Original Article

Kidney Dysfunction in HIV-Positive Patients on HAART in a Nigerian Tertiary Hospital: A Comparative Study

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Abstract

Background: There has been improvement in the overall outcomes of people living with human immunodeficiency virus (PLWHIV) following the advent and use of highly active antiretroviral therapy (HAART). However, there is an increased risk of nephrotoxicity from using HAART in PLWHIV as their life expectancy improves. This study assessed and compared renal dysfunction among PLWHIV on tenofovir-based and non-tenofovir-based HAART.

Methodology: This comparative cross-sectional study determined and compared glomerular and tubular dysfunction among PLWHIV on tenofovir-based and non-tenofovir-based HAART. Urine beta2-microglobulin, fractional excretion of bicarbonate, uric acid, and Phosphate were used to assess proximal tubular function. The modification of diet in renal disease (MDRD) formula was used to estimate the glomerular filtration rate (eGFR)

Result: There were 120 participants with a mean age of 42.2 ±9.2 years. Sixty participants were on tenofovir-based HAART, and 60 were on non-tenofovir-based HAART. The overall prevalence of proximal renal tubular dysfunction among PLWHIV on HAART was 9.1%. The proximal renal tubular dysfunction prevalence was higher in the tenofovir-based group (15.0%vs3.3% P= 0.01). The mean urine β_2 MG level was higher in the tenofovir-based HAART group (0.21±0.15ug/ml vs 0.14±0.12ug/ml; P= 0.01). The mean eGFR was lower in the tenofovir-based HAART group (86.99±18.51mls/min/1.73m² vs 99.59±34.48mls/min/1.73m²; P=0.01)

Conclusion: Tenofovir-based HAART was associated with a significant decrease in GFR and proximal renal tubular dysfunction compared to non-tenofovir-based HAART. Those on tenofovir should be regularly monitored with markers of tubular dysfunction.

Keywords: HAART; Tenofovir; β_2-Microglobulin; Kidney Dysfunction; Tubular Dysfunction.

Introduction

There has been improvement in the overall outcomes of people living with human immunodeficiency virus (PLWHIV) following the advent and use of highly active antiretroviral therapy (HAART).[1] This development has come with an increased risk of nephrotoxicity from the use of HAART in PLWHIV as their life expectancy increase, and the duration of HAART use increases considerably.[2] The kidney is involved in the breakdown and removal of medications, making it

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susceptible to acute kidney injury, tubular dysfunction and chronic kidney disease. One of the major manifestations of tubular dysfunction in patients on HAART is complete or partial Fanconi syndrome, an indicator of proximal tubular dysfunct ion. This is characterized by aminoaciduria, phosphaturia, hypophosphataemia, glycosuria and low molecular weight proteinuria.[3]

Tenofovir disoproxil fumarate (TDF) is a commonly used antiretroviral agent as first-line therapy in managing HIV. [4,5] TDF is the most common HAART that is associated with nephrotoxicity. The risk factors for TDF-induced renal toxicity include pre-existing kidney disease, prolonged use of TDF, uncontrolled HIV disease, genetic polymorphism involving proximal tubular transporters (ABCC2), concomitant hepatitis C viral infection, older age, CD4 < 200cells/mm^3, black race, female gender and co-administration of medications that are potentially nephrotoxic. [3, 6 - 8, 9] The reported prevalence of proximal renal tubular dysfunction in PLWHIV on tenofovir is between 6-35%. [10-16]

There are conflicting reports about the reversibility of TDF-induced nephrotoxicity if detected early. [17] Experimental studies show that rosiglitazone, antioxidants and melatonin may reverse early TDF-induced nephrotoxicity; however, these medications are yet to be proven beneficial in man. [17]Although tenofovir tends to cause nephrotoxicity, the renal function of PLWHIV on this medication is presently not adequately monitored. Renal function is still routinely monitored with serum creatinine instead of using markers of tubular dysfunction that may diagnose tubulopathies even when serum creatinine and estimated GFR are normal. This study assessed and compared the glomerular and proximal tubular dysfunction among PLWHIV who were on tenofovir and non-tenofovir containing HAART regimens.

Methods

Ethical Approval and Consideration

The hospital's Human Research and Ethical Committee gave the ethical approval for this study on 5thOctober 2017. The reference number was (/HREC/PR/2017/08/099). All the study participants gave informed consent. The researchers ensured that all information obtained in the course of the study was treated as confidential.

Study Design and Area

The study was a cross-sectional comparative study conducted at the Special Treatment Clinic of the University Teaching Hospital. The study was conducted over six month's period from January 2018 to June 2018.

Sample Size Calculation and Study Participants

The sample size was calculated using the formula for a case-control studies. [18] The proportion of PWHIV on tenofovir and non-tenofovir-based HAART with renal dysfunction was 28% and 4.4%, respectively, from previous studies. [12][19]. The confidence interval and power of the study were 95% and 80%, respectively. The sample size for each group was 47; however, 60 participants were recruited in each group.

Consenting PLWHIV who were 18 years and above, that have been on HAART for a minimum of 6 months, and were without evidence of kidney dysfunction at the commencement of HAART were consecutively enrolled for the study. Those with pregnancy-established chronic kidney disease, diabetes mellitus, hepatitis B and C, sickle cell disease, hypertension, and active urinary tract infections were excluded.

The researchers administered questionnaires to the study participants and obtained their biodata, socio-demographic information, clinical history and medication profile. Blood samples were collected for creatinine, bicarbonate, uric acid, and phosphate assay. Spot mid-stream urine samples were collected, and spot urinalysis was done using a combi 9 urine test strip to determine glycosuria. Urine samples were all stored in cryovials at -80ºC to estimate β_2 -microglobulin, urine creatinine, bicarbonate, uric acid, and phosphate. Fractional excretion (FE) of Phosphate, uric acid, and bicarbonate were estimated for all patients. The modification of diet in renal disease (MDRD) formula was used to estimate the glomerular filtration rate (eGFR). [20]

Definition of Variables

Raised FE of Phosphate was defined as FE≥20% [16].

Raised FE of uric acid was defined as FE≥ 10%. [21]Raised FE of bicarbonate was defined as FE≥ 100%. The presence of β2-microglobulinuria and at least 1 of the following abnormalities: non-diabetic glycosuria, raised FE of Phosphate, raised FE of uric acid, or raised FE of bicarbonate was used to define proximal renal tubular dysfunction. [15]

Statistical Analysis

The statistical package of social sciences (SPSS) software version 20 was used for data entry and analysis. Frequencies and percentages were used to present categorical variables. Mean with standard deviation was used to show continuous variables, while proportions and percentages were used to express categorical variables. Chi-square was used to determine the association between categorical variables. Student t-test was used to compare the mean of the two groups. P-value of <0.05 was taken as significant.

Results

One hundred and twenty participants were involved in this study. Their mean age was 42.2 ±9.2 years, and the M: F ratio was 1:3. Sixty patients were on tenofovir-based HAART and 60 were on non-tenofovir-based HAART. Their mean ages were 42.6±8.4 years and 41.7±10.1 years, respectively, with no significant difference (p=0.58).

The average treatment duration was 7.36 years ±3.94 years, and a higher proportion of the study population had been on HAART for ≥ 6 years (56.6%). (Table 1)

Table 1: Socio-demographic Information of Study Participants

Characteristics	Non-TDF based HAART n (%)	TDF based HAART n (%)	Total n (%)	P-value
Age groups (years)				
Mean (SD)	42.6(8.4)	41.7(10.1)	42.15(9.24)	0.58
	6(10.0)	8(13.3)	14(11.7)	
31 –40	22(36.7)	24(40.0)	46(38.3)	
41 –50	19(31.7)	17(28.3)	36(30.0)	
	13(21.7)	11(18.3)	24(20.0)	
Sex				
Male	19(31.7)	11(18.3)	30(25.0)	0.14
Female	41(68.3)	49(81.7)	90(75.0)	
HAART Duration				
Mean (SD)	8.1(3.9)	6.6(3.9)	7.36(3.94)	0.10
	21(35.0)	31(51.7)	52(43.3)	
6 10	24(40.0)	19(31.7)	43(35.8)	
	15(25.0)	10(16.7)	25(20.8)	
Educational status				
Primary	5(8.3)	4(6.7)	9 (7.5)	0.25
Secondary	16(26.7)	9(15)	25(20)	
Tertiary	39(65)	47(38.3)	86(71.7)	
Marital status				
Married	36(60%)	41(68.3)	77(67.2)	0.39
Single	17(28.3)	16(26.7)	33(27.5)	
Divorced/separated	2(3.3)	2(3.3)	4(3.3)	
Widowed	5(8.3)	1(1.7)	6(5)	
Occupation				
Public Servant	17(28.3)	21(35)	38(31.7)	0.17
Private employ	28(46.7)	32(53.3)	60(50)	
Unemployed	15(25)	7(11.7)	22(18.3)	
BMI (kg/m²)				
Mean (SD)	25.05(3.68)	23.81(3.94)	24.43(2.84)	0.08

BMI=Body Mass Index, HAART=Highly Active Antiretroviral Therapy, SD=Standard deviation

The difference between the mean serum creatinine, uric acid, bicarbonate, and Phosphate of the two groups was insignificant. There was also no significant difference between the two groups' mean urine phosphate, uric acid, Phosphate, and bicarbonate. (Table 2)

Table 2: Comparison of Mean Values of Biochemical Parameters between Tenofovir-based HAART group and Non-tenofovir based HAART group

	TDF-based HAART group Mean±SD	Non-TDF-based HAART group Mean±SD	P-Value
Serum Creatinine(umol/L)	83.13–17.13	87.90–14.91	0.11
eGFR (mls/min 1.73m²)	99.59⊥34.48	86.99–18.51	0.01
Serum Uric Acid (umol/L)	301.93⊥77.4	295.62⊥73.33	0.18
Serum Phosphate (mmol/L)	1.35–1.21	1.30–1.28	0.29
Serum Bicarbonate (mmol L)	24.48=2.40	23.17=4.06	0.15
Urine creatinine(mg dl)	160.67⊥36.50	169.53⊥40.35	0.52
Urine Uric Acid(mg/dl)	56.47⊥23.60	60.01⊥20.48	0.58
Urine Phosphate (mmol/L)	22.36⊥9.62	23.77⊥11.65	0.69
Urine Bicarbonate(mmol/l)	28.82⊥2.90	30.15⊥3.98	0.83
	0.14⊥0.12	0.21⊥0.15	0.01

The fractional excretion of uric acid, bicarbonate, and Phosphate was higher in the tenofovir group compared to the non-tenofovir group, although this was not statistically significant. (Table 3)The mean urine β2 -microglobulin level was higher in the Tenofovir-based HAART group compared to the non - tenofovir – based HAART group (0.21±0.15ug/ml vs 0.14±0.12ug/ml; P=0.01). The mean eGFR was significantly lower in the tenofovir-based HAART group (86.99±18.51 mls/min/1.73m² vs 99.59±34.48mls/min/1.73m²;*P*=0.01). (Table2).

The overall prevalence of proximal renal tubular dysfunction among the study participants on HAART was 9.2%. (Table 3) The prevalence of proximal renal tubular dysfunction was higher in the tenofovir-based group (15.0%vs3.3% *P*= 0.03).The proportion of those with elevated urine β_2 - microglobulin levels was significantly higher in the tenofovir-based HAART group (18.3%vs5.0% *P*=0.01). (Table 3)

Table 3: Prevalence of biochemical indicators of proximal tubular dysfunction in study population

Biochemical indicators of Proximal Tubular Dysfunction	Non-TDF based HAART n (%)	TDF-based HAART n (%)	Total n(%)	p-value
Beta-2microglobulinuria				
Normal	57(95)	49(81.7)	106(88.3)	
Increased	3(5)	11(18.3)	14(11.7)	0.04
Fractional excretion of Uric Acid				
Normal	58(96.7)	55(91.7)	113(94.2)	
Increased	2(3.3)	5(8.3)	7(5.8)	0.44
Fractional excretion of Phosphate				
Normal	48(80)	43(71.7)	91(75.8)	
Increased	12(20)	17(28.3)	29(24.2)	0.66
Fractional excretion of bicarbonate				
Normal	60(100)	59(98.3)	119(99.2)	
Increased	0 (0)	1(1.7)	1(0.8)	1.00
Proximal Renal Tubular Dysfunction				
Present	2(3.3)	9(15.0)	11(9.2)	
Absent	58(96.7)	51(85.0)	109(90.8)	0.03

Discussion

This study assessed and compared renal function among PLWHIV on tenofovir-based and non-tenofovir-based HAART. The overall prevalence of proximal renal tubular dysfunction among PLWHIV in this study was 9.1%. The prevalence of proximal renal tubular dysfunction among PLWHIV on tenofovir-based and non-tenofovir-based HAART were 15.0% and 3.3%, respectively. In this study, the overall prevalence of proximal renal tubular dysfunction is within the range of 6.0-35% reported in some previous studies. [10-16] The wide variation in the prevalence rates reported in different studies may be due to some methodological differences, such as the inclusion and exclusion criteria used in the studies. Casado et al. [12] reported a relatively higher prevalence of 28% in a study where participants with renal disease risk factors such as hypertension, chronic hepatitis infection and diabetes mellitus were not excluded, unlike our study. The prevalence of proximal renal tubular dysfunction was significantly higher among PLWHIV who were on tenofovir-based HAART than those on non-tenofovir-based HAART.

The underlying pathogenesis of TDF-associated nephrotoxicity is profound mitochondrial damage of proximal tubular cells.[22] TDF is removed unchanged in the urine through filtration and tubular secretion in the kidneys. The concentration of TDF builds up within the tubular cells of the nephron when the amount filtered in the nephrons is high, or there is reduced secretion. This leads to partial inhibition of mitochondrial DNApolymerase γ, reduction in mitochondrial DNA, and oxidative respiratory chain abnormality.[23] This results in the shortage of adenosine triphosphate production and impaired reabsorption of substances such as glucose, uric acid, bicarbonate, amino acids, Phosphate and β_2-microglobulin by the tubular cells. Hence these substances are found in the urine in abnormal quantities.[22]

The prevalence of proximal renal tubular dysfunction among those on tenofovir-based HAART in this study is comparable to 16.0% and 16.5% reported by Villa et al. [14] and Rodriguez et al. [15], respectively. This prevalence is lower than the 32% and 35% reported by Casado et al [12] and Chadwick et al. [16], respectively. Factors that may also account for these different prevalence rates include differences in duration of ART by study participants; the presence of renal disease risk factors such as hypertension, and diabetes mellitus, presence of other potentially nephrotoxic medications such as co-trimoxazole, ART components, and genetic predisposition. Rodriguez et al. [15] identified certain genes, such as the ABCC2 gene, as a risk factor for tenofovir-induced proximal renal tubular dysfunction. This study shows that PLWHIV, particularly those on TDF-based HAART, are more likely to develop proximal renal tubular dysfunction considering this study was conducted in participants with apparently normal glomerular function without traditional risk factors for renal disease such as hypertension and diabetes mellitus. These findings underscore the need to monitor renal function, particularly proximal tubular renal function, in those on tenofovir, even when the glomerular function appears normal.

The fractional excretion of urate, bicarbonate, and Phosphate was higher in the tenofovir-based HAART than in non-tenofovir-based HAART, although not statistically significant. The urinary β2-microglobulin was significantly higher in the tenofovir-based group. This finding corroborates that the nephrotoxic effect of TDF is primarily on the proximal renal tubules. The estimated GFR was significantly lower in those on tenofovir-based HAART than in those on non-tenofovir-based HAART. This is similar to a report by Beaudrap et al. [24] that showed a significant moderate decline in GFR in PLWHIV who were on TDF compared to those on non-tenofovir-based HAART in a study conducted in Senegal. Mtisi et al. [25] also reported a significant decrease in renal function of PLWHIV who were on tenofovir in a systematic review of studies from Africa. This suggests that TDF may also reduce glomerular function in patients which may progress to advanced CKD over time. Gupta et al. [26] showed that tenofovir alafenamide (TAF) has better renal safety than TDF in a pooled analysis that involved 26 clinical trials. TAF is a pro-drug of tenofovir that produces a lower plasma tenofovir exposure associated with a reduced risk of nephrotoxicity compared to TDF. [27] Therefore, TAF may be a better substitute for PLWHIV, which has a higher risk of developing nephrotoxicity associated with TDF. However, the cost of TAF is higher than TDF and may limit its availability in low-resource countries.

The limitation of this study was that the criteria used for assessing proximal renal function did not include aminoaciduria. This might have resulted in an underestimation of this study's prevalence of proximal tubular dysfunction.

In conclusion, this study showed that TDF-based HAART is associated with proximal renal tubular dysfunction and a significant decrease in GFR. Therefore, given the high prevalence of TDF-associated kidney damage, TAF should be preferred over TDF in tenofovir-based HAART in PLWHIV, who have an increased risk of developing TDF-associated nephrotoxicity. We also recommend regular monitoring with markers of tubular dysfunction in HIV patients on the TDF regimen.

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