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Comparison of creatinine clearance in HIV/AIDS Patients on Tenofovir and two non-Tenofovir- based NRTIs after one year of therapy

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Abstract

The main objective was to compare the Creatinine Clearance (CL_{cr}) in HIV/AIDS patients on treatment with Tenofovir (TDF) based regimen to those on non- TDF- based regimen (Stavudine (D4T) and Zidovudine (AZT) after 1 year of initiation of therapy. An analytical cross- sectional designed was applied to data on files of 275 HIV/AIDS patients on TDF and 274 HIV/AIDS patients on either D4T or AZT making a total of 549 files. The median age of participants in the study group was 29 years (Q_1:19 years, Q_3: 35 years) while the median age of participants on D4T or AZT was 20 years (Q_1:17 years, Q_3: 30 year). CL_{cr} was calculated at baseline and at 1 year of therapy using the Cockcroft- Gault formula from the Serum Creatinine (SCr), weight, age and gender of the patients. There was no significant difference between themedian baseline CL_{cr} in the study group and control group and both were in the normal CL_{cr} range according to Kidney Disease Outcome Quality Initiative (K/ DOQI) criteria; 99.39 mL/min verses 104.58 mL/min, P= 0.0574. It was also found that more patients on TDF developed abnormal creatinine clearance at 1 year from normal baseline kidney function compared to those on either D4T or AZT; 51 vs. 8. In logistics regression it was found that treatment with TDF increased the odds of developing abnormal kidney function to 8.77 times compared to AZT or D4T; P<0.001. Gender was not associated with increased odds of abnormal CL_{cr} while with every unit increase in age, the odds of increased by 1.07, P= 0.001. In conclusion, treatment with TDF increased the odds of developing abnormal CL_{cr} at 1 year of treatment from having normal CL_{cr} at baseline and increase in age was associated with developing abnormal CL_{cr} in treatment with TDF.

Key words: Creatinine clearance, Cockcroft- Gault formula, renal dysfunction

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Introduction

Sub- Saharan Africa endures over 60 % of the world's burden of the HIV disease [2]. In 2007, it was estimated that over 22 million people were living with HIV in Sub- Saharan Africa according to Naicker (2009) and it remains the epicenter of the epidemic [1]. An estimated 66 % of adults, 86 % of children with HIV are in the Sub- Sahara; and 70 % of all AIDS deaths occurred in the same region [13, 15]. In Zambia, approximately 82,700 people had HIV in 2009; the overall adult prevalence of the disease was 14 %, and 1.6 % of the adult population became newly infected with HIV each year [13].

Renal disease disproportionately affects patients living with HIV [2]. HIV infected patients of African origin have a greater risk of renal diseases [18]. Chronic kidney disease is three to four folds more frequent in Africa than in industrialized countries in non-HIV patients [3, 15]. From some

outpatient renal screening, the prevalence of renal dysfunction in HIV was reported to be varying from 6 % to 50 % according to Mulenga (2008). Mulenga, (2008) described a prevalence of renal dysfunction of 34 % among HIV infected outpatients commencing Highly Active Antiretroviral Therapy (HAART) and added that depending on the criteria used to define renal dysfunction, the prevalence may be up to 10 times higher in hospitalized HIV infected patients [2,14].

Kidney disease remains an important cause of morbidity and mortality among persons living with HIV in the HAART era and they exhibit a higher risk of renal insufficiency, proteinuria, and End Stage Rinal disease (ESRD) compared to the general population [10]. Death within 90 days of initiation of Antiretroviral Therapy (ART) was found to be more common amongst HIV/ AIDS patients who had preexisting renal insufficiency than those who had no renal insufficiency and the risk of death increased with the severity of the preexisting renal insufficiency [14].

Nephrotoxicity has been shown to be an important complication of HIV infection, particularly in patients with preexisting renal dysfunction [3]. Nephrotoxicity and renal tubular injury may be induced by the antiretroviral drug Tenofovir Dysoproxil Fumarate (TDF) which is a Nucleoside Reverse Transcriptase Inhibitor (NRTI) [7, 16, 19, and 20].

However, in June, 2007 Zambia became one of the first African countries to include TDF in their first line of ART regimen following recommendation by World Health Organization (WHO) as TDF demonstrated comparable efficacy when compared with other first- line regimens containing Stavudine (D4T), Zidovudine (AZT) or Abacavir (ABC) and also because TDF had the additional advantage of low toxicity and availability as a once daily [8, 26]. Initially, D4T- based regimen or AZT- based regimen with Lamivudine (3TC) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), either nevirapine (NVP) or Efavirenz (EFV), were recommended as first line ARV agents. It was then changed to TDF which substituted D4T- based regimen and AZT- based regimen as the preferred NRTI alongside 3TC for patients with a creatinine clearance of 50mL/minute or more [13]. But, since creatinine clearance was often not calculated, TDF was routinely prescribed in patients with serum creatinine of 120µmol/L or less and ABC was prescribed instead of TDF for those with impaired renal function [13].

This study, therefore, was aimed at determining whether patients on treatment with TDF-based regimen develop renal dysfunction at one year of therapy compared to those on non- TDF- based regimen (these patients were on either Stavudine-based regimen or Zidovudine- based regimen). The study was done at Centre for Infectious Disease Research in Zambia (AIDC).

Materials and Methods

The study was conducted at the University Teaching Hospital (UTH) at Centre for Infectious Disease Research in Zambia (AIDC). UTH is the largest hospital in Zambia and a referral for all the hospitals in the country. It provides HIV/AIDS treatment services, research and follow- ups to most patients in Lusaka through the AIDC. An analytical cross sectional study design was used. It involved analysis of data obtained from files of HIV/AIDs patients' files that began treatment with antiretroviral drugs in the period between 30th September, 2007 and 30th January, 2013. The study included all HIV/AIDS patients aged 16 years old and above that started ART on TDF- based regimen or D4T- based regimen or AZT- based regimen who came for treatment under routine standard of care. HIV- infected patients whose files had missing necessary information were excluded and HIV/AIDS patients with record of preexisting renal diseases, hypertension, diabetes, and hepatitis B or C virus co- infection at the time they were initiated on therapy were excluded from the study. A systematic random sampling method was employed were a total of 549 files of HIV/AIDS patients on TDF, AZT and D4T were selected. A total of 1396 HIV/AIDS patients were on treatment with TDF- based regimen while 4,453 patients were either on AZT- based regimen or D4T- based regimen in the mentioned period. Out of the total of 1,396 on TDF- based regimen, 275 participants were systematic randomly selected at intervals of 5 starting from position 26 making the study group. Out of a total of 4,453 patients on AZT or D4T, 274 participants with sex matching with the participants in the study group were selected in making the control group.

From the obtained files, patient demographics like age at initiation and 1 year of therapy, body weight and sex were obtained from the follow- up forms. Parameters like Serum Creatinine (SCr) at the initiation and 1 year of antiretroviral therapy (ART) were obtained from result transcripts present in the patients' files. Creatinine clearance was

calculated from the SCr, weight, age and sex of the patients at initiation and 1 year of therapy using the Cockcroft- Gault formula as follows:

Estimated CL_{cr} (mL/min) = (140 - age [years] × weight [kg]) / (0.815 × SCr (umol/ L))
Multiplied by 0.85 for females

Renal dysfunction was defined by K/DOQI criterion. According to K/DOQI criterion; renal dysfunction calculated from Cockcroft- Gault equation was classified as follows: $CL_{cr} \geq 90$mL/min was considered no renal dysfunction; CL_{cr} of 60 - 89mL/min was mild renal dysfunction (K/DOQI stage 2); CL_{cr} of 30 - 59mL/min as moderate dysfunction (K/DOQI stage 3); and CL_{cr} lower than 30mL/min was severe dysfunction (K/DOQI stage 4 and 5).

The machine used for determination of SCr at UTH in the period was the Beckman Coulter AU400 which is form of spectrophotometer which measure SCr based on the fact that creatinine reacts with picric acid in an alkaline medium to form creatinine picrate which is a yellow- orange colored compound. The rate of change in the absorbance at 520nm and at 800nm was directly proportional to the concentration of creatinine [5].

(NaOH)
Creatinine + picric acid → creatinine picrate complex

According to UTH chemical pathology laboratory Standard Operating Procedures (SOPs), the Beckman Coulter underwent Internal Quality Assessment (IQA) attained through maintenance of the machine and quality control [24]. The machine was maintained on a daily, weekly, monthly and quarterly basis which was done according to the guidance in the Olympus AU400 user guide [5]. In addition, the UTH Chemical Pathology laboratory participated once every three months in External Quality Assessment (EQA) through proficiency testing by National Health Laboratory (NHLS) which is in the Republic of South Africa [25].

Statistics

The data was entered into STATA software version 12 for analysis. Univariate analysis was done in order to describe the distribution of single variables in the cases and controls. Multivariate analysis was done in order to describe the relationship of multiple variables to each other. Medians and quartiles were used come up with descriptive statistics for continuous variables. Continuous and categorical variables were compared using the student's t- test and chi- square test respectively. Frequency tables were used to establish the prevalence of abnormal CL_{cr} in the study population. Multivariate logistic regression was done to determine the likelihood of developing abnormal CL_{cr} with respect to factors like age, sex and treatment with TDF which are believed to be associated with abnormal CL_{cr}.

Results

Characteristics of participants at baseline and after 1 year of exposure to ART

Participants in study group were significantly older than those in control group. The median age of participants in the study group was 29 years with lower quartiles at 19 years and upper quartile 35 years verses the median age of 20 years with lower quartiles at 17 years and upper quartile at 30 years in the control group, $P<0.001$. The median baseline CL_{cr} was not significantly different between the study group and control group; both were in the normal CL_{cr} range; 99.39 mL/min verses 104.58 mL/min, $P= 0.0574$. On the other hand, the median 1 year CL_{cr} in the study group was significantly lower than the median CL_{cr} in the study group; 93.87 mL/min verses 115.07 mL/min, $P< 0.001$.

Severity of renal dysfunction categorized by exposure to TDF

Using the K/DOQI criteria of classifying renal dysfunction, the cases of renal dysfunction were identified and graded in the study group and control group at baseline and after 1 year of therapy. A total of 162 participants out of a total number of 549 participants in the study population had renal dysfunction at baseline which translated into a prevalence preexisting renal dysfunction of 29.5 % in the study population. A total of 170 participants out of a total number of 549 participants in the study population had renal dysfunction after 1 year of treatment which translated into a prevalence of renal dysfunction of 31 % in the study population after 1 year of ART.

Comparison between the baseline and 1 year creatinine clearances in the controls group

Paired t- test was done to compare the baseline CL_{cr} to the CL_{cr} after 1 year of treatment in the control

group. The median CL_{cr} in the control group significantly increased at 1 year compared to the baseline CL_{cr} by a mean of 10.75mL/min with 95 % Confidence Interval (95 % CI) ranging from 8.36mL/min to 13.14mL/min and $P<$ 0.001.

Variables	Control			Cases			
	25 %	50 %	75 %	25 %	50 %	75 %	P-Value
Age (years)	17	20	30	19	29	35	0.0001
Baseline weight(Kg)	46	52	60	48	55.5	64	0.0053
1 year weight(Kg)	48.5	54.5	63	50.9	58	66	0.004
Baseline SCr(µmol/L)	59	67	75.1	63	71.8	86	0.0001
1 year SCr(µmol/L)	54.2	63.3	73	66	78.9	94	0.0001
Baseline CL_{cr}(mL/min)	90.1	104.5	118.2	78.9	99.39	120.6	0.0574
1 year CL_{cr}(mL/min)	96.1	115.1	132.4	79.5	93.87	115.9	0.0001

Table 1: Summary statistics of the study population

		Baseline Renal dysfunction		1 year Renal dysfunction	
		Count	Percent %	Count	Percent %
Control	No renal dysfunction	207	75.55	229	83.58
	Mild renal dysfunction	60	21.9	38	13.87
	Moderate renal dysfunction	7	2.55	7	2.55
	Severe renal dysfunction	0		0	
Case	No renal dysfunction	180	65.45	150	54.55
	Mild renal dysfunction	81	29.45	108	39.27
	Moderate renal dysfunction	14	5.09	14	5.09
	Severe renal dysfunction	0		3	1.09
	Total	549		549	

Table 2: Severity of Renal Dysfunction Categorized by Exposure to TDF

Variable	Obs	Mean	Std.Dev.	[95% Confidence interval]	
Baseline CL_{cr}	274	106.61	26.54	103.45	109.76
1 year CL_{cr}	274	117.36	30.99	113.67	121.05
Diff	274	-10.75	20.09	-13.14	-8.36

Table 3: Paired t- test Results for Baseline and 1 year CL_{cr} in control group. **Note:** mean(diff)= mean(Baseline CLcr - 1 year CLcr); t= -8.8603; degrees of freedom= 273**;** Ho: mean(diff)= 0 P(|T|> |t|)< 0.001

Table 4: Paired t- test results for baseline and 1 year creatinine clearance in the study group. **Note:** Mean(diff)= mean(Baseline CLcr - 1 year CLcr); t= -3.1289; degrees of freedom= 274; Ho: mean(diff)= 0; *P*(|T|> |t|)= 0.0019

Variable	Obs	Mean	Std. Dev.	[95 % Confidence Interval]	
Baseline CL_{cr}	275	102.08	29.09	98.63	105.54
1 year CL_{cr}	275	97.79	28.29	94.43	101.15
Diff.	275	4.29	22.76	1.59	7.00

Comparison between the baseline and 1 year creatinine clearances in the study group

Paired t- test was done to compare the baseline CL_{cr} to the CL_{cr} after 1 year of treatment in the study group. Results showed that the CL_{cr} after 1 year significantly decreased by a mean of 4.29mL/min from the baseline CL_{cr}, 95 % CI ranging from 1.59mL/min to 7mL/min and P= 0.0019

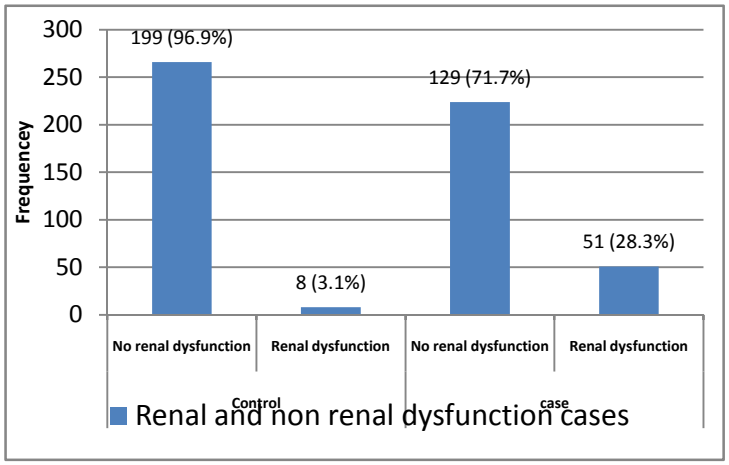

Figure 1: Frequency of developing abnormal CL_{cr} (renal dysfunction) after 1 year of ART in the study population

TDF Exposure	RD after 1 year		Total Patients
	Yes	No	
Cases	51(28.3 %)	129(71.7 %)	180
Controls	8(3.1 %)	199(96.9 %)	207
Total	59(15.2 %)	328(84.8 %)	387

Table 5: Frequency of Renal Dysfunction Development (RD) in Cases and Controls after 1 year of treatment

Frequency of developing abnormal CL_{cr}(renal dysfunction) at 1 year of ART in the study population

The frequency of developing abnormal CL_{cr} (renal dysfunction) after one year of ART from having normal CL_{cr} (no renal dysfunction) at baseline was compared between the study group and control group. Results showed a larger number of participants in the study group developed renal dysfunction compared to participants in the control group; 51 out of 180 in the study group verses 8 out of 207 in the control group.

The chi- square test (χ^2- test) was done to assess the strength of evidence that exposure to TDF really affected the probability of patients developing renal dysfunction after 1 year in participants who had no renal dysfunction at baseline. The model was statistically significant with χ^2= 44.6114 and P< 0.001. These findings showed that the participants in the study group had a higher probability of developing renal dysfunction after 1 year from having no renal dysfunction at baseline compared to the participants in the control group.

Independent Variables	Odds Ratio	Std. Err.	*P*	[95 % Confidence Interval	
Age	1.07	0.02	0.001	1.03	1.11
Gender	1.62	0.50	0.122	0.88	2.98
TDF exposure	8.77	3.54	0	3.97	19.34
Constant	0.01	0.00	0	0.00	0.02
N=387					

Table 6: Logistic regression model with developing abnormal CL_{cr} (renal dysfunction) after 1 year of ART as the dependent variable

Comparison of likelihood of developing abnormal CL_{cr} (renal dysfunction) after 1 year of ART in the study population

The final model in logistics included age; gender and the outcome CL_{cr} at one year in relation to exposure toTDF- based regimen. The model was statistically significant for exposure to TDF and age but not significant for gender. The odds of patient developing renal dysfunction after one year of therapy with TDF- based regimen controlled for age and sex was 8.77 (95 % CI 3.97 to 19.34). Increase in age also significantly increased the odds of developing renal dysfunction after one year of

treatment with TDF- based regimen, $P< 0.001$. The odds of developing renal dysfunction at one year of treatment with TDF- based regimen increased by 1.07 per unit increase in age with 95 % CI ranging from 1.03 to 1.11. However, gender showed no significant association with developing renal dysfunction after one year of treatment with TDF-based regimen, $P= 0.12$.

Discussion

The study aimed at determining whether HIV/AIDS patients treated with TDF- based regimen at UTH develop renal dysfunction at one year of treatment more than those treated with D4T- based regimen or AZT- based regimen. Findings of this study showed a decrease in the median creatinine clearance after 1 year of therapy by a mean of 4.39mL/min compared to the baseline CL_{cr}, $P< 0.001$ in the study group which meant a reduction in kidney function after 1 year of treatment with TDF. In addition to that, findings in this study also showed an association between treatments with TDF- based regimen and renal dysfunction where HIV/AIDS patients on treatment with TDF- based regimen were 8.77 times more likely to develop abnormal CL_{cr} after 1 year of therapy compared to those on D4T- based regimen or AZT- based regimen containing regimen, $P< 0.001$. This evidence of TDF being associated with renal dysfunction has been accentuated in many studies [4, 6, 7, 4, 9, 11, 12, 17, 21, 22, 23 and 28] all of which talked of the association of TDF with renal dysfunction. Mauss (2005) showed that patients on tenofovir had significantly lower mean eGFR and cystatin C clearance compared to patients on non-TDF- based regimen which lead them to conclude that even though the eGFR was still in the normal range, treatment with TDF- based regimen was associated with lower eGFR a finding coinciding to this study in that patients on TDF had a reduction in CLcr which entails a reduction in eGFR. Gallant (2005) alongside found that patients on TDF- based regimen had CL_{cr} significantly decreased by 4 % after 1 year of treatment compared to patients on other NRTI which is equally coinciding with the findings of this study. Significant correlation between Ctrough-TDF and the decrease in GFR highlights a toxic concentration-dependent effect of TDF on glomerular filtration also found by Poizot- Martin (2013) and is concurrent with previous studies reporting a tubular nephropathy in patients on a TDF-based regimen. However, the findings of this study disagree with Banda's (2010) study, the controversy can be ascribed to the fact that Banda used a combination of SCr, eGFR and urine output as explained by RIFLE as criteria of determining renal dysfunction which was too wide because it encompassed three different methods at once as opposed to the K/ DOQI criterion in this study, in fact, this also explains why Banda found a baseline prevalence of renal dysfunction of 42% vs. the 29.5% of this study. However, it is noteworthy that the prevalence baseline renal dysfunction of 29.5% in this study somewhat agrees with the 34.5% prevalence found in Mulenga's (2008) who also used the CL_{cr} in determining renal dysfunction and K/ DOQI criterion in classifying it. Therefore, with the evidence from the research findings, the null hypothesis that HIV/AIDS patients on treatment with TDF- based regimen at UTH do not have a threefold likelihood of developing renal dysfunction at one year of therapy compared to those on D4T- based regimen or AZT- based regimen was rejected.

Conclusion

Since the paired t- test, the chi-square test and the logistic regression model were all significant with $P< 0.001$. It was concluded that adults with HIV/AIDS on treatment with TDF- based regimen were 8.77 times more likely to develop abnormal CL_{cr} after one year of therapy from having no renal dysfunction at beginning of therapy compared to those on non- TDF - based regimen.

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