Adverse drug reaction: A response to a drug which is harmful and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function

Baseline investigation: Any measurement or investigation done between 60 days prior to or 30 days after antiretroviral drug initiation

Renal disease: an estimated glomerular filtration rate (eGFR) of less than 50ml/min/1.73m^2

ABSTRACT

Introduction

As patients infected with human immunodeficiency virus (HIV) live longer while receiving antiretroviral therapy, kidney diseases have emerged as significant causes of morbidity and mortality. Black race, older age, hypertension, diabetes, low CD4+ cell count, and high viral load remain important risk factors for kidney disease in this population. Chronic kidney disease should be diagnosed in its early stages through routine screening and clinicians should pay careful attention to changes in glomerular filtration rate or creatinine clearance. With early detection and treatment, it is possible to prevent kidney disease and its complications from worsening.

Objectives:

The broad objective of this study was to evaluate the incidence and risk factors of renal dysfunction in HIV adult patients on Nevirapine based regimens.

Methodology:

This was a descriptive (right censored arm) hospital based retrospective cohort study. It was carried out at the Kenyatta National Hospital Comprehensive Care Center and targeted HIV patients on Nevirapine based regimens seen at the KNH-CCC. Data was collected between May and August 2014. The participants were sampled by convenient sampling technique. Ethical approval was obtained from the KNH-UoN Research and Ethics Committee. Quantitative data which was obtained from the patient interviews and abstraction of patient files was analyzed using STATA version 10 software. Ordered Logistic regression modeling was used to identify covariates that determine the severity of nephrotoxicity.

Results:

In total, 241 HIV-infected adult patients were included in this study. There were 56 male and185 female patients. The median age was 39 years [IQR 35-44]. The duration of follow up for most of the patients was 5 years. The prevalence of renal dysfunction at baseline was 6.3% and the incidence in the study was 4.3%. In this study

five (2.1%) patients had estimated GFR (eGFR) < 50 mL/min per 1.73 m^2, while ten (8.3%) patients had elevated serum creatinine (above 120µg/l). In the multivariate ordered logistic regression the significant predictor variables for renal dysfunction that were significant were age at diagnosis, current age at the time of study, the sex, alcohol consumption and the duration of therapy.

The females had a higher risk of developing renal dysfunction (adjusted O.R 0.48 (95% C.I 0.24-1.04) p=0.04). Alcohol consumption was a significant predictor of renal dysfunction (adjusted O.R 1.84 (95% C.I 1.01-3.29) p=0.04). Intensity of alcohol consumption has not been reported as a predictor of renal disease in HIV patients on HAART. This is the first study to report alcohol use as a risk factor.

Conclusion and Recommendation:

Renal dysfunction might occur in HIV patients on nevirapine based regimens evidenced by the incidence of 4.3%. The risk factors identified in this study include age at diagnosis, alcohol consumption, duration of therapy and the female gender.

The elevated serum creatinine level at baseline is a key indicator in the management of renal dysfunction. Routine eGFR calculations should be done at each clinical visit. Early detection and vigilant monitoring is required for patients with the known risk factors; systematic screening and appropriate referrals for kidney disease management should be advocated for improved patient care. Larger studies comparing the contribution of other NNRTIs is recommended

CHAPTER ONE: INTRODUCTION

1.1 Background

HIV/AIDS is a global epidemic that has been steadily growing. According to the WHO-UNAIDS report 2012, 34 million people were living with HIV by the end of 2011. An estimated 0.8% of adults aged 15-49 years worldwide are living with HIV. The burden of the epidemic continues to vary considerably between countries and regions. It is a major cause of morbidity and mortality especially in Africa. The high prevalence of HIV/AIDS in Sub-Saharan Africa cannot be overemphasized with this region accounting for 68% of the estimated 33.2 million cases worldwide in. An estimated 1.8 million new infections occur each year.

From previous estimates of prevalence, there has been 27% increase in number of people living with HIV/AIDS globally in a span of a decade. Despite a decrease in the rate of new infections, HIV prevalence rate has not changed due to improved survival with use of antiretroviral therapy (UN Joint Programme on HIV, AIDS, Global Report, 2010). In Kenya the prevalence of HIV among adults aged 15-49 years stands at 5.6% which corresponds to approximately 1,192,000 persons living with HIV in 2012 (Kenya AIDS Indicator Survey, 2012)

The collective efforts of developed nations and international organizations have significantly reduced the impact of the HIV epidemic in developing countries, by scaling up care and treatment. Millions of eligible HIV infected patients have access to life prolonging ARV drugs. This has led to an appreciable decrease in HIV related morbidity and mortality. Expansion of antiretroviral programs raises the prospects of improving the long term prognosis of these patients provided they survive the acute phase of the illness (Kenya Aids Indicator Survey, 2007).

Renal dysfunction is an important complication of HIV infection and is becoming increasingly important as patients live longer in the era of combined antiretroviral therapy (ART). Cross sectional studies described a 4-17% prevalence of reduced

kidney function in diverse HIV-infected populations (Cheung et al 2007, Mocroft et al 2007, Fernando et al 2008). An understanding of each component of an ART regimen, HIV markers and demographic factors related to renal dysfunction is important to establish the relationship between ART, HIV infection and renal dysfunction (Flandre et al., 2011).

Although HIV associated renal disease has been documented in Sub Saharan Africa little is known about its prevalence or impact (Peters et al, 2008). Renal dysfunction is a severe complication of advanced HIV disease. Renal dysfunction may complicate antiretroviral treatment because some medications require dose adjustments (Izzedine at al 2003, Perazella et al 2003, Peyriere et al 2004).

The understanding of the pathogenesis of HIV/AIDS, its replication cycle and the mechanism of HAART related kidney disease is essential to adapt to future preventive measures such as dose adjustment, avoiding nephrotoxic drugs in patients at risk of developing kidney disease or having underlying renal diseases is important (Kundani et al 2011). Most related renal toxicities that have been studied are efavirenz based or protease inhibitors based ART and data on nevirapine based regimens is scanty (Manosuthi et al, 2010).

Nevirapine is one of the recommended first line NNRTIs and forms the backbone in HIV management. The most common adverse reactions to NVP are hypersensitivity reactions which include hepatotoxicity and skin rash. Most of these reactions are experienced within the first six months of treatment (Kesselring et al 2009). Across different populations the female gender and low CD4 counts are the most consistent risk factors for hypersensitivity reactions. Knowledge regarding whether there is renal injury when on treatment with nevirapine based regimens is lacking.

1.2 Problem statement

Renal dysfunction is mainly attributed to Tenofovir and protease inhibitors but no studies have been done to determine the contribution of other antiretroviral agents.

A study done in India (Dravid et al 2010) and an unpublished study done in Kenya (Masese et al 2009) found that patients on Tenofovir and Efavirenz combination had a higher incidence of renal dysfunction compared to patients on Tenofovir and Nevirapine combined therapy. On the other hand a study done in Thailand found that renal dysfunction was higher in patients receiving Tenofovir and Nevirapine combined therapy compared to Tenofovir and Efavirenz (Manosuthi et al 2009) It is therefore entirely plausible that other HAART components may play an important role in ARV associated renal dysfunction. Consequently clinical studies are required to examine the contribution of NNRTIs to renal dysfunction.

An unpublished preliminary pilot study of patients on Nevirapine based regimens indicates a seemingly high incidence of elevated creatinine levels .This elevation may be caused by co-administration with Tenofovir or other ARVs.

It is worth noting that Nevirapine is currently the most widely used NNRTI in the Kenyan setting and is structurally related to efavirenz. Therefore there is need to investigate the potential role of NVP based ART in the causation of HIV related kidney disease and determine the frequency of creatinine elevation and incidence of risk factors in our setting.

In addition data currently available on renal dysfunction is collected by high income countries and very few studies have been done in Sub Saharan Africa. Therefore, local data is needed. This is because available data may not be well representative as demographics, genetic background, concurrent medication and co-morbidities vary substantially.

1.3 Research question

What is the incidence and risk factors of renal dysfunction in HIV positive patients on Nevirapine based regimens attending the Comprehensive Care Clinic at the Kenyatta National Hospital?

1.4 Objectives

1.4.1 Broad objective

To evaluate the incidence and risk factors of renal dysfunction in HIV positive patients on Nevirapine based regimens at the Kenyatta National Hospital.

1.4.2 Specific objectives

1. To determine the incidence of renal dysfunction in patients on Nevirapine based HAART regimens as evidenced by creatinine elevation and reduced glomerular filtration rate (GFR).
2. To identify the risk factors of renal dysfunction in HAART patients on Nevirapine based regimens.

1.5 Study justification

There is limited data on the impact of ART on renal disease in Africa, and the long-term nephrotoxicity of Nevirapine has not been studied in resource limited settings in which unfavorable combinations of risk factors are common. A number of studies have been done in the developing countries assessing renal dysfunction associated with TDF but few have been done in African population as a group that have been reported to be vulnerable.

Since there is no published information on the incidence on chronic kidney disease or acute kidney disease or other related disorders amongst patients on NNRTIs, studies are required to systematically evaluate the renal toxicity associated with NNRTIs containing regimen and plausible risk factors. The study will provide insight on risk factors that cause renal disease in HIV and will contribute better to patient management.

CHAPTER TWO: LITERATURE REVIEW

2.1 Spectrum of kidney disease in HIV/AIDS infection

Renal complications of HIV infection are numerous and are classified as direct and indirect complications. Direct complications include HIV associated nephropathy (HIVAN), immune complex kidney disease and acute renal failure. Indirect renal complications are caused by opportunistic infections and medication. Currently there is evidence of more prominent role for drug related adverse effects than nephropathy caused by the virus itself (Kundani et al 2010).

The kidney plays a major role in metabolism and excretion of ARVs and this makes it vulnerable to various types of injuries from some of these agents (Hall et al, 2009). Approximately 6% of HIV infected patients develop one or multiple episodes of AKD and 15% of patients have evidence of CKD (Campbell et al, 2009).

2.2 Classification of kidney complications

2.2.1 Acute and Chronic Kidney Disease

Acute Kidney Disease is a clinical syndrome defined as an abrupt decrease in GFR over days to weeks. For toxicity grading purposes, it has been defined as an increase in serum creatinine level to values >1.5mg/dl, that returns to baseline values within 3 months.

Chronic Kidney Disease is defined as either evidence of kidney damage or GFR<60 ml/min per 1.73 m^2 that persists for $\geq$ 3 months. The severity of CKD is graded according to renal function, on the basis of estimates of creatinine clearance, calculated using the Cock-Craft Gault equation or MDRD equations presented in Table 1 (Gupta et al 2005).

Table 1.1: Stages of chronic kidney disease (Gupta et al., 2005)

Stage	Description	GFR, ml/min per $1.73m^2$
I	Kidney damage with normal or increased GFR	≥90
II	Kidney damage with mildly decreased GFR	60-89
III	Moderately decreased GFR	30-59
IV	Severely decreased GFR	15-29
V	Kidney failure	<15 (or dialysis)

2.2.2 RIFLE classification of acute kidney disease

According to the RIFLE criteria, AKD is divide into three grades of increasing severity.The following three categories of increasing severity are used; Risk, Injury and Failure. In addition there are two other grades of severity which are Loss and End stage.This classification is as presented in shown Figure 1.1.

The RIFLE classification has been validated in clinical settings for predicting patient outcome (Zhuang et al 2013). Several studies have shown the RIFLE classification to be a simple, readily available clinical tool to classify acute kidney injury in different populations (Park et al 2010).

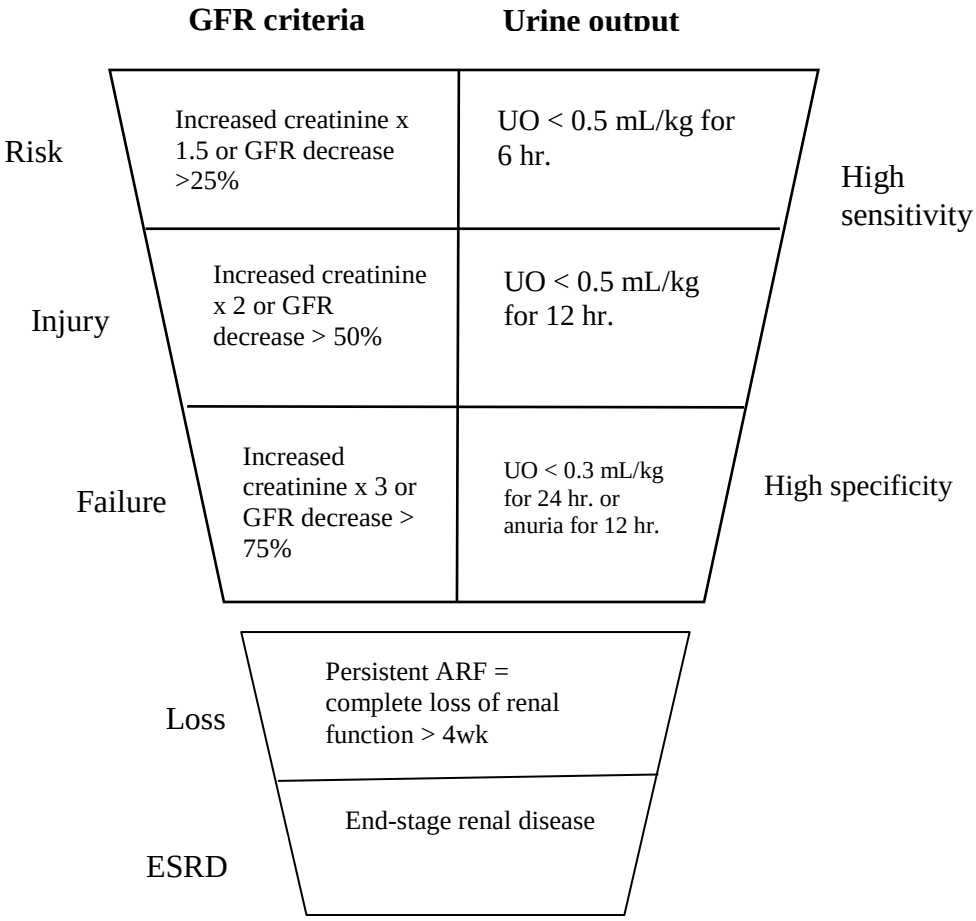

Figure 1.1: RIFLE classification of drug induced kidney disease
Adopted from the Risk Factors and Outcomes of Acute Kidney Injury by Park W.Y Korean Journal of Internal Medicine 2010

2.3 Epidemiology of HAART induced renal dysfunction

Acute Kidney Disease (AKD) that develops in the setting of HIV infection typically occurs with severe opportunistic infections, rather than as a sole consequence of direct toxicity of anti-retroviral therapy. However, antiretroviral nephrotoxic effects accounted for 14% of late onset AKD episodes, occurring after 3months of initiating HAART. Antiretroviral therapy has also been associated with CKD. The major drugs implicated in this include indinavir, atazanavir and tenofovir.

The Development of Antiretroviral therapy in Africa (DART) trial examined 3,316 symptomatic ARV naïve adults from Uganda and Zimbabwe with CD4< 200 cells who were initiated on HAART with zidovudine -lamivudine plus tenofovir (74%); nevirapine (16%) or abacavir (9%). The study concluded that severe kidney dysfunction (GFR <30ml/min as estimated by the Cockcroft – Gault formula) occurred only in 2.7% of patients on all regimens and kidney disease contributed to death in a minority of patients, which was generally related to concurrent disease (Kalyesubula et al, 2011).

2.4 Risk factors for drug induced renal dysfunction

Risk factors for renal dysfunction are numerous and depend on underlying patient characteristics as well as the drug regimen under consideration. The risk factors for kidney disease in HIV infection include: African descent, female gender, older age, elevated baseline creatinine concentration, low CD4 counts (<200 cells/ml), high viral load (>4000 copies/ml), low BMI, co-morbidities especially diabetes, hypertension, hepatitis B and C infection. Life style habits such as cigarette smoking, use of nephrotoxic drugs and longer overall antiviral treatment duration pose as risks of the same which create a vicious cycle (Campbell et al 2009; Rho & Perazella, 2007; Kalyesubula et al 2011).

Diabetes mellitus and hypertension are the two most frequent causes of CKD in the general population. They increase the risk of CKD by 10 fold and account for 71% of all ESRD cases (Winston et al 2008). Acute Kidney Disease usually occurs in the setting of severe (opportunistic) infections, malignancy or liver disease. Both AKD and CKD are associated with advanced immunodeficiency.

Many known nephrotoxic drugs have been implicated in the setting of HIV infection. The drugs include aminoglycosides, amphotericin B, cidofovir, foscarnet; pentamidine, co-trimoxazole in high IV doses. acyclovir, rifampicin, sulphadiazne, β-lactam antibiotics and non-steroidal anti-inflammatory drugs (NSAIDS).

2.5 Clinical presentations of HAART related kidney disorders

Clinically, HAART causes various kidney syndromes including various electrolyte and acid base disorders, AKD, lactic acidosis and CKD. These injuries occur via multiple mechanisms, including direct tubular toxicity, allergic reactions and precipitation of insoluble drug crystals within renal tubular lumens (Kalyesubula et al 2011).

The signs and symptoms of kidney disorders include hematuria, flank pain with extra renal signs such as edema and hypertension. Patients are usually asymptomatic. Laboratory signs include elevated serum creatinine and abnormal urinalysis results

2.6 Patient monitoring and screening for renal dysfunction

Kidney disease is frequent in and /or co-morbidity in HIV infection affecting up to 30% of HIV infected persons. It tends to be asymptomatic and is usually not the primary focus of a visit to an HIV clinic. The presence of kidney disease should be anticipated, screening and proper interpretation of the relationship between serum creatinine level and GFR are recommended (Winston et al 2008)

The HIV Epidemiology Research Study (HERS) emphasized the importance of closely monitoring serum and urine chemistries in HIV – infected patients, especially those with risk factors for renal dysfunction (Gardner et al 2003). As per the current guidelines for ARV therapy, all HIV-infected patients should be screened for kidney disease at the time of HIV diagnosis or entry into care. Patients with additional risk factors or exposure to nephrotoxic medication should be screened annually. Individuals without risk factors may be rescreened based on clinical signs and symptoms.

The screening tests include dipstick urinalysis and calculated estimate of renal function (using the Cockroft-Gault Equation). If screening shows elevated creatinine clearance (CrCl) or estimated GFR (eGFR) <60 ml/min/1.73 m2, or proteinuria ≥1+ on urine dipstick analysis consultation with a specialist physician

is advised (Ministry of Health, 2011). The screening of kidney disease in HIV infection is as presented in figure 1.2

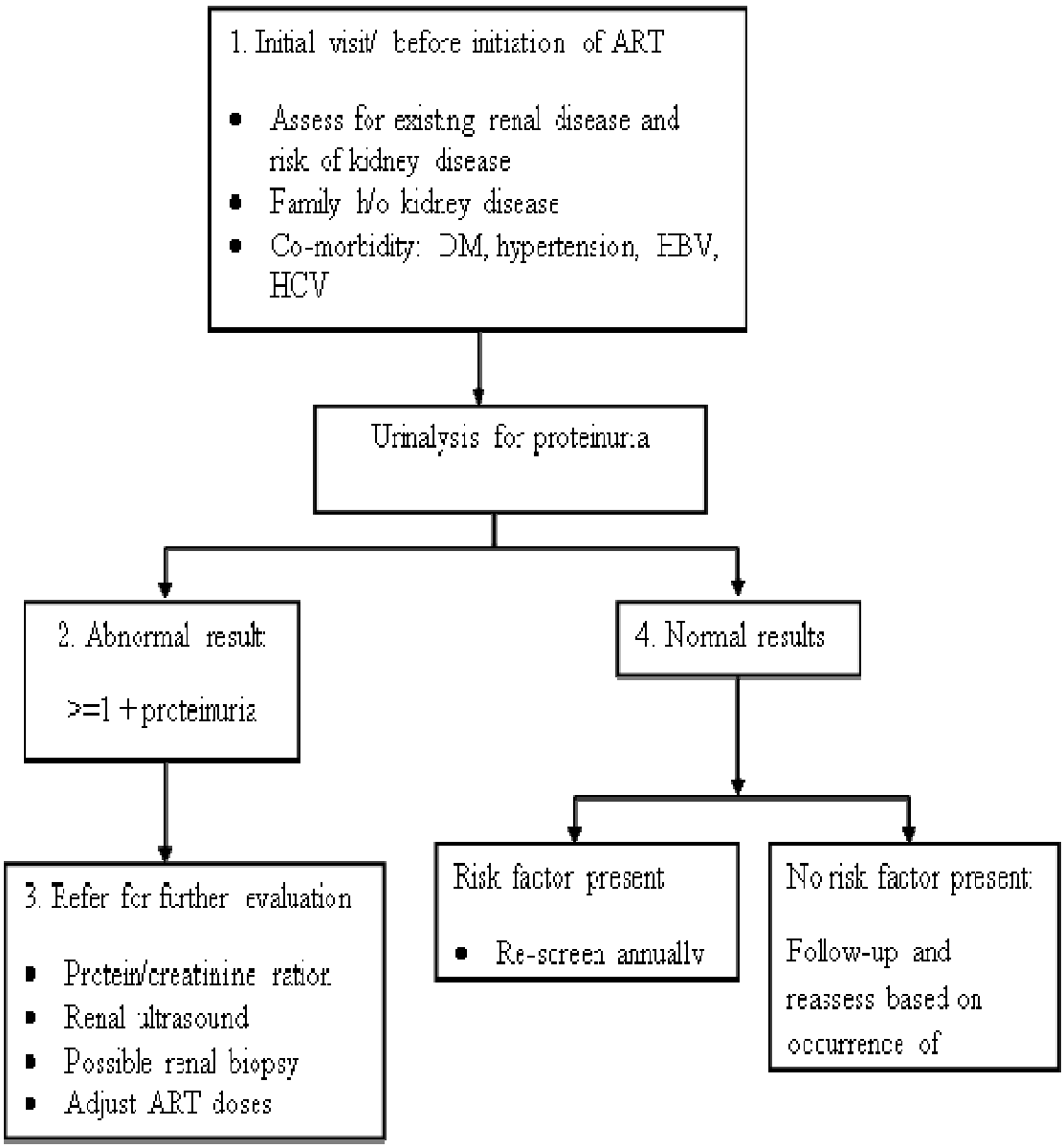

Figure 1.2**: Screening of kidney disease in HIV infection**

Adopted from the Ministry of Health Guidelines for antiretroviral therapy in Kenya (4th edition 2011)

The management of kidney disease is summarized in Table 2.1 (Ministry of Health Guidelines 2011).

Table 2.1**: Management of kidney disease in HIV infection**

Intervention	**Comments**
General measures Treat dehydration promptly and aggressively Avoid nephrotoxic drugs Life style measures (smoking, weight, diet) Treat dyslipidemia, diabetes and hypertension Adjust drug dosages where necessary	Refer for further evaluation patients with Persistent proteinuria, CrCl<60, HBC/HCV co-infection
Start ACE inhibitors if: a) Hypertension, and/or b) Proteinuria	Target BP: SBP <130mm/Hg, DBP <80 mm/Hg
ART	Start ART in ALL HIV-positive patients with persistent proteinuria and oedema irrespective of CD4 count

Adopted from the Ministry of Health Guidelines for antiretroviral therapy in Kenya (4th edition 2011)

CHAPTER THREE: METHODOLOGY

3.1 Study Design

This study design was a descriptive (right censored arm) hospital based retrospective cohort study to determine the incidence and establish the risk factors of renal dysfunction among HIV positive patients on nevirapine-based.

Censoring occurred at the time of recruitment since data was not collected after the date of recruitment. This study was selected since it allowed retrospective evaluation of patient records as well as active recruitment of the patients to supplement the data abstracted from the files.

3.2 Study Area

This study was conducted from May to August 2014 at Kenyatta National Hospital Comprehensive Care Clinic (CCC). The hospital is located at the Kenya's capital city of Nairobi and is the largest teaching and referral Hospital in the country. The hospital CCC is among the first clinical units established by government to provide specialized HIV/AIDS care and treatment services. The CCC is one of the chronic follow-up clinics, with over 5,000 patients enrolled on care and treatment. Usually patients visit the clinic for routine medical follow up and medication refills. During these visits, patients are routinely monitored for liver and renal function and their CD4 cell count. Viral load testing is conducted selectively to confirm suspected treatment failure.

The site was ideal for this study because of the diversity of patients who are enrolled at the clinic, large number of patients on ART and excellent set up with specialized personnel and facilities.

3.3 Study Population

The target population was HIV/AIDs positive adult males and female aged between 18 and 55 years on any Nevirapine containing HAART regimen and seen at the CCC between May and August 2014.

3.4 Inclusion and Exclusion criteria

Patients were included into the study if they were HIV positive adult patients, on nevirapine-containing regimen for at least 6 months, aged between 18 and 55 years, should not have had a history of kidney disease prior to use of anti-retroviral drugs and willingly consented to take part in the study.

Patients were excluded if they were on nevirapine-containing regimen for less than 6 months, declined to give consent and aged below 18 years or above 55 years. In the study participants below 18 years were excluded because they could not give consent and those above 55 years because of the likelihood of predisposition to nephrotoxicity.

3.5 Sample size determination

The sample size was calculated using the formula described by Hulley et al (2013) for estimation of sample size of a dichotomous variable in a cohort study. The calculated minimal sample was 138 based on literature review of local studies that reported an expected prevalence of renal dysfunction of 10% (Wools-Kaloustian et al, 2007). The following formula was used;

$$\mathbf{N= 4\ Z\alpha^2\ P\ (1-P) \div w^2}$$

Where

N is the total sample required for the study

Zα is the standard normal deviate for a two sided α (for a 95% confidence level Zα = 1.96).

P is the expected prevalence of renal dysfunction (for this study it is 10%)

W is the width of the confidence interval (in this case, set at 10%)

$N= \{4 \times 1.96^2 \times 0.1(1-0.1)\} \div 0.1^2$

=138

To accommodate for expected missing files or incomplete data entries of about 20%, the calculated sample size was inflated by 20%. Therefore a minimum sample size of 166 participants was targeted.

3.6 Sampling method and patient recruitment strategy

Participants were sampled by convenient sampling method. Trained Pharmacy personnel for the study were involved in participant recruitment. They administered the informed consent form and any unresolved matters were resolved by the principal investigator. Patients were recruited as they collected their drugs from the CCC pharmacy in the privacy of the dispensing booths to minimize interruption. All adult patients on NVP based regimens and who meet the eligibility criteria were invited to participate. The appended consent forms (Appendix B) was administered by the Pharmacy personnel. Recruitment was continued until required sample size was achieved. Out of the 300 patients recruited, 241 met the eligibility criteria. A list of patients who agreed to participate was generated and given to the Records Department for the purpose of retrieving the patient files for data abstraction.

3.7 Data collection procedure

This was divided into 2 parts: the first part involved patient interview using a questionnaire; part two entailed retrospective assessment of patient records to abstract laboratory and clinical information, including evidence of the risk factors and clinical signs of renal dysfunction.

Patient interview

Patients were taken through a brief interview with the aid of a case report form. This was done to obtain information on, self-reported medication related problems, marital status, alcohol use, use of herbal and non-prescription preparations smoking status and educational level. This was used to supplement information obtained from patient medical records. The data collection form that was used is attached (Appendix C).

Abstracting patient files

During the patient interview, the patient file number was noted. This file number was given to the Records Department who were asked to retrieve the medical records. All notes and abstraction were done in the records office and files returned immediately.

The medical files of recruited patients were retrieved and the following information abstracted: socio demographic characteristics; medical and medication history; laboratory values which included creatinine levels, baseline CD4 count; history of pre-existing kidney disease, any adverse drug event; history of hypertension and diabetes and documented clinical signs of nephrotoxicity. The data collection form is appended (Appendix D).

3.8 Case Definition

The following approaches were used to access the presence of renal dysfunction

a.) Simple elevation of measured serum creatinine using a cut off value of 120µg/l which is the upper limit of the normal in KNH-CCC

b.) Second approach was based on the four variable modification of diet in renal disease(MDRD) equation for the classification of chronic kidney disease(CKD).This classification was based on values given in literature (Gupta et al 2005).

$$\textbf{GFR (ml/min/1.73m}^2\textbf{=186*serum creatinine (mg/dl)}^{-1.154}\textbf{*age (years)}^{-0.203}\textbf{*0.742(if female)*1.212(if black)}$$

Where the serum creatinine was in mg/dl and the age is in years. If the serum creatinine was in micromole /L, it was divided by 88.4 to convert it to mg/dl.

An eGFR cut off value of <50ml/min/1.73m^2 was used to dichotomize patients into renal insufficiency and relatively normal renal function. This has been obtained in studies done both locally (Western Kenya study) (Wools-Kaloustian et al 2007) and internationally. The <50ml/min threshold is usually used for dose adjustment in most guidelines (Cockcroft et al 1999).

3.9 Variables and outcomes

The main outcome of interest was developing renal dysfunction as defined in section 3.8. The covariates that were considered in the identification of the key risk factors for renal dysfunction included patient demographics, baseline tests, co-morbidities (diabetes and hypertension),drugs taken (especially known nephrotoxic drugs) and ART regimen. Confounders in the study were, use of other nephrotoxic drugs, low BMI, low CD4 cell count (<200) and age above 40 years.

3.10 Quality Assurance

A pretest study was done before initiating data collection and the findings were used to improve and modify the design of the data collection tools. Using the data collection tools in Appendices C and D, data was collected from 20 patients who were selected randomly. Significant shortcomings in the design of the tools were noted. Adjustments were made to the tools so as to eliminate any ambiguities, improve clarity and the quality of data collected.

All parties involved received training on the study; this included the data clerks and research assistant. All data entries were double checked against the source document by the investigator. The raw data generated during the course of the study and the final report was subjected to inspection and quality audit for conformity to set protocols by the investigator.

3.11 Data Management

Confidentiality was maintained by not recording the patients name and number in the data collection forms. Each study participant was allocated a unique identifier number that was used throughout the study. All the raw data collected was filed and kept under lock and key by the researcher. The data identifying each study participant by name was kept confidential and was accessible only to the principal investigator.

All data generated during the study was directly entered in the raw data recording forms (Appendices C and D). All the data was examined for any inconsistencies and any errors noted and duly corrected. The patient's files were revisited for verification of any missing information. The data was entered on an excel spread sheet and later copied into the STATA version 10. The data was cleaned and any changes made to the original copy were recorded. Accuracy of the data entry was checked randomly by sampling at least 30 case files; data on these files was compared with the hard copies and data entered into the spread sheet.

All the data and documents were backed up at the end of each day in a CD and flash disc, a second copy was stored by the supervisors under lock and key. This was done regularly to avoid loss or tampering. All the data was password protected

3.12 Statistical Analysis.

Data collected was coded and entered into an excel sheet. It was analyzed using STATA intercooled version 10. Descriptive data analysis was carried out on all variables. The Shapiro wilk test was used to determine which continuous variable conformed to normal distribution. For those continuous variables that were not normally distributed, the median and interquartile range (IQR) was reported.

For all categorical variables the proportionate comparison and the 95% confidence intervals (95% C.I) was reported. Pearson chi square test was done to compare the distribution of various variables with the major outcome of interest.

The key risk factors for development of renal dysfunction were determined using ordered regression modeling. All variables with a P-value lower than 0.20 at bivariable analysis were entered into a multivariate model (if clinically meaningful) use forward stepwise selection method. Since some variables are not significant on bivariable analysis while in reality, they become significant om multivariable analysis a less stringent cut-off of p-value of ≤ 0.2 was used to select variables to include in the multivariable model. All analyses were performed using STATA version 10 (StataCorp 4905 Lakeway Drive College Station, Texas 77845 USA). For multi-variable analysis P values less 0.05 were considered statistically significant

3.13 Ethical Considerations

Ethical approval for this study was sought from KNH-UoN Ethics and Research Committee (Ref; P92/02/2014). Written informed consent was obtained from the patients. Potential participants were informed about the study through an oral presentation regarding the purpose, procedure to be carried out, potential hazards and rights of the participant. They were required to understand and sign a consent form summarizing the discussion prior to admission in the study (Appendix A). A copy of the informed consent was given to participants and a second copy was retained by the principal investigator.

There were no direct benefits to the patients whose files were used in the study neither were there any risks involved in carrying out the study. However, the findings were communicated to the KNH- CCC to contribute to improving of the quality of services offered there.

Participants were informed that they are free to drop-out from the study at any time without stating a reason. Details of withdrawal of participants who withdrew were recorded and reported. Every effort was made to obtain a complete follow-up for any withdrawal.

Confidentiality of patient records was assured by reviewing the patient files in the pharmacy department and storing the files were under lock and key when not in use. The abstracted information was stored in password protected computer files to restrict access. Patient names were not included in the data collection tool and patients were assigned patient numbers in place of hospital identification numbers. The data extracted was stored securely.

CHAPTER 4: RESULTS

4.1 Study Cohort

Three hundred patients were assessed for eligibility and 241 patients were finally included in the study as they met the inclusion criteria. Out of the 300 patients 30 patients did not meet the inclusion criteria,12 patient files had missing data,9 patient files did not have their baseline laboratory records and 8 patient files could not be traced at the time of the study. The final study cohort had 241 patients. Figure 4.1 presents the consort diagram for the cohort.

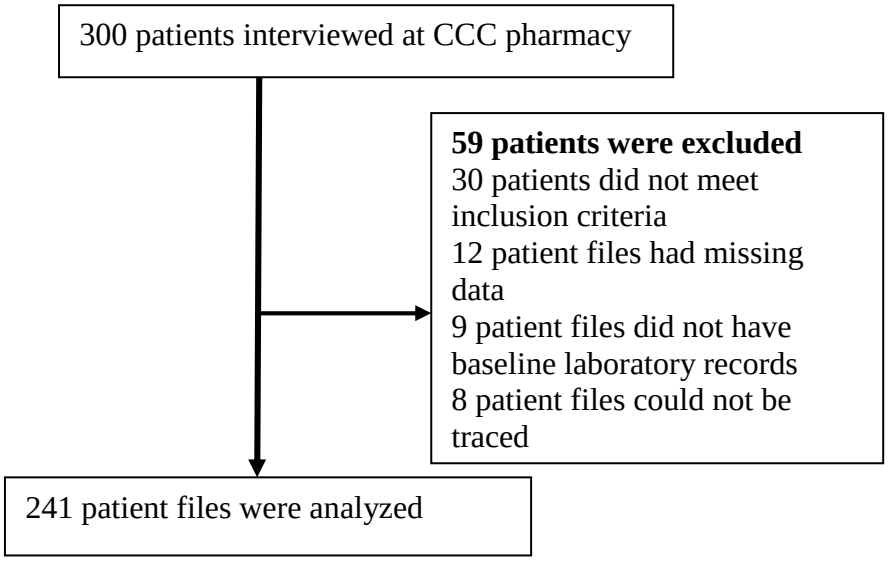

Figure 4.1**: Consort diagram for the patient recruitment strategy**

4.2 Baseline characteristics of the study participants

The baseline characteristics of the 241 patients included in the study are summarized in Table 4.1.Most of the patients [185 (76.8%)] were females. The median age was 39 years (IQR 35-44). Nearly half [116(48.1%)] were more than forty years old. The median body weight at baseline was 63.4kg (range 52-70kg). More than half [147(61%)] weighed less than 65kg. Seventy two (29.9%) participants took alcohol occasionally (less than twice a month) whereas two participants (0.8%) took alcohol regularly. Five (2.1%) patients were smokers. The duration of follow up for most of the patients was 5 years. The median duration of follow up for the entire cohort was 4.75 years (range 3.34-6.6). Most (68.5%) patients had attained primary and secondary education.

Table 4.1**: Demographic and Clinical characteristics of the study cohort**

Variables	Median [IQR] or n (%)
Sex	
Male	56 (23.2)
Female	185 (76.8)
Age at diagnosis (years)	39 [35,44]
Weight at diagnosis (kg)	62 [56,70]
Age	
≤40	125 (51.9)
≥40	116 (48.1)
Weight (kg)	
≤65	147 (61)
≥65	94 (39)
Height (cm)	162 [158,168]
Marital status	
Married	155 (64.3)
Single	57 (23.7)
Divorced	4 (1.7)
Widowed	24 (10.0)
Separated	1 (0.4)
Education	
Primary	48 (19.9)
Secondary	117 (48.6)
Diploma	57 (23.7)
Degree	19 (7.9)
Employment status	
Unemployed	18 (7.5)
Employed	108 (44.8)
Self-employed	115 (47.7)
Alcohol use	
Never	167 (69.3)
Occasionally	72 (29.9)
Regularly	2 (0.8)
Smoking	
No	236 (97.9)
Yes	5 (2.1)
CD4 cell count x10^9/L	206[127-270]
≤200	158 (65.6)
≥200	68 (28.2)
Missing values	15 (6.2)
BMI at initiation of HAART	23.38[21.34-25.95]
≤18.5	15 (6.2)
≥18.5	226 (98.3)
Concurrent illness	
None	182 (75.5)
Hypertension	36 (14.9)
Diabetes	3 (1.2)
PUD	4 (1.7)
Asthma	3 (1.2)
Chronic pain	5 (2.1)
Other conditions	8 (3.6)
Regimens at initiation of HAART	
TDF, 3TC, NVP	71 (29.5)
AZT, 3TC, NVP	78 (32.4)
D4T, 3TC, NVP	85 (35.3)
D4T, 3TC, EFV	1 (0.4)
AZT, 3TC, EFV	3 (1.2)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index, calculated as the weight in kilograms divided by the square of height in meters; IQR, interquartile range ;PUD-peptic ulcer disease, URTI-upper respiratory tract infection**.**

At the initiation of treatment 158 (65.6%) patients had a CD4 cell count of less than 200cells/mm^3. Fifteen (6.2%) had a body mass index (BMI) of below 18.5kg/$m.^2$ Ten (4.2%) participants had an elevated serum creatinine (above 120μmol/l). The median serum creatinine level was 80 (66-92) μmol/l.

The prevalence of most co-morbidities in the subjects was less than 24.7%.The most prevalent conditions were hypertension (14.5%) and diabetes (1.2%). Most of the patients [203 (84.2%)] were not taking concomitant medications. Five patients (2.1%) took analgesics, 5 others took supplements and 6 patients were on an antihistamine.

4.3 Antiretroviral treatment regimens used by participants

Two hundred and thirty four (97%) patients had been started on Nevirapine based regimens, the other seven (3%) were initiated on efavirenz based regimens. Those previously on efavirenz based regimens had been switched to a Nevirapine based regimen at the time of the recruitment into the study. The most widely regimen patients were initiated on was compromised of stavudine, lamivudine and Nevirapine [85(35.3%].

Of the 241 patients in the study cohort, ninety two patients experienced regimen switches in the course of their therapy. Most of the patients 70 (29.0%) were switched from D4T/3TC/NVP to TDF/3TC/NVP. The most common reason for regimen switch was development of an adverse drug reaction, such as skin rash and a change in the treatment guidelines. The types of regimens at treatment initiation and at the time of study for the study patients are presented in Table 4.2

Table 4.2: **HAART regimens at treatment initiation and time of the study**

Regimen at initiation	**Regimen at time of study**	**Patient (%)**
Patents who did not switch regimens		
D4T/3TC/NVP	D4T/3TC/NVP	10 (4.1)
AZT/3TC/NVP	AZT/3TC/NVP	72 (29.8)
TDF/3TC/NVP	TDF/3TC/NVP	68 (28.0)
Subtotal		150 (62.0)
Patients who switched regimens		
TDF/3TC/NVP	AZT/3TC/NVP	3 (1.2)
AZT/3TC/NVP	TDF/3TC/NVP	6 (2.5)
AZT/3TC/NVP	ABC/3TC/NVP	1 (0.4)
D4T/3TC/NVP	TDF/3TC/NVP	70 (29.1)
D4T/3TC/NVP	AZT/3TC/NVP	5 (2.1)
D4T/3TC/EFV	TDF/3TC/NVP	1 (0.4)
AZT/3TC/EFV	AZT/3TC/NVP	3 (1.2)
TDF/3TC/EFV	TDF/3TC/NVP	3 (1.2)
Subtotal		92 (38.0)

TDF: Tenofovir; 3TC: Lamivudine; NVP: Nevirapine; AZT: Zidovudine; D4T: Stavudine; ABC: Abacavir; EFV: Efavirenz.

4.4 Renal function at initiation of therapy

Based on the renal function twenty patients (20) did not have their baseline creatinine levels recorded and with reference to the eGFR calculation in addition two patients did not have their age recorded making the missing values on eGFR to be twenty two (22).

For the 221 patients with complete data, 211 patients (87.6%) had normal serum creatinine levels (≤ 120 up/dl). Ten patients (4.2%) had elevated baseline serum creatinine values (>120 up/dl). The median serum creatinine was 80 (IQR 66-92) ug/dl.

The estimated GFR was calculated using the MDRD formula which is used to measure the severity of CKD. The cut off was set at <50ml/min/1.73m^2. Five

(2.1%) of the 219 patients with complete data had renal insufficiency (eGFR <50ml/min).

A summary of the baseline renal parameters is presented in Table 4.3

Table 4.3**: Baseline renal function of the study participants**

Renal Parameter	**Median [IQR] or n (%)**
Serum Creatinine (absolute)(ug/dl)	80[66-92]
≤ 120	211 (87.6)
≥120	10 (4.2)
Missing values	20 (8.3)
Estimated GFR (ml/min/1.73m^2)	101.67[80.72-120.19]
eGFR>50	214(88.8)
eGFR<50	5(2.1)
Missing values	22(9.1)

4.5 Severity of Renal dysfunction at baseline.

The criteria which used to classify the severity of renal disease, was the four variable modification of diet in renal disease (MDRD) classification. It was noted that in most publications the cut off for chronic kidney disease (CKD) using the MDRD classification has been set at <60ml/min/1.73m^2 (Peters et al 2008). When this cut off was applied in this study 70% of the patients would have been classified as having mild renal disease, with 14% having moderate to compromised renal function. As this was seemed exaggerated a conservative cut off of <50ml/min/1.73m^2 was selected which captured 10(4.6%) patients as having renal dysfunction.

Based on the MDRD criteria, 139 patients (63.5%) were found to have normal renal function; 70 (32.0%) were had borderline renal disease; 10 (4.6%) had moderate renal function. This is summarized in Figure 4.2

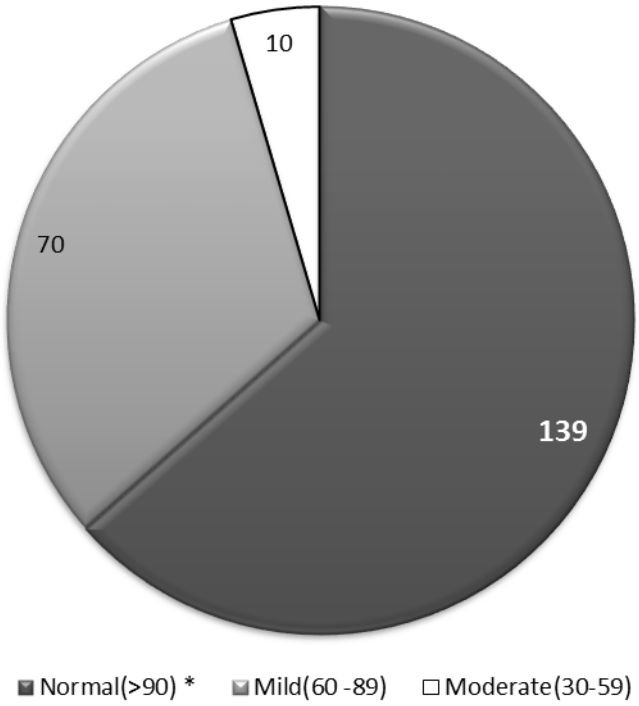

Figure 4.2: **Classification of renal dysfunction using the MDRD criteria at baseline (Gupta et al, 2005)**

4.6 Prevalence and incidence of renal disease in study cohort.

The prevalence of renal disease at baseline in our study cohort was 6.3% (95% C.I, 3.20-9.44), it will be noted that five patients already had renal disease at baseline. Out of the 241 patients 22 patients had no baseline serum creatinine readings hence their eGFR could not be calculated therefore this may not be the true prevalence for this cohort. In this study cohort 10 patients who had normal renal function at baseline developed renal disease; the incidence was 4.3% (95% C.I 1.68-6.94).

4.7 Changes in estimated GFR with time

In order to examine the trend in changes in estimated GFR with time, lowess plots were generated using Stata version 10. A lowess plot is a summary measure of the weighted median of a series of estimated GFR readings. The graph for the patients who had normal estimated GFR at baseline is presented in Figure 3.3.

Renal function showed initial improvement, followed by almost linear deterioration with time. Renal function declined by about 10 units from 104 to 94ml/min, over an 8 year period.

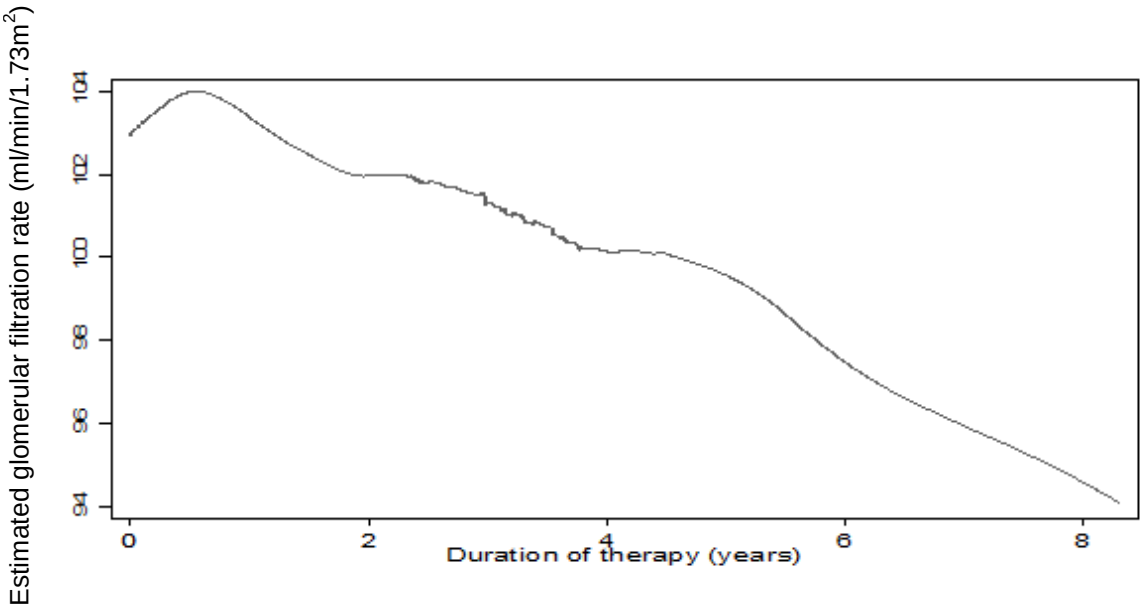

Figure 4.3: **The Lowess graph of patients whose eGFR was normal at baseline**

Figure 4.4 represents the lowess plot for patients who had compromised renal function at baseline. In this the patients, initiation of HAART caused a steep improvement in estimated GFR within the first year of initiation. This improvement plateaued and after the fourth year of treatment there was a decline in estimated GFR.

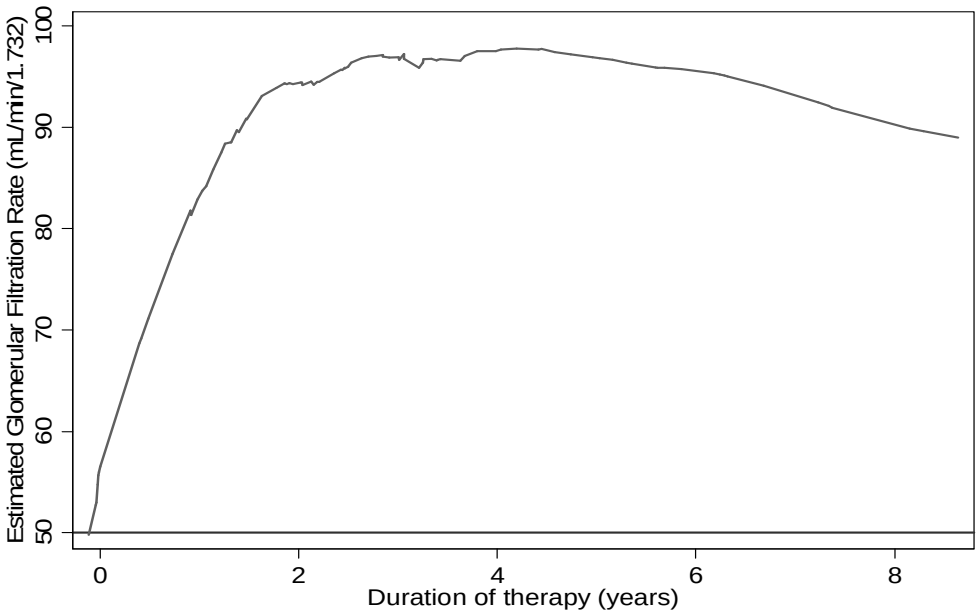

Figure 4.4**: The Lowess graph of median changes in eGFR in patients whose baseline eGFR was less than 50ml/min/1.732m^2.**

4.8 Comparison of baseline characteristics of patients with and without renal disease

The baseline characteristics of patients with and without renal disease were compared and summarized in Table 4.4. Complete data was available for 219 patients.

On comparison of the distribution of the variables across those who developed renal disease and those who did not there was a statistically significant difference for the following: age at ART initiation, alcohol consumption, baseline serum creatinine levels, and the CKD severity based on the GFR (p=<0.01).

Though there were no statistically significant differences across arms for sex (p=0.76), more females than males developed renal disease. Twelve (6.6%) female patients showed signs of renal disease compared to the male who were only 3 (5.5%). Four patients (3.3%) less than forty years developed renal disease. Those more than 40 years were 11(9.6%). This showed that age was a significant factor (p=0.04). The fifteen patients who had BMI above 18.5kg/m^2 developed renal disease

Table 4.4: **Comparison of the baseline characteristics by the status of renal function**

Predictor variable	NO RENAL DISEASE (%) (eGFR>50ml/min/1.73m^2)	RENAL DISEASE (%) (eGFR<50ml/min/1.73m^2)	P value[a]
Age at ART initiation (years)			
≤ 40	118 (96.7)	4 (3.3)	
> 40	104 (90.4)	11 (9.6)	**0.04**
Weight (kg)			
<65	136 (93.8)	9 (6.2)	
>65	86 (93.5)	6 (6.5)	0.92
Sex			
Female	170 (93.4)	12 (6.6)	
Males	52 (94.5)	3 (5.5)	0.76
Alcohol use			
Never	158 (95.8)	7 (4.2)	
Occasionally	64 (90.1)	7 (10.9)	
Regularly	0 (0)	1 (100.0)	**<0.01**
Smoking			
Non	217 (93.5)	15 (6.5)	
Yes	5(100.0)	0 (0)	0.56
Regimen at ART initiation			
TDF,3TC,NVP	66 (94.3)	4 (5.7)	
AZT, 3TC, NVP	74 (96.0)	3 (4.0)	
D4T, 3TC, NVP	77 (91.7)	7 (8.3)	
D4T, 3TC, EFV	1 (100.0)	0 (0)	
AZT, 3TC, EFV	2 (66.7)	1 (33.3)	
TDF, 3TC, EFV	2 (100.0)	0 (0)	0.38
Concurrent illnesses			
None	168 (93.9)	11 (6.1)	
Hypertension	32 (91.4)	3 (8.6)	
Diabetes	2 (66.7)	1 (33.3)	
PUD	4 (100.0)	0 (0)	0.87
Asthma	3 (100.0)	0 (0)	
Chronic pain	5 (100.0)	0 (0)	
Depression	1 (100.0)	0 (0)	
URTI	1 (100.0)	0 (0)	
Anemia	1 (100.0)	0 (0)	
Other illnesses	7 (100.0)	0 (0)	
Body mass index(kg/m2)			
< 18.5	15 (100.0)	0 (0)	
>18.5	207 (93.2)	15 (6.8)	0.30
Serum Creatinine (absolute)[b]			
≤ 120	201 (95.7)	9 (4.3)	
>120	4 (40.0)	6 (60.0)	**<0.01**
CKD Severity(eGFR<50ml/min)[b]	135 (97.1)	4 (2.9)	
Stage 1 (normal)	66 (94.3)	4 (5.7)	**<0.01**
Stage 2 (mild)	3 (30.0)	7 (70.0)	
Stage 3 (moderate)			
CD4 cell count×10^9/L[b]			
≤ 200	144 (92.9)	11 (7.1)	
>200	63 (94.0)	4 (6.0)	0.76

[a]Chi square measure of association was used to assess whether there was significant association between the various predictor variables and the renal disease status [b] Twenty patients did not have baseline serum creatinine values and CD4 cell count values. Significant P-values are in **bold**

The only patient who reported regular alcohol consumption developed renal disease. Seven out of 158 patients (4.2%) of those who did not consume alcohol developed renal disease as opposed to 7 out of 64 (9.9%) who occasionally took alcohol. Therefore the occasional alcohol consumption was associated with in a higher incidence of renal disease ($p<0.01$).

The patients who developed renal disease and had baseline serum creatinine levels below 120 were 9 (4.3%); those with more than 120 were 6 (60%). Serum creatinine levels above 120 was statistically significant ($p<0.01$). Therefore baseline serum creatinine levels can be used as an early tool to rule out risk of developing renal disease. The baseline CD4 cell count of <200cells/mm^3 was not a statistically significant predictor ($p=0.76$) despite the fact that it is a documented risk factor.

With reference to the HAART regimen at initiation of therapy, it was notable that 7 patients (8.3%) on D4T, 3TC and NVP, developed renal disease. Patients who were initiated on stavudine based regimens had the highest rate of renal impairment (8.3%), this was followed by patients on tenofovir (5.7%) and patients initiated on zidovudine had the lowest of (4.0%). One out of the three patients who were initiated on AZT/3TC/EFV developed renal disease but it was not possible to determine whether this was clinically significant because of the small number of patients. However there was no statistically significance in the distribution of renal dysfunction across the regimens ($p=0.38$).

Having concurrent illnesses was not a statistically significant predictor ($p=0.8$). Out of the 32 patients who were hypertensive, three patients (8.6%) developed renal disease and one patient (33.3%) who had diabetes also developed renal disease

4.9 Multivariable analysis- Risk factors for nephrotoxicity in with normal baseline function

Ordered Logistic Regression was done to identify variables predictive of the severity of nephrotoxicity. Bivariable and multivariable analyses were conducted and the results are presented in Table 4.5.

Table 4.5: **Risk factors for renal disease in patients with normal baseline renal function**

Variable	Crude OR (95% CI)	P-value*	Adjusted OR (95% CI)	P-value*
Age at diagnosis(years)	1.005(1.004-1.008)	**0.03**	1.004 (1.10-1.47)	**0.03**
Current age(years)	1.11 (1.06-1.17)	**<0.01**	1.09 (1.05-1.15)	**<0.01**
Initial weight(kg)	0.99 (0.97-1.01)	0.28	-	
Height (cm)	0.60 (0.02-27.33)	0.80	-	
Sex	0.61 (0.31-1.20)	0.15	0.48 (0.24-1.04)	**0.04**
Marital status	1.25 (0.94-1.66)	0.13	-	
Education	1.05 (0.75-1.47)	0.77	-	
Smoking	5.43 (0.09 -3.36)	0.52	-	
Alcohol	1.58 (0.89-2.83)	0.12	1.84 (1.01-3.29)	**0.04**
Concurrent illnesses				
Hypertension	2.09 (0.91-4.82)	0.08	-	
Diabetes	5.15 (0.54-49.50)	0.16	-	
Other conditions	16.57(1.74-158.2)	**0.02**	-	
Concurrent medications				
Calcium channel blocker	5.98 (1.04-33.99)	**0.05**	4.27 (0.69-26.29)	0.12
Insulin	52.03(0.83-3264.9)	**0.06**	36.39(0.58-2266.5)	0.08
Initial BMI	0.96 (0.90-1.03)	0.25	-	
CD4 count at baseline	0.99 (0.99-1.00)	0.20	0.99 (0.99-1.00)	0.5
Duration before switching regimens	0.81 (0.33-3.73)	0.14	0.57 (0.38-1.18)	**<0.01**
Duration of therapy	1.29 (0.62-1.07)	**<0.01**	1.35 (1.07-1.69)	0.01
Regimen at initiation	1.01 (0.85-1.47)	0.44	-	
Regimen switched to	1.04 (0.39-2.76)	0.97	-	
Switched regimen	2.31 (1.26-4.26)	**<0.01**	1.46 (0.74-2.95)	0.27

*Significant P-values are in **bold**

On bivariable analysis the most important predictor variables which had p values less than 0.2 included alcoholism, sex, marital status, concurrent illness, switched regimen, use of a calcium channel blocker+diuretic and insulin, baseline CD4 cell count, age, duration switched, duration of therapy, age at diagnosis and the current age.

After adjusting for confounders in the multivariable analysis, five predictor variables were found to be significantly associated with kidney dysfunction. These were: alcoholism, patient sex, current age of patient, duration of therapy up to the point of switching regimens and age at diagnosis**.**

All variables with a p-value of ≤ 0.20 at bivariate analysis were included in multiple analysis models, if clinically meaningful. Most of the variables identified as key risk factors on bivariable analysis were also identified as predictor variables for severity of renal dysfunction.

Intensity of alcohol use and age increased the severity of renal disease. Those who frequently used alcohol had a 1.8-fold risk of developing more severe renal disease compared to non-users (Adjusted OR: 1.84, 95% CI: 1.03-3.29), p = 0.04). For every one year increase in patient age, the probability of developing renal disease increased by 10% (adjusted OR: 1.1, 95% CI: 1.05-1.15), p < 0.01.

Sex was not statistically significant of severity of renal disease on bivariable analysis but became significant on multivariable analysis. This was reflected by the fact that more females had renal disease. Males were 52% less likely to develop nephrotoxicity compared to females (adjusted OR: 0.48, 95% CI: 0.24-1.04), p = 0.04).

The duration of therapy was identified as a key risk factor in this cohort. The patients who had been on therapy for long were 1.3 times more likely to develop renal disease (OR 1.29, 95% C.I: 0.62-1.07).

CD4 cell count at baseline was not a statistically significant predictor of renal disease in this study cohort. Nonetheless in the comparative analysis more patients with CD4 count of less than 200 cells/ml developed renal disease. The one patient put on insulin had more severe renal disease. There were two patients on a calcium channel blocker (CCB) and a diuretic; this indicated that they had hypertension. Patients with diabetes and hypertension had a greater risk of developing more severe renal disease due to nephropathy associated with these conditions. However the presence of diabetes/hypertension was not statistically significant in this cohort; although this could have been due to the small sample size.

CHAPTER 5: DISCUSSION

Renal disease before start of HAART therapy is quite common in HIV infected patients. Although Sub-Saharan Africa has over 60% of the world's HIV/AID's burden, there is limited data in the region on HIV related kidney disease, with most of the available data coming from the developed countries (Banda et al., 2010). As HIV treatment programs scale up in this region data on the incidence, prevalence and risk factors of kidney disease are necessary in order to prioritize resources and ensure patient safety.

Extensive literature searches on the incidence of nephrotoxicity in patients on NVP based regimens revealed there have never been search studies that may have been done but if any they have not been published to date. Therefore to our knowledge this study constitutes the first retrospective cohort study on the same. Most previous studies tended to focus exclusively on tenofovir based regimens (Gallant et al 2005, Izzedine et al 2005, Fux CA et al 2007, Sorli et al 2008, Hoberg et al, 2009)

The prevalence of renal disease among HIV infected patients has been reported to be between 2 to 10%. The prevalence is about 3.5% in patients of black origin (Gardener et al 2003). The prevalence of renal dysfunction at baseline in this cohort which included all patients regardless of baseline eGFR was 6.3% (95% C.I 3.20-9.44). This implied that at treatment initiation about 6 out of every 100 patients require dose adjustments for nucleoside analogues like stavudine and lamivudine. This prevalence was much higher than that reported from a U.S cross-sectional study (3%) (Crum-Cian flone et al 2009) Similarly a prospective cross-sectional study in Western Kenya reported a prevalence of (4.8%). The prevalence in this study was much higher than that reported in Western Kenya and that could be explained by the fact that while the MDRD formula for calculating eGFR was used in this study, the Western Kenyan cohort made use of the Cockcroft-Gault formula (Wools-Kaloustian et al, 2007)

An observational analysis of HIV patients on HAART therapy in Uganda estimated the prevalence of renal dysfunction was 20% (Peters et al 2008). The findings of the current study are therefore much lower than the findings of the Ugandan study.

The incidence of renal dysfunction was 4.3% (95% C.I 1.68-6.94). These results compared well with a retrospective cohort analysis of HIV-infected patients that was done in France on a large cohort of seven reference centers and they found an incidence of 4.7%. (Flandre et al 2011). The French study included patients on all regimen types.

Serum creatinine level can be used as a crude measure of renal disease in routine practice. In this study cohort the number of patients who developed renal disease on starting HAART with baseline elevated serum creatinine levels (above 120µg/l) were 6. This was statistically significant on bivariable analysis ($p<0.01$). The clinical implications are that patients with elevated serum creatinine should be followed keenly for worsening of renal disease.

Out of the 241 patients enrolled in the study 22 patients did not have their baseline serum creatinine readings. This is a poor practice as it limits the early intervention in routine practice. This is against guidelines and standards of care.

It is also important to remember that many patients with HIV may present with muscle wasting while receiving HAART, which can lower serum creatinine concentration and falsely support the presence of normal kidney function. Conversely, with HAART therapy patients may gain weight, and creatinine may increase without renal injury (Kalyesubula & Perazella, 2011). Thus the findings of this study should be interpreted with caution. Nonetheless changes in body weight may not have interfered with the calculation of eGFR because the MDRD formula adjusts for body surface area.

A Zambian cohort study showed that the mean creatinine appeared to decrease over time in patients initiated on HAART (Mwango et al, 2010). In this study eGFR decreased with time. This could be attributed to normal age related decline

in renal function. It is probable that the rate of decline of renal function is higher in patients on HAART compared to normal populations. It was noted that estimated GFR declines with time. In this study cohort the decline was observed between the second and eighth year. It agrees with other studies because of the age effect. A Swiss cohort has reported a reduction of the estimated GFR with prolonged ART exposure (Flandre et al 2011).

Risk factors for nephrotoxicity are numerous and depend on underlying patient characteristics as well as the drug regimen under consideration. A number of observational studies have documented TDF-associated nephrotoxicity (Gallant et al 2005, Izzedine et al 2005, Fux et al 2007,Sorlt et al 2008, Hoberg et al, 2009) In this study we sought to find out if other ARV agents other than TDF could be causing nephrotoxicity and the possible risk factors for this nephrotoxicity.

This study identified a variety of risk factors which included age above 40 years, regular consumption of alcohol, female gender, and use of concurrent medication and duration of therapy. Though not statistically significant on multivariable analysis the patients with low CD4 cell count, concurrent illnesses (hypertension and diabetes) and patients initiated on stavudine based regimens were also at risk of developing renal disease. This agrees with the known traditional risk factors and studies that have been done both locally and internationally (Wools-Kaloustian et al, 2007, Kamga et al 2010, Peter's et al 2008).

Age is a known and well documented traditional risk factor for renal disease. The median age in the study population was 39 years which was consistent with the situation in Sub–Saharan Africa where the condition is reported to affect mainly the young adults aged between 20-50 years of age (Naicker, S 2009). Renal function has been found to decline with age at a ratio of 1% decline per year beginning at 4^{th} decade of life (Stevens et al 2006).

Alcohol consumption was a significant predictor in the development of renal disease (adjusted OR 1.84 95% C.I (1.01-3.29) p=0.04). Intensity of alcohol consumption has not been reported as a predictor of renal disease in HIV patients

on HAART. This is the first study to report alcohol use as a risk factor. However caution is needed in interpreting this observation as the sample size for those who reported taking alcohol was small.

In this study cohort of 241 patients, the females were 185 (76.8%). Furthermore, more females developed renal disease (adjusted O.R 0.48 (95% C.I 0.24-1.04). This gender distribution compares well with the NASCOP estimates that there are more infected women in Kenya (Ministry of Health, AIDS Kenya Trends Intervention and Impact 2005 7th edition).

Duration of therapy was a seen as a risk factor for developing renal disease (adjusted O.R 1.35(95% C.I 1.07-1.69 (p=0.01)). This could be attributed to cumulative effects of drug toxicity. The elimination of ARVs is primarily renal hence the higher nephrotoxicity potential.

Patients with advanced HIV disease at baseline indicated by low CD4 cell counts are at a risk of developing renal disease such as HIVAN (Winston et al 1999**).** In our study, a CD4 count below 200cells was not associated with renal dysfunction (p=0.212). A similar result was found in a Cameroon cohort (Kamga et al 2010). In other studies, a low CD4 count was a predictor of renal dysfunction. The small sample size may as well explain the difference in our observation. Nonetheless in the comparative descriptive analysis in our cohort more patients with CD4 count below 200 cells developed renal disease.

Hypertension and diabetes have are significant factors for development of renal dysfunction. (Banda et al 2010). In these study cohort 3 patients with hypertension and one patient with diabetes developed renal dysfunction although it was not statistically significant. This could be attributed to the small sample size and the fewer number of patients with comorbidities. Conversely, HAART may increase the risk of hypertension, diabetes mellitus and other metabolic complications creating a vicious cycle (Kalyesubula & Perazella, 2011).

It was noted that patients who initially were on a stavudine based regimen were at higher risk of renal disease though this was not statistically significant p=0.44 on bivariable analysis.

STUDY LIMITATIONS

The gold standard measurement of eGFR for practical reasons, instead the MDRD evaluation of GFR was used. This is because it has been previously shown to have a level of precision and accuracy sufficient for clinical decision making (Flandre et al 2011**).**

This being partially retrospective cohort study, it relied heavily on pre-recorded information which may have been incomplete and inaccurate. In this study we had missing data for about 30 patients and this reduced the sample size. The information obtained from the records could not be verified. The results may have been affected by unmeasured confounding despite controlling for the same by Ordered Logistic regression modelling.

Objective measures of efficacy of antiretroviral therapy such as viral load counts a known risk factor for CKD could not be obtained for majority of the patients since it is not routinely done on all the patients. Therefore the analysis of this important clinical indicator could not be conducted.

Data on proteinuria, other urinary markers, serum phosphate level, biopsy findings and family history of renal disease were not available in the patient files as they are not routinely monitored.

CHAPTER SIX: CONCLUSION and RECOMMENDATIONS

6.1 Conclusion

Renal dysfunction might occur in HIV patients on nevirapine based regimens evidenced by the fact that prevalence of renal dysfunction in this study cohort was high at 6.3% as well as incidence at 4.3%.

The risk factors identified in this study include age at diagnosis, alcohol consumption, duration of therapy and the female gender. The elevated serum creatinine levels and reduced eGFR at baseline is a key indicator in the management of renal disease.

6.2 Recommendation

Based on the findings we recommend that routine eGFR calculations be done at each clinical visit. Dose adjustments need to be done routinely done for patients with renal dysfunction. Patients who take alcohol should be keenly followed and dose adjustment be done as necessary.

Early detection and vigilant monitoring of risk factors, systematic screening for chronic causes of CKD, and appropriate referrals for kidney disease management should be advocated for improved patient care.

A larger study comparing the contribution of other NNRTIs to renal dysfunction is recommended.

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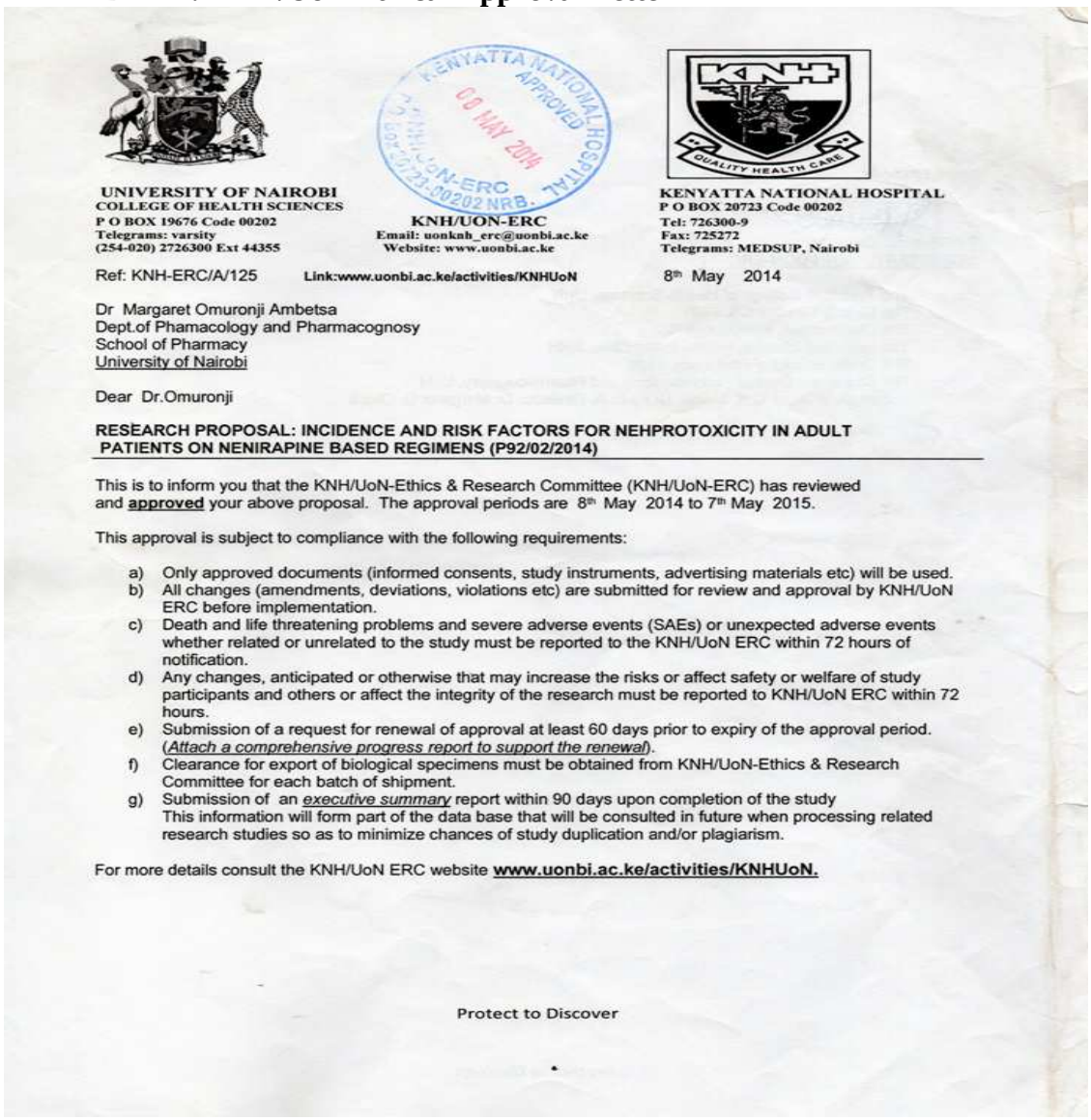
APPENDICES

APPENDIX A: KNH/UoN Ethical Approval Letter



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Ref: KNH-ERC/A/125 Link:www.uonbi.ac.ke/activities/KNHUoN 8th May 2014

Dr Margaret Omuronji Ambetsa
Dept.of Phamacology and Pharmacognosy
School of Pharmacy
University of Nairobi

Dear Dr.Omuronji

RESEARCH PROPOSAL: INCIDENCE AND RISK FACTORS FOR NEHPROTOXICITY IN ADULT PATIENTS ON NENIRAPINE BASED REGIMENS (P92/02/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 8th May 2014 to 7th May 2015.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

Protect to Discover

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chairperson, KNH/UoN-ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chairman, Dept.of Pharmacology and Pharmacognosy, UoN
Supervisors: Prof. C.K. Maitai, Dr.Faith A. Okalebo, Dr.Margaret O. Oluka

APPENDIX B: Volunteer information and consent form

INTRODUCTION

All classes of antiretroviral drugs can cause varying degrees of abnormalities in laboratory tests. Patients on ART should be monitored closely for drug intolerance and side effects. In this study I am assessing the risk factors for nephrotoxicity as you continue taking antiretroviral therapy.

Permission is requested from you to enroll in this medical research study. This consent gives information about the study. Once you understand and agree to take part, I will request you to sign your name on this form. You need to understand the following general principles.

i. Your agreement to participate in this study is voluntary
ii. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal
iii. Refusal to participate in the research will not affect the treatment that is being given in the hospital

Purpose of the study

The primary objective of this study is to determine the patterns and levels of serum creatinine during ARV therapy and establish their association with the clinical signs of nephrotoxicity among HIV patients using Nevirapine containing regimen. The second objective is to determine the risk factors of nephrotoxicity.

Procedures to be followed

With your permission I will go through your medical records to obtain information on Laboratory investigations which have been conducted since you were initiated on ART. I will also check whether you have suffered any bad reactions to drugs suggestive of kidney disease.

Selection criteria

You will be selected to take part in this study if you meet the following criteria:

a) You are an adult above 18 years.

b) You must have been started on a Nevirapine based ART between January 2009 and December 2012.

c) You must have attending the Comprehensive Care Clinic at KHN for at least one year.

d) You must have agreed to take part in the study.

Risks or/and discomfort.

There will be no risks involved in this study to you.

Benefits

The study may be of benefit to you and other HIV patients in that it will be used to enhance detection of early warning signs of nephrotoxicity. It may also inform policy makers on the need to review guideline on laboratory monitoring of toxicity.

Assurance on confidentiality

All information obtained from your file will be kept confidential and used for the purpose of this study only. Your name will not be used during data handling or in any resulting publications, codes will be used instead. Your medical records will be kept under lock and key and information will be accessible to authorized persons only.

Contacts

For any further information about this study you may contact me, my academic department or the Kenyatta National Hospital/University of Nairobi Ethics and research Committee using the contacts provided below:

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P.O Box 19676- 00202 Nairobi. Tel: 0724-725759

Supervisor;
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School of Pharmacy
University of Nairobi
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The secretary, Prof.Chindia,

The Kenyatta National Hospital/University of Nairobi Research and Ethics Committee,

P.O Box 19676- 00202 Nairobi. Tel: 020-2726300 Ext 44355

STATEMENT OF CONSENT

I have understood the information on the consent form. I have had a chance of discussing the research study with the investigator and I have had my concerns addressed.

I_____ give consent to the investigator to use my medical records in his study. The nature of the study has been explained to me by Dr. Margaret Ambetsa.

Signature_____ Date _____

Investigator;

I confirm that I have explained the nature and effect of the study to the participant named above and believe that the participant has understood and has willingly given his/her consent.

Signature _____ Date _____

Witness

Signature…….Date……..

APENDIX C: Data collection form during patient recruitment
Patient unique number_____

SECTION 1: PARTICIPANT ELIGIBILTY CHECK LIST
Inclusion criteria: (if any the criteria is marked "NO" the participant is not eligible for enrollment)

	YES	NO
1. Participant is a HIV infected male or female on Nevirapine containing ART	[ ]	[ ]
2. Participant is aged above 18 but below 55 years	[ ]	[ ]
3. Participant has been on NVP containing regimen for at least 6 months	[ ]	[ ]
4. Participant has signed voluntarily informed consent	[ ]	[ ]

Exclusion criteria: (if any the criteria is marked "YES" the participant is not eligible for enrollment)

	YES	NO
1. Participant is not on Nevirapine containing regimen	[ ]	[ ]
2. Participant has declined to give consent	[ ]	[ ]
3. Participant is aged below 18 years or above 55 years	[ ]	[ ]
Is the participant eligible for participation in this study?	[ ]	[ ]

SECTION 2: REPORTED ADVERSE DRUG REACTIONS

Have you ever reacted abnormally to the medicines that you are given in this clinic? Yes [ ] No [ ]

(*If yes in the above question indicate the type of reaction)*

TYPE OF REACTION	**YES**	**NO**
Skin problems (rash, itching)		
Kidney problem (swollen feet or ankles, fatigue, high blood pressure)		
Stomach problems (gastrointestinal bleeding, vomiting, diarrhea, stomach aches)		
Any other (specify)		

If yes to any of the above, were you able to carry out your normal duties?

	YES	NO
1. Fully active and was able to continue with normal duties without restriction	[ ]	[ ]
2. Could not carry out normal duties fully but could do light work in the office and at home	[ ]	[ ]
3. Could do on work at all	[ ]	[ ]
4. Were you admitted to hospital as a result of the reaction to the drug?	[ ]	[ ]

When did the reaction occur?

1. [ ] Within the first month of starting treatment
2. [ ] Within the first six months of starting treatment
3. [ ] Others
4. [ ] Cannot remember

Did you inform the doctor at the CCC about the reaction to the drugs?

Yes [ ] No [ ]

SECTION 3: PATTERNS ON NON PRESCRIPTION DRUG/HERBAL PRODUCTS USE

In the last one month have you ever used and medicines (supplements, family planning) or herbal medicines that were obtained somewhere else? YES [ ] NO [ ]

If yes the above, what products have you used?

Product name	**Dose and duration of use**	**Reasons for use**	**Where sourced**

APPENDIX D: Data collection form for extraction of information from patient files

Patient unique number…….

SECTION I: SOCIAL DEMOGRAPHIC CHARACTERISTICS OF THE PARTICIPANT

Date of birth	_____
Gender	Male [ ] Female [ ]
Marital status	Married [ ] Single [ ] Divorced [ ]
Highest education level	Degree [ ] Diploma [ ] High school [ ] Primary[ ]
Occupation	Employed [ ] Unemployed [ ] Self-employed [ ]
Ethnicity	_____
Alcohol use	Never [ ] Occasionally [ ] Regularly [ ]
Smoker	Yes [ ] No [ ]

SECTION II: MEDICAL HISTORY

Date diagnosed with HIV/AIDs	
Date commenced HAART	
Weight at HAART initiation	
Height	
Concurrent medical conditions at the time of data collection	1 2 3 4 5

SECTION 111: MEDICATION HISTORY

ARVs regimen the patient is currently using

DRUG NAME	DOSE	FREQUENCY

Are there any concurrent medications being used with ARVs?
Yes [ ] No [ ]
If yes specify below

DRUG NAME	DOSE	FREQUENCY

SECTION IV: SELECTED BASELINE VALUES

Parameter	Date	Value	Normal value
Bilirubin			
Creatinine			
CD4 cell count			
Viral load			
Weight			

SECTION V: LABORATORY VALUES DURING FOLLOW UP

Date						
Parameter	1st	2nd	3rd	4th	5th	6th
Creatinine						
CD4 counts						
Viral load						
Weight						

Date						
Parameter	7th	8th	9th	10th	11th	12th
Creatinine						
CD4 counts						
Viral Load						
Weight						