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Research Article

Incidence and Risk Factors of Renal Dysfunction in Patients on Nevirapine-Based Regimens at a Referral Hospital in Kenya

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Introduction: Nevirapine-based regimens are the most commonly used ART in Kenya. There is little literature on the renal toxicity of NNRTIS in Kenyan settings. Some studies in Asia have demonstrated an association of NNRTIs and renal toxicity. Given that NNRTIs may cause renal toxicity, clinical studies on their contribution to the same are required.

Objectives: To evaluate the incidence and risk factors for renal dysfunction in HIV adult patients on Nevirapine based regimens.

Methodology: The design was a descriptive (right censored arm) hospital based retrospective cohort study carried out at a national referral hospital. Ethical approval was obtained. The study population was patients on Nevirapine based regimens seen between May and August, 2014. Convenient sampling was used to recruit 241 patients. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Patients with eGFR < 50ml/min/1.73m^2 were considered to have renal dysfunction. Data obtained by the patient interviews and abstraction of patient files and was analyzed using STATA software. Ordered Logistic regression was used to identify covariates that determine the severity of renal dysfunction.

Results: The incidence of renal dysfunction was 4.3% (95% C.I, 1.68-6.94).Five (2.1%) patients had a low eGFR at baseline, while ten (8.3%) patients had elevated serum creatinine (above 120µg/l). None of the patients developed severe renal dysfunction. Seventy (32%) and ten (4.6%) had mild and moderate renal dysfunction respectively. 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).All fifteen patients with a BMI of over 18.5 had elevated eGFR of below 50ml/min/1.73m.^{2}Patients who had been initiated on stavudine based regimens had the highest incidence of renal dysfunction.

Conclusion: Routine eGFR calculations should be done at each clinical visit. Early detection of risk factors and systematic screening should be advocated for improved patient care.

Key Words: Body Mass Index, Renal dysfunction, Stavudine, Nevirapine

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1. Introduction

Highly Active Antiretroviral Therapy (HAART)has reduced morbidity and mortality associated with HIV/AIDS across the globe (Mwagomba et al, 2008).However, long term exposure to HAART may also be associated with significant toxicity (Manosuthi et al, 2010). Renal dysfunction is mainly attributed to Tenofovir and protease inhibitors but very few studies have been done to determine the contribution of other antiretroviral agents.

A study conducted in Thailand found that patients on TDF/NVP had higher creatinine levels and lower estimated glomerular filtration rate (eGFR) levels compared to patients on TDF/EFV (Manosuthi et al, 2010). An unpublished study done in Kenya (Masese et al, 2009) found that Tenofovir and Efavirenz combination had a higher incidence of renal dysfunction compared to patients on Tenofovir and Nevirapine combined therapy. It is therefore entirely plausible that other HAART components may play an important role in Antiretroviral agents (ARV) associated renal dysfunction. Consequently, clinical studies are required to examine the contribution of Non-Nucloeside Reverse Transcriptase inhibitors (NNRTIs) to renal dysfunction.

Nevirapine (NVP) is one of the recommended first line NNRTIs and forms the backbone in HIV management. It is a key component of HAART regimens in Kenya. As per the Kenyan 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 exposed to nephrotoxic medication should be screened annually. Individuals without risk factors may be rescreened based on clinical signs and symptoms (NASCOP, 2011).

Given that NNRTIs may contribute to nephrotoxicity, clinical studies on their contribution to renal toxicity are required. This study therefore sought to determine the incidence and risk factors of renal dysfunction in patients on NVP based regimens.

2. Methodology

2.1 Study Design, Site and Population

The study design was a descriptive (right censored arm) hospital based retrospective cohort study. The target population was HIV positive adult patients seen at Kenyatta National Hospital, Comprehensive Care Centre (CCC) between May and August 2014. Kenyatta National Hospital is the largest public teaching and referral hospital in Kenya.

2.2 Inclusion and Exclusion criteria

The patients were included if they were HIV infected males or females, aged between 18-55 years and had been on any NVP containing regimen for at least 6 months.

They should not have had a history of kidney disease prior to use of anti-retroviral drugs. In addition they were required to provide informed consent at the start of the study.

2.3 Sample size determination and sampling procedure

The sample size was calculated using the formula described by Hulley et al (2013) for estimation of sample size of a dichotomous outcome. The minimal calculated sample which could detect an incidence of 10% was 166 patients. Patients were sampled by convenient sampling method. They were screened beforehand to determine whether they meet the eligibility criteria and were recruited as they collected refills of their prescriptions in the pharmacy.

2.4 Data Collection

A pilot study was done before initiating data collection and the findings were used to improve and modify the design of the data collection tools. Patients were taken through a brief interview to obtain information on alcohol consumption, smoking status and use of herbal and non-prescription preparations. This was used to supplement information obtained from patient medical records.

The medical files of recruited patients were retrieved from the records department and the following information abstracted: socio demographic characteristics; medical history; medication history; laboratory values which included creatinine levels, baseline CD4 count, history of pre-existing kidney disease and any adverse drug event.

2.5 Case Definition

The creatinine levels from the treatment initiation till patient recruitment were used to calculate eGFR using the MDRD formula (Levey et al., 1999). A cut value of $<50ml/min/1.73m^2$ was used to dichotomize patients into abnormal and normal renal function. This cut off has been used in a number of studies (Wools-Kaloustian et al 2007, Peters et al, 2008). The severity of renal dysfunction was measured using the MDRD criteria (Gupta et al 2005).

2.6 Data management and Analysis

All data generated was entered in an Excel spread sheet (Microsoft®). 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. Descriptive data analysis was carried out on all variables. The Shapiro Wilk test was used to determine which continuous variables conformed to normal distribution. For those continuous variables that are not normally distributed, the median and interquartile range (IQR) was reported. For all categorical variables the proportionate composition and 95% confidence intervals (95% C.I) were reported. Pearson chi square test, t-test, and Kruskal Wallis test were done to compare the distribution of variables in patients with normal and abnormal renal function.

The key risk factors for development of renal dysfunction were determined using ordered logistic regression modeling. The main outcome of interest was severity of renal dysfunction. The covariates that were considered in the identification of the key risk factors for severity of renal dysfunction included patient

demographics, baseline creatinine levels, co-morbidities (diabetes and hypertension),drugs taken (especially known nephrotoxic drugs) and ART regimen. The other covariates were low BMI, low CD4 cell count (<200) and age above 40 years.

All variables with a P-value lower than 0.20 at bivariable analysis were entered into a multivariate model (if clinically meaningful). Model building was done using a manual forward stepwise selection approach. All analyses were performed using STATA version 10 (StataCorp 4905 Lakeway Drive College Station, Texas 77845 USA).P values less than 0.05were considered statistically significant.

2.7 Ethical Considerations

Ethical approval was granted by the Kenyatta National Hospital/University of Nairobi Research and Ethics Committee (KNH-UoN ERC) as per the letter referenced KNH-ERC/A/125 dated 8th May 2014. The files were stored under lock and key, access to data was restricted. Patient names were not included in the data collection tool.

3. Results

3.1 Study Cohort

Three hundred patients were assessed for eligibility. The reasons for exclusion are presented in **Figure 1** and 241patients were finally included in the study as they met the inclusion criteria.

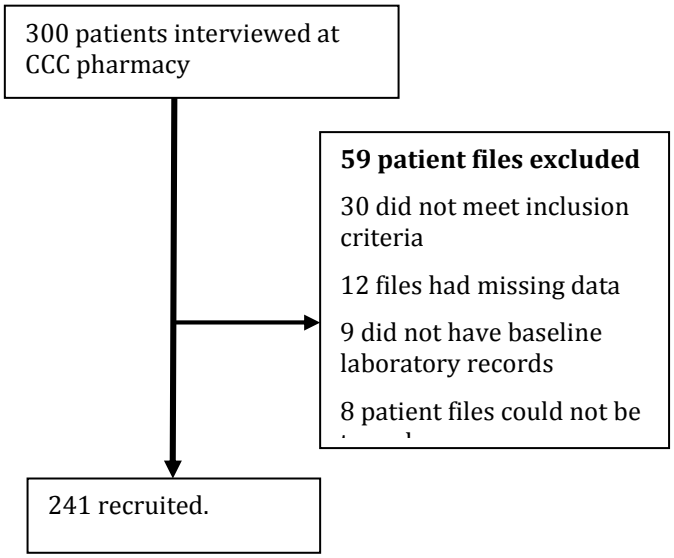


Figure 1: Summary of patient selection

3.2 Baseline characteristics of the study participants

The baseline characteristics of the 241 patients included in the study are summarized in **Table 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 63.4 kg (range 52-70 kg). More than half 147 (61%) weighed less than 65kg.

Table 1: Demographic and Clinical characteristics

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)
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	
Yes	5(2.1)
No	236(97.9)
CD4 cell count x10^9/L	206[127-270]
≤200	158 (65.6)
≥200	68 (28.2)
Missing values	15 (6.2)
BMI at HAART initiation	23.38[21.34-25.95]
≤18.5	15 (6.2)
≥18.5	226 (98.3)
Chronic Co-morbidity	
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)

Seventy two (29.8%) participants took alcohol occasionally (less than twice a month) whereas two (0.8%) took alcohol regularly. Five (2.1%) patients were smokers. Most (70%) patients had attained primary and secondary school education. The median duration of follow up for the entire cohort was 4.75 years (range 3.34-6.6). At the initiation of treatment 158 (65.6%) patients had a CD4 cell count of less than200cells/mm^3. Fifteen (6.2%) had a body mass index (BMI) of above 18.5kg/m^2. The most prevalent chronic co-morbidities 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.

Table 2: HARRT 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)

Table 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/1.73m²)	101.67[80.72,120.19]
eGFR>50	214(88.8)
eGFR<50	5(2.1)
Missing values	22(9.1)

3.3 Antiretroviral treatment regimens used by participants

The HAART regimens at treatment initiation and time of the study are presented in **Table 2**. 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 who had been started on efavirenz based regimens had been switched to a nevirapine based regimen at the time of the recruitment into the study. Majority of the patients were initiated on was stavudine, lamivudine and nevirapine (85, 35.3%). 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 lipodystrophy, skin rash and a change in the treatment guidelines.

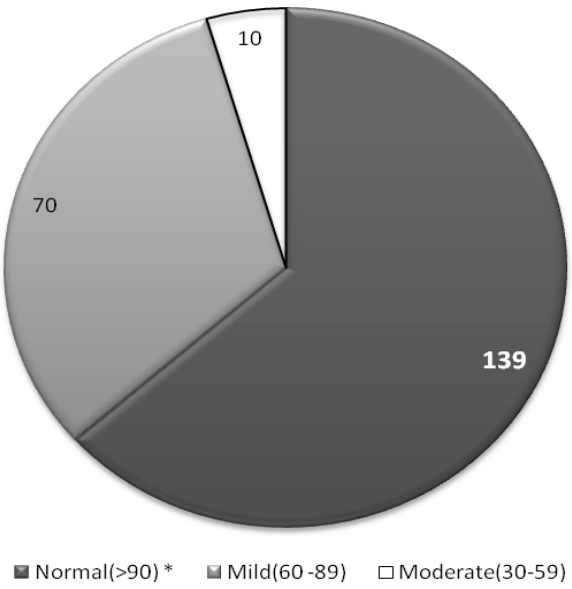
3.4 Renal function at initiation of therapy

A summary of the baseline renal parameters is presented in **Table 3**.

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

In many 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.

Severity of renal disease at treatment initiation ranged from mild to moderate. None of the patients had severe renal dysfunction. This is summarized in **Figure 2**.



**classification of severity of renal dysfunction using MDRD criteria (Gupta et al, 2005)*

Figure 2: Severity of renal dysfunction at baseline.

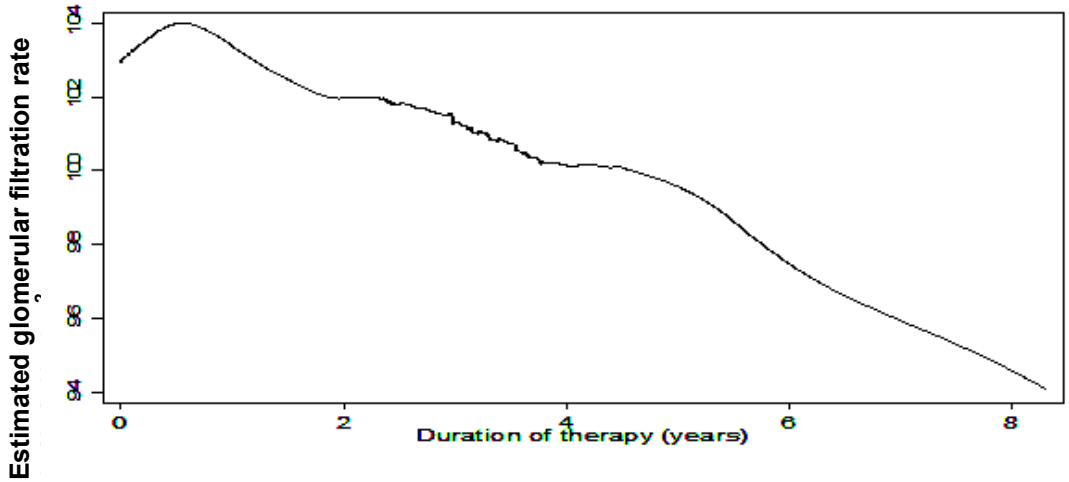


Figure 3: The Lowess graph of patients whose eGFR was normal at baseline

Table 4: Comparison of the baseline characteristics by renal status

Predictor variable	No renal disease (%) (eGFR>50ml/min/1.73m²)	Renal disease (%) (eGFR<50ml/min/1.73m²)	P value
Age at ART initiation (years)			
≤ 40	118 (53.2)	4 (26.7)	
> 40	104(46.8)	11 (73.3)	**0.04**
Weight (kg)			
<65	136 (61.3)	9 (60.0)	
>65	86 (38.7)	6 (40.0)	0.92
Sex			
Female	170 (76.6)	12 (80.0)	
Males	52 (23.4)	3 (20.0)	0.76
Alcohol use			
Never	158(71.2)	7 (46.7)	
Occasionally	64 (28.8)	7 (46.7)	
Regularly	0 (0)	1 (6.7)	**<0.01**
Smoking			
No	217 (97.7)	15 (100)	
Yes	5(2.3)	0 (0)	0.56
Regimen at ART initiation			
TDF,3TC,NVP	66(29.7)	4 (26.7)	
AZT, 3TC, NVP	74 (33.3)	3(2)	
D4T, 3TC, NVP	77 (34.7)	7 (46.7)	
D4T, 3TC, EFV	1 (0.5)	0 (0.0)	
AZT, 3TC, EFV	2 (0.9)	1 (6.7)	
TDF, 3TC, EFV	2(0.9)	0 (0.0)	0.38
Concurrent illnesses			
None	168(75.7)	11(73.3)	
Hypertension	32 (14.4)	3 (20.0)	
Diabetes	2 (0.9)	1 (6.7)	
PUD	4(1.8)	0 (0.0)	
Asthma	3 (1.4)	0 (0.0)	
Chronic pain	5 (2.3)	0 (0.0)	
Depression	1 (0.5)	0 (0.0)	0.87
URTI	1 (0.5)	0 (0.0)	
Anemia	1 (0.5)	0 (0.0)	
Other illnesses	7 (3.2)	0 (0.0)	
Body mass index(kg/m2)			
< 18.5	15 (6.8)	0 (0.0)	
>18.5	207(93.2)	15 (100.0)	0.30
Serum Creatinine (absolute)*			
≤ 120	201(98.1)	9 (60.0)	
>120	4 (2.0)	6 (40.0)	**<0.01**
CKD Severity(eGFR<50ml/min)*			
Stage 1 (normal)	135(66.2)	4(26.7)	
Stage 2 (mild)	66(32.4)	4(26.7)	**<0.01**
Stage 3 (moderate)	3(1.5)	7(46.7)	
CD4 cell count×10^9/L*			
≤ 200	144 (69.6)	11 (73.3)	
>200	63 (30.4)	4(26.7)	0.76

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3.5 Incidence of renal dysfunction and changes in estimated GFR with time

In this study, ten patients who had normal renal function at baseline developed elevated serum creatinine levels which resulted in a drop in the eGFR; the incidence of nephrotoxicity was 4.3% (95% C.I 1.68-6.94).In order to examine the trend in changes in estimated GFR with time, a lowess plot was generated. Renal function showed initial improvement, followed by almost linear deterioration with time. Renal function declined by about 10units from 104 to 94ml/min, over an 8 year period. This is as shown in **Figure 3**.

3.6 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** for 237 patients who had complete data at baseline. It included all patients who had renal disease at baseline as well as those who developed renal disease.

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 variables: age at ART initiation, alcohol consumption, baseline serum creatinine levels, and the CKD severity (p=<0.01).

Though there were no statistically significant differences across sex, more females than males developed renal disease. Twelve (80%) female patients compared to three males (20%) developed renal disease.

Four patients (26.7%) aged below forty years developed renal disease compared to 11 (73.3%) who were aged above 40 years. Age was a statistical significant predictor of renal dysfunction (p=0.04). All fifteen patients who had BMI above 18.5kg/m2 developed renal disease.

The only patient who reported regular alcohol consumption developed renal disease. About (4.2%) of those who did not consume alcohol developed renal disease as opposed to 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 with a CD4 cell count below 200cell/mm^2(11(73%) developed renal disease. The baseline CD4 cell count of <200cells/mm3 was not a statistically significant predictor in this study(p=0.76) despite the fact that it is a documented risk factor.

The patients who developed renal disease and had baseline serum creatinine levels below 120µg/dl were 9(60%); those with more than 120µg/dl were 6(40%).Serum creatinine levels above 120µg/dl was a statistically significant predictor (p<0.01).

The regimen at HAART initiation did not affect the renal disease status (p=0.38). It was notable that 7 patients (46.7%) initiated on D4T, 3TC and NVP, developed renal disease. Patients who were initiated on stavudine based regimens had the highest prevalence of renal impairment (8.3%), this was followed by patients on tenofovir (5.7%) and patients initiated on zidovudine had the lowest of (3.9%). 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 statistically significant because of the small number of patients.

Concurrent illnesses were not statistically significant predictor (p=0.8).Out of the 32 patients who were hypertensive, three patients (20%) developed renal disease and one patient (6.7%) who had diabetes also developed renal disease.

3.7 Multivariable analysis- Risk factors for renal dysfunction in patients with normal baseline renal function

Ordered Logistic Regression was done to identify variables predictive of the severity of renal dysfunction. Bivariable and multivariable analyses were conducted and the results are presented in **Table 5**.

On bivariable analysis the most important predictor variables which had p values less than 0.2 included, sex, marital status, concurrent illness, switched regimen, use of a calcium channel blocker+diuretic and insulin, baseline CD4 cell count, age, duration of therapy before switching regimens, 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: frequency of alcohol consumption, sex, current age of patient, duration of therapy up to the point of switching regimens and age at diagnosis. 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 odds 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 more likely to develop renal disease (OR 1.35, 95% C.I 1.07-1.69).

CD4 cell count at baseline was not a statistically significant predictor in our study cohort. Nonetheless in the comparative analysis more patients with CD4 count of less than 200 developed renal disease. The one patient put on insulin had more severe disease.

There were two patients on anti-hypertensives, a calcium channel blocker (CCB) and a diuretic. Patients with diabetes and hypertension had a greater risk of developing more severe renal disease. However this was not statistically significant; this could have been due to the small sample size.

We found statistical interaction between BMI of above 20 and age (O.R 0.90, 95% C.I 081-1.00; p=0.035). On stratification analysis patients with a BMI >20 had a greater risk of developing more severe renal disease if they had been initiated on stavudine. This was statistically significant.

Table 5: Determinants of severity* of 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	-	
[a]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)	0.21	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

4. 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 burden, there is limited data in the region on HIV related kidney disease, with most available data coming from the developed countries (Banda et al, 2010). As HIV treatment programs scale up in this region, data on the incidence and prevalence of risk factors of kidney disease are necessary in order to prioritize resources and ensure patient safety. An extensive literature searches on the incidence of nephrotoxicity in patients on NVP based regimens revealed no published studies to date. Therefore, this study may constitute the first retrospective cohort study on the same. Most studies have tended to focus exclusively on tenofovir based regimens (Gallant et al, 2005, Izzedine et al, 2005,Fux et al 2007, Sorli et al, 2008, Hoberg et al, 2009).

The prevalence of renal disease among HIV infected patients varies from to be 2 to 10%(Peters at el,2008).The overall prevalence of renal dysfunction in this cohort was 6.3% (95% C.I 3.20-9.44). This falls within the range of prevalence of renal disease in HIV patients. This implies that about 6 out of every 100 patients require dose adjustments for nucleoside analogues like stavudine and lamivudine. This

prevalence in our study was higher than that reported from a U.S cross-sectional study (3%) (Crum-Cian Flone et al, 2009) and that reported in a survey conducted in Western Kenya (4.8%). This could be explained by the fact that while the MDRD formula for calculating eGFR was used in this study, the Western Kenya cohort made use of the Cockcroft-Gault formula (Wools-Kaloustian et al, 2007).

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.

Our study identified a variety of risk factors which included age, regular consumption of alcohol, female gender, and use of concurrent medication and duration of therapy. It was notable that there was statistical interaction between age and BMI (p=0.035). Patients with a BMI of over 18.5 all developed renal impairment.

In a study conducted in Japan in healthy individuals aged over 40 years increased BMI (>22.0) was associated with reduced eGFR which was measured using the MDRD formula. In the Japanese study, the other risk factors for a low eGFR were age, triglyceride and low lipid density lipoprotein (LDL) levels and fasting glucose levels (Ryuichi Kawamoto et al, 2008). This may explain the influence of BMI on our study findings.

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 et al, 2009). Renal function declines with age at a rate of 1% per year beginning at 4th decade of life (Stevens et al, 2006).

We found that 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 never 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.

Females were expected to suffer from less nephrotoxicity because estrogen has protective effects on the kidney and this places men at a higher risk of developing nephrotoxicity (Antoniou et al, 2005). Oestrogens protect the kidney by enhancing cellular repair and modulating effects on the rennin-angiotensin system. In our study females had a higher risk(adjusted O.R 0.48(95% C.I 0.24-1.04; p=0.04).This finding was therefore contrary to our expectations.

Duration of therapy was 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.

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, Peters et al, 2008, Kamga et al, 2010).

Patients with advanced HIV disease at baseline indicated by low CD4 cell counts are at a risk of developing renal disease such as HIV associated nephropathy(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 Cameroonian cohort (Kamga et al, 2010). In other studies, a low CD4 count was a predictor of renal dysfunction.

Hypertension and diabetes are significant factors for development of renal dysfunction. (Banda et al 2010). In our study cohort 3 patients with hypertension and one patient with diabetes developed CKD. These two co-morbidities were not statistical significant predictors in our study. This could be attributed to the small sample size and the small 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).

Serum creatinine level can be used as a crude measure of renal disease in routine practice. Out of the 241 patients enrolled in the study 22 patients did not have their baseline readings. This is a poor practice as it limits the early intervention in routine practice. This is against guidelines and standards of care.

Patients with elevated serum creatinine levels at baseline (>120µg/l) were more likely to develop more severe renal dysfunction, serum creatinine. Therefore baseline serum creatinine levels can be used as an early tool to rule out risk of developing renal disease. Patients with elevated serum creatinine at treatment initiation should be followed on more keenly for worsening of renal disease. 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).

A Zambian cohort study showed that the mean creatinine appeared to decrease over time in patients initiating on HAART (Mwango et al, 2010).In our study eGFR decreased with time. This could be attributed to normal age related decline in renal function. It is probably that the rate of decline is higher in patients on HAART compared to normal populations. The decline was observed between the second and eighth year of treatment. This observation is in agreement with other studies. A Swiss cohort reported a reduction of the estimated GFR with prolonged ART exposure (Flandre et al, 2011).

The effects of ART regimen was not statistically significant (p=0.44). However it was noted, that the incidence of renal dysfunction amongst patients who

had been initiated on D4T/NVP was almost twice the incidence of renal dysfunction of patients initiated on a TDF/NVP regimen. NVP is excreted primarily in the renal tubules by active secretion into urine via multidrug resistance protein(MRP) in the proximal cells of the renal tubule (Cihlar et al, 2007).There is therefore a potential drug interaction with other ARVs that are excreted through the same pathway.

An analysis of the data of a study done in India found that patients on TDF/EFV combinations had a higher risk of renal dysfunction. However the authors of this study did not highlight this finding.We postulate that co-administration of D4T/NVP results in greater renal dysfunction. Nevirapine may have a protective effect in patients on TDF based formulations (Masese et al, 2009). We propose that more studies should be done to verify this observation. There may be drug-drug interaction between TDF and NVP because both agents are excreted actively in the renal tubules. A deeper understanding of renal toxicity of NVP is therefore required.

We chose to use the MDRD formula to estimate GFR because it has been previously shown to have a level of precision and accuracy sufficient for clinical decision making (Flandre et al, 2011).Body weight may not have interfered with the calculation of eGFR because the MDRD formula adjusts for differences in body surface area (Kamga et al, 2010).

Our study had a number of limitations, this being retrospective observational study, it relied heavily on 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. Data on proteinuria, serum phosphate level and family history of renal disease were not available.

5. Conclusion

The incidence of renal dysfunction (4.3%) was similar to that reported for TDF based regimen. Patients with a high BMI and on alcohol may require close monitoring for renal impairment. A comparative study of nephrotoxicity between TDF/NVP and TDF/EFV regimens may be required.

Conflict of Interest declaration

The authors declare no conflict of interest.

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