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Renal Tubular Dysfunction Linked to Tenofovir in Antiretroviral Therapy in HIV-Infected Patients

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Abstract: Tenofovir disoproxil fumarate (TDF) has low general toxicity and can lead to a moderate reduction in glomerular filtration rate (GFR) and a more significant prevalence of renal tubular dysfunction (RTD). The mechanism of RTD has been attributed to the mitochondrial lesion in the proximal tubule cells caused by the increase of the intracellular TDF concentration. Additionally, the host's genetic polymorphisms have been considered one of the TDF concentration increasing causes. RTD can be characterized by the deficiency in the solutes reabsorption as bicarbonate, uric acid, phosphate, glucose, and low weight molecular proteins. Research Objectives: verify the prevalence of renal tubular dysfunction in people living with HIV (PLWH) on TDF treatment, identify the risk factors associated and compare the 24-hour urine findings with the serum creatinine and its calculated clearance for the RTD identification. Research methods: prospective case-control study, performed between January 2011 to December 2015. Research results: 163 patients were included in the study, in which 106 (68.4%) did not receive TDF, and 57 (31.6%) received TDF. RTD occurred in 8 patients that used TDF, a prevalence of 14%. The patient's age was identified as a significant risk factor for the development of RTD. Proteinuria and phosphaturia were substantial for the diagnosis of RTD. Conclusions: age was considered as a risk factor for RTD, mainly in patients over 60-year-old. Phosphaturia and proteinuria showed the highest diagnosis sensitivity for RTD. The serum creatinine and phosphorus concentration, the creatinine clearance, and the stand-alone hyperproteinuria should not be considered as diagnosis predictors for RTD.
Keywords: renal tubular dysfunction; tenofovir; antiretroviral therapy; HIV

INTRODUCTION

Currently, HIV (Human Immunodeficiency Virus) is a chronic and relatively controlled disease. However, its new challenges are clinical conditions secondary to antiretroviral therapy (ART), the presence of HIV and its chronic inflammatory activity, early aging, genetic predisposition and patient's life habits[1,2,3].

Although ART reduces AIDS (acquired immunodeficiency syndrome) mortality and increases the life expectancy of HIV-infected individuals, it may contribute to the onset of long-term adverse effects, including kidney disease. Tenofovir disoproxil fumarate (TDF), is considered a first-line antiretroviral treatment because of its general toxicity. However it can lead to a moderate reduction in the glomerular filtration rate (GFR) and a higher

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prevalence of renal tubular dysfunction (RTD) in patients who received TDF compared with those who did not[4]. Decreased renal function in patients may be acute or chronic[9].

The RTD mechanism is not completely understood, it might be attributed to mitochondrial lesions in proximal tubule cells as a result of an increase in intracellular TDF concentration and the potential influence of genetic polymorphisms[5]. The RTD is characterized by a deficiency in the reabsorption of solutes such as bicarbonate, uric acid, phosphate, glucose, and low molecular weight proteins[6].

The proximal tubule (PT) is primarily responsible for the excretion of TDF. Its dysfunction leads to the loss of substances through urine, which is normally filtered in the glomeruli and reabsorbed by the tubular portion. TDF's tubular secretion occurs via organic anion transport in the PT using specific transporters located in the basal and apical membranes of tubular cells. Uptake from the bloodstream occurs through human anion organic transporter types 1 and 3, located in the basolateral portion of the cell. Secretion to the tubular lumen occurs through multidrug resistance-associated protein (MRP) types 2, 4, and 7, which locates in the apical portion of the cell. The MRPs are encoded by the genes ABCC2, ABCC4, and ABCC10[5,11,12].

Originally, TDF nephrotoxicity was described as the manifestation of Fanconi syndrome, a tubular disease characterized by phosphaturia, aminoaciduria, uricosuria, and glycosuria not associated with hyperglycemia[8]. Subsequently, to characterize TDF nephrotoxicity as RTD, new studies have suggested the presence of at least two tubular abnormalities, such as hyperphosphaturia, glycosuria without hyperglycemia, hyperuricosuria, hypophosphatemia and/or proteinuria[4,6].

In renal biopsy analysis of patients on TDF treatment, the main finding is PT lesions, which can be severe and diffuse or moderate and localized, combined with variable degrees of chronic tubular atrophy and interstitial fibrosis. No focal segmental glomerulosclerosis or tubular microcysts, typical of HIV-associated nephropathy, have been found[7].

Risk factors associated with RTD have high variability. It has been suggested that age, being an attenuated patient with low weight, hypertension, metabolic disorders, simultaneous use of other nephrotoxic medications, and TDF administration combined with ritonavir-boosted protease inhibitors (IP/r) are important risk factors[8].

The novelty of this research is the evaluation of RTD, excluding patients with glomerulopathies and HIV-associated nephropathy due to detectable viral load. This research aims to verify the prevalence of RTD in the people living with HIV (PLWH) on TDF treatment, identify the risk factors associated with RTD and compare the 24-hour urine findings with the serum creatinine and its calculated clearance for the RTD identification.

MATERIALS AND METHODS

This research was a case-control longitudinal study conducted at a specialized outpatient clinic in the State of São Paulo. HIV-infected patients receiving ART were followed up at a medical center from January 2011 to December 2015. The inclusion criteria was: HIV patients using TDF with undetectable viral load (VL) (less than 20 copies/mL of blood). The exclusion criteria was: HIV infected with other types of nephropathy.

Definition of cases and controls: To assess risk factors associated with RTD, patients were divided into two groups; patients on ART with TDF (exposed patients) and those on ART without TDF (non-exposed patients). Exposed and non-exposed patients were studied in regards to exposure to independent variables assumed to be risk factors. Exposed individuals were those on ART with TDF until RTD development. Non-exposed individuals were those on ART without TDF.

Renal tubular dysfunction: RTD is defined as generalized proximal tubulopathy that combines the presence of at least one of the following alterations; hypophosphatemia, hyperphosphaturia, glycosuria without hyperglycemia and tubular proteinuria. That occurs due to the use of TDF in combination with other antiretroviral drugs.

Laboratory tests: Blood samples for the T-CD4 lymphocyte count and HIV VL count were performed every six months throughout treatment. Blood samples for serum creatinine test was collected at the beginning of the treatment and once annually throughout follow-up. Twenty-four-hour urine and serum phosphorus were collected once annually in the monitoring of ART with TDF.

Continuous numerical variables studied as risk factors were age, time of HIV infection, T-CD4 lymphocyte level, total time on ART, time on ART with TDF, initial serum creatinine, initial creatinine clearance, creatinine at RTD diagnosis, serum phosphorus at RTD diagnosis and 24-hour urine (proteinuria, phosphaturia and creatinine clearance) at RTD diagnosis. Gender was considered a dichotomous (present or absent) risk factor.

The statistical analysis used in this study were as follows t-Student test, Pearson chi-square test, Odds ration, Exponential Distribution, Kolmogorov-Smirnov normality test, ANOVA test, and Levene's Homogeneity Test.

This study was approved by the ethical committee of the Faculdade de Medicina de São José do Rio Preto – FAMERP - reference number 1.573.409 and also performed under the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULT AND DISCUSSION

A total of 163 patients were included in the study. One hundred and six patients (68.4%) were not on TDF treatment (non-TDF group), and 57 (31.6%) were on TDF treatment (TDF group). RTD occurred in 8 patients in the TDF group, indicating a prevalence of 14% (Table 1).

Table 1. Distribution of Patients in the TDF and Non-TDF Groups and RTD Prevalence.

		RTD			
		Not applicable	Yes	Total	P *
Non-TDF	n	106	0	106	0.000
		100.0%	0.0%	100.0%	
TDF	n	49	8	57	0.000
		86.0%	14.0%	100.0%	

RTD: renal tubular dysfunction; TDF: tenofovir.

* Pearson chi-square test ($p < 0.01$).

Patient age ranged from 20 to 75 year-old, with a mean age of 43.9 years ± 10.9 (p = 0.01 in the univariate analysis and logistic regression) (Tables 2 and 3).

Table 2. Distribution of Demographic, Clinical, and Laboratory Variables as Risk Factors for the Development of RTD.

Variables	Mean	95% CI Lower Limit	Upper Limit	Standard Deviation	P *
Age	43.93	42.24	45.61	10.913	0.011
Time with contagion (months)	105.02	93.46	116.58	74.749	0.481
Current CD4 count (cells/mm^3)	550.82	511.89	589.75	250.899	0.415
Total time on ART (months)	81.53	71.69	91.38	63.656	0.579
Time on ART with TDF (months)	55.42	48.62	62.23	43.999	0.319

CI: confidence interval.
* Univariate analysis, ANOVA test (p <0.05).

Table 3. Logistic Regression of Demographic, Clinical, and Laboratory Variables, Analysed as Risk Factors for the Development of RTD.

Variables	Coefficient	P	OR
Sex (1)	0.190	0.819	1.209
Age	0.089	0.016	1.093
Time with contagion (months)	0.003	0.708	1.003
Current CD4 count (cells/mm^3)	-0.001	0.588	0.999
Total time on ART (months)	-0.001	0.953	0.999
Time on ART with TDF (months)	-0.017	0.168	0.983

1: female; OR: odds ratio.

For each year, the risk for developing RTD was 9% (Table 3). For people over 60 year-old, the risk for developing RTD was 14 times higher than those people in the group younger than 60 year-old (Table 4).

Table 4. Logistic Regression of Demographic, Clinical, and Laboratory Variables, by Range, Analyzed as Risk Factors for the Development of RTD.

Variables	Coefficient	P	OR
Sex (1)	0.347	0.676	1.414
Age range (2)	2.646	0.004	14.091
Time with contagion (months)	0.005	0.543	1.005
Current CD4 range (3)	-1.270	0.174	0.281
Total time on ART (months)	0.004	0.666	1.004
Time on ART (months)	-0.019	0.128	0.981

1: female; 2: age range > 60 years old. 3: CD4 > 500 cells/mm^3.
OR: odds ratio.

Age was identified as a significant risk factor for the development of RTD (Tables 2 and 3). Initial serum creatinine ranged from 0.40 mg/dL to 1.30 mg/dL, with a mean of 0.88 mg/dL ± 0.19 (p = 0.96, and the serum creatinine level at RTD diagnosis was 0.82 mg/dL ± 0.21 (p = 0.001) (Table 5). The comparison of initial and current (at RTD diagnosis) serum creatinine levels showed a reduction in serum creatinine levels at RTD diagnosis (p = 0.002) (Table 6).

Table 5. Distribution of Laboratory Variables, Analyzed as Diagnostic Criteria for RTD, in the TDF Group.

		95% CI			
	Mean	Lower limit	Upper limit	Standard deviation	P *
Initial creatinine (mg/dL) RV 0.4 to 1.3 mg/dL	0.8853	0.8554	0.9151	0.19305	0.967
Current (at RTD diagnosis) creatinine (mg/dL) RV 0.4 to 1.3 mg/dL	0.8216	0.7886	0.8546	0.21334	0.001
Estimated initial creatinine clearance (mL/min) RV 70 to 140 mL/min/1.73 m^2	107.39	103.56	111.22	24.771	0.040
Current (at RTD diagnosis) creatinine clearance (mL/min) RV 70 to 140 mL/min/1.73 m^2	114.59	108.04	121.14	42.360	0.015
Current (at RTD diagnosis) phosphorus (mg/dL) RV 2.5 to 5.6 mg/dL	3.410	3.250	3.570	0.6207	0.089
Current (at RTD diagnosis) proteinuria (mg/24 h) RV < 200 mg/24 h	109.29	91.54	127.03	68.097	0.125
Current (at RTD diagnosis) phosphaturia (mg/24 h) RV 400 to 1300 mg/24 h	791.97	610.11	973.83	697.847	< 0.001

RV: reference value; CI: confidence interval; * univariate analysis, ANOVA (p <0.05).

Table 6. Student's t-test for Analysis of Initial and Current (at RTD Diagnosis) Serum Creatinine and Initial and Ongoing (at RTD Diagnosis) Creatinine Clearance.

			IC 95%		
	Mean	Standard Deviation	Lower Limit	Upper Limit	P
Current (at RTD diagnosis) creatinine (mg/dL) RV 0.4 to 1.3 mg/dL - Initial creatinine (mg/dL) RV 0.4 to 1.3 mg/dL	-0.06368	0.26175	-0.10417	-0.02320	0.002
Current (at RTD diagnosis) creatinine clearance (ml/min), RV 70 to 140 ml/min/1.73 m^2 - Estimated initial creatinine clearance (ml/min), RV 70 to 140 ml/min/1.73 m^2	7.202	40.192	0.986	13.419	0.023

RV: reference value; p <0.01.

The estimated initial creatinine clearance, calculated by the Cockcroft-Gault formula, ranged from 26 mL/min to 205 mL/min, with a mean of 107 mL/min ± 24 (p = 0.04) (Table 5). Current (at RTD diagnosis) creatinine clearance, evaluated via 24-h urine, ranged from 26 mL/min to 285 mL/min, with a mean of 114 mL/min ± 42.3 (p = 0.01) (Table 5). A comparison between current (at RTD diagnosis) and initial creatinine clearances did not indicate statistical significance (p = 0.02) (Table 6).

Only one patient exhibited abnormal serum phosphorus levels at RTD diagnosis (Table 7). Current (at RTD diagnosis) serum phosphorus ranged from 2.1 mg/dL to 4.9 mg/dL, with a mean of 3.41 mg/dL ± 0.62, and was not significant (p = 0,296) (Table 8).

Table 7. The Absolute Number of Patients with Changes in Current (at RTD Diagnosis) Phosphorus, Proteinuria, and Phosphaturia in the TDF Group.

		RTD		
		No n (%)	Yes n (%)	Total n (%)
Phosphorus	There was no change	50 (96.15)	7 (87.5)	57 (95)
	There was a change	2 (3.85)	1 (12.5)	3 (5)
	Total (n)	52 (100)	8 (100)	60 (100)
Proteinuria	There was no change	47 (92.15)	5 (62.5)	52 (88.13)
	There was a change	4 (7.85)	3 (37.5)	7 (11.87)
	Total (n)	51 (100)	8 (100)	59 (100)
Phosphaturia	There was no change	51 (100)	1 (14.28)	52 (88.13)
	There was a change	0 (0)	7 (85.72)	7 (11.87)
	Total (n)	51 (100)	8 (100)	59

RTD: renal tubular dysfunction.

Table 8. Pearson Chi-Square Test and Levene Homogeneity Test for The Analysis of Laboratory Variables at RTD Diagnosis in the TDF Group.

	Coefficient	P	Coefficient *	P *
Current (at RTD diagnosis) phosphorus (mg/dL) RV 2.5 to 5.6 mg/dL	1.093	0.296	0.496	0.496
Current (at RTD diagnosis) proteinuria (mg/24 h) RV < 200 mg/24 h	5.816	0.016	0.441	0.441
Current (at RTD diagnosis) phosphaturia (mg/24 h) RV 400 to 1300 mg/24 h	50.632	0.000	0.000	< 0.001

RV: reference value; p <0.01.
* Levene homogeneity test, p <0.01.

Alteration in proteinuria was observed in 3 patients diagnosed with RTD (Table 8). Current (at RTD diagnosis) proteinuria, measured by the 24-hour urine, averaged 109.2 mg/24 h ± 68 (p = 0.016), ranged from 29 mg/24 h to 367 mg/ 24 h and was significant for the diagnosis of RTD (Table 8).

Alteration in phosphaturia was observed in 7 patients at RTD diagnosis (Table 7). Current (at RTD diagnosis) phosphaturia, evaluated in 24-hour urine, ranged from 134 mg/24 h to 5,254 mg/24 h, had a mean of 791.9 mg/24 h ± 697 (p < 0.01) and was significant for the diagnosis of RTD (Table 8).

This research was a case-control longitudinal study, performed along five years, in which patients with detectable HIV VL at any time were excluded and there was minimal inclusion of patients with comorbidities such as systemic arterial hypertension, diabetes mellitus and chronic hepatitis B and C. These diseases, if not controlled, and detectable HIV VL may cause undesirable mechanisms of renal injury for the adequate evaluation of RTD, thus preventing the accurate identification of laboratory abnormalities for the diagnosis of RTD.

Regarding the time of patient follow-up, most studies in the literature are meta-analysis, which mix non-uniform populations, large numbers of variables, dozens of comorbidities and old periods of analysis, when RTD was not well defined or diagnosed[10,13,15,17].

A notable feature of this study was the exclusion of patients with detectable HIV viral load, avoiding the inclusion of nephropathy associated with direct HIV injury as a mechanism for the kidney injury, which would interfere with the results. Furthermore, it enabled the analysis of immunity (T-CD4 lymphocyte count) as a risk factor for RTD.

Renal tubular injury in this study was defined by the presence of at least one alteration analyzed annually in the 24-hour urine (proteinuria, phosphaturia, and/or creatinine clearance) and/or hypophosphatemia. Studies defined these alterations as tubular abnormalities, ranging from 0 to 5, and showed differences in number to identify RTD. The characterization of RTD based on 0 up to 5 tubular alterations leads us to reflect that RTD's diagnostic criteria remains undefined. The use of 5 alterations (similar to

Fanconi syndrome) as a diagnostic criterion stems from outdated studies and reduces RTD detection sensitivity. More recent studies have been suggesting the presence of 2 or more tubular abnormalities for the diagnosis of RTD. However they still do not define which alterations are more or less sensitive[15,16,18].

The prevalence of RTD in this study was 14% (Table 1). This result was also seen in other studies, 13.9% until 72%[4-6,9,13,15,17]. Age was the only risk factor for the development of RTD. Annually, the percentage of development of RTD increased in 9% (Table 3). The risk of development of RTD in people over 60 year-old was 14-fold (Table 4). Age is considered a physiological factor for the RTD onset because the natural and progressive decrease in renal function and reduction in tubular anion transporter function. Some studies have shown age (35.5 to 46.7 years) as a risk factor for DTR development[4-6,9,13-15,17].

The risk for a patient with T-CD4 lymphocyte blood count (mean 550 cells/mm^3) to develop RTD was 72% lower (Table 4). These finding indicates high immunity is a protective factor.

Several researches showed T-CD4 lymphocytes blood count less than 500 cells/ mm^3 was considered a risk factor for RTD development. However, the afore mentioned studies included patients with HIV viral activity (detectable viral load). These approach might have weakened the statistical test of the immunity variability without AIDS interference. Consequently, immunity could not be considered an influence factor for RTD development[4,9,13,15].

Another interesting finding in our study was that the contamination time (mean of 105 months) was not considered a risk factor for RTD development. Other studies with contamination time varying from 88 to 164 months also showed contamination time was not considered a risk factor[5,6,9,13,14]. Conversely, one study with contamination time of 147 months was considered a risk factor.

In this study, time on ART with TDF was not a risk factor for RTD development. This result might be due to time course of the treatment. Two other studies with time course treatment of 9 and 66 months respectively, was considered a determinat factor for RTD development. Long term studies are necessary to standardize these variable.

Initial serum creatinine (mean 0.88 mg/dL) and current (at RTD diagnosis) serum creatinine (mean 0.82 mg/dL) of the patients studied were not considered as risk factors for the onset of RTD (Table 6). Studies in the scientific literature do not consider creatinine as a risk factor for RTD. Creatinine is a marker for glomerular kidney diseases and should not be used for the diagnoses of tubular renal diseases[18,19].

The initially estimated urine creatinine clearance (mean of 107 mL/min) when compared with the current (at RTD diagnosis) creatinine clearance (mean of 114 mL/min) did not showed to be a risk factor for the diagnosis of RTD (Table 6). In people free of renal disease is expected descrease of 0,4mL/min/year in the estimated urine creatinine clearence. In patient under TDF treatment the reduction of 3.92mL/min/year has been reported[16].

Additionally, current (at RTD diagnosis) serum phosphorus should not to be considered a variable to diagnose RTD. In our study, only one patient showed hypophosphatemia (Tables 7 and 8). Reduction in serum phosphorus from 9% up to 15% was reported in other reasearches[4,6,19].

Increased urine protein concentration in the 24-hour urine indicates RTD. Hyperproteinuria was observed in 37.5% (3/8) patients (Tables 7 and 8). Studies reported proteinuria as the predominant tubular alteration in diagnose RTD, and its prevalence was between 13% and 72%[4,6,9,13,15,17]. These studies included patients with several comorbidities, other nephrotoxic drugs, and HIV patients with detectable viral loads. In ou study, patients under those conditions were excluded. Hyperproteinuria should not be used valuated alone to diagnose RTD, once it might be found out in other tubular, glomerular and non renal diseases[18].

The most importante variable of RTD was the 24-hour urine phosphate concentration. Hyperphosphaturia was observed in 87.5% (7/8) of the patients (Tables 7 and 8). Hyperphosphaturia is a specific alteration for renal tubular diseases. Othe studies showed hyperphosphaturia occurred in 43% of the patients with RTD. Hypophosphatemia has been associated with hyperphosphaturia and suggests the diagnosis of RTD[4,6,19].

Renal tubular dysfunction remains without definitive diagnostic criteria and associated risk factors. Meanwhile, the most effective method for diagnosing RTD is to perform 24-hour urine test in patients under antiretroviral therapy using TDF once a year and finding at least two tubular alterations in this test[15,17,18].

CONCLUSION

The prevalence of RTD was 14%. Age was considered to be an important risk factor for RTD, especially in those patients above 60-year-old. The clinical pathological variables that showed the highest diagnostic sensitivity for RTD were phosphaturia and proteinuria. Serum creatinine and phosphorus concentration, creatinine clearance and hyperproteinuria did not show sensitivity as diagnostic predictors for RTD.

Renal tubular dysfunction still remains without diagnostic criteria and definitive risk factors. Currently, the most effective method for diagnosis is monitoring 24-hour urine annually in patients on ART with TDF and finding at least two tubular alterations in this test. The overall risk is mild and corroborates the recommendations of the majority international guidelines for the use of TDF as first-line ART for most patients, once that they are adequately monitored.

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CONFLICT OF INTEREST

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