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Renal Function Recovery and HIV Viral Suppression Following Tenofovir Discontinuation for Renal Impairment

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Abstract

Background: Tenofovir associated nephrotoxicity (TDFN) is well recognized. This study describes the trend of renal function recovery and virologic consequences after cessation of tenofovir (TDF) for suspected TDFN.

Methods: This was a retrospective chart review of 241 patients who underwent HLA-B*5701 allele testing between January 2007-December 2010. Demographics and clinical characteristics were compared at baseline, 3, 6, and 12 month between patients that continued and discontinued TDF. Factors associated with renal function recovery were assessed by multivariable logistic regression.

Results: Eighty patients were identified with TDFN; 84% male, 74% African American (AA) with a median age of 55 years, and median length of TDF use for 122 weeks. Renal recovery at 12 months differed in those who stopped versus (vs.) continued TDF (83% vs. 57% p=0.03). In a crude analysis, baseline chronic kidney disease was negatively associated with renal recovery (p=0.01). An adjusted analysis showed that those who stopped TDF had 3.76 higher odds of renal recovery compared to those who did not stop TDF (95% CI: 1.26-11.27, p=0.02). There were no significant differences in virologic response after switching TDF to an alternative agent.

Conclusion: In this mostly AA male population with suspected TDFN, discontinuation of TDF was strongly associated with renal function recovery without affecting viral suppression.

Keywords: Tenofovir; Nephrotoxicity; Renal failure

Introduction

Tenofovir Disoproxil Fumarate (TDF) is a Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI) approved by the US Food and Drug Administration (FDA) in 2001 for the treatment of HIV. Its potency, low toxicity profile and favorable pharmacokinetic properties allowing for convenient once a day dosing, has granted TDF as a preferred backbone agent for HIV treatment-naïve patients [1]. As with other structurally similar nucleotide analogues such as cidofovir and adefovir, the use of TDF has been associated with a risk of renal toxicity [2]. Initial post-marketing data supported the renal safety of the drug but multiple case reports, case control and randomized trials have shown a modest decline in renal function with TDF use [3-9].

In clinical practice the development of renal failure in HIV infected patients is generally multifactorial and recognition of TDF exposure as the etiology of renal dysfunction can be difficult [10-14]. Risk factors that have been linked with TDF associated renal impairment include advanced age, low body weight, high pre-treatment serum creatinine levels, co-morbidities such as diabetes, hypertension and hepatitis C, as well as advanced HIV infection [8,10,11]. Renal function usually recovers with discontinuation of the drug but incomplete recovery and chronic kidney disease (CKD) can remain as a sequela [9,12]. Data on reversibility, time to resolution and virologic response after switching to an alternative NRTI is limited [15]. Our objective is to describe renal function and viral suppression after cessation of TDF secondary to suspected TDF-associated nephrotoxicity.

Methods

This is a retrospective, single center, chart review study of HIV infected patients that underwent HLA-B*5701 allele testing between January 1, 2007 and December 31, 2010 while receiving care at the Ruth M. Rothstein CORE Center clinic in Chicago, IL. We utilized this test as a screening tool to identify patients with presumed TDF nephrotoxicity. This test is done routinely in patients before starting an abacavir based antiretroviral regimen, usually as an alternative to TDF. Among 241 patients who underwent HLA-B*5701 allele testing, 80 were identified to be done for suspected TDF nephrotoxicity defined by the primary care provider and/or ordering physician. Patients on renal replacement therapy or absence of kidney function

assessment within the last 3 months of HLA testing were excluded. Renal toxicity was classified as proteinuria (random positive urine dipstick ≥ 1 + or quantified microalbuminuria of ≥ 30 mg/dl), acute kidney injury(increase in serum creatinine and/or drop in estimated glomerular filtration rate (GFR) by Crockoft-Gault method compared to most recent prior value within 3 months) and Fanconi syndrome (presence of ≥ 2 criteria: normoglycemic glucosuria, hyperphosphaturia or hypophosphatemia, new onset proteinuria, renal tubular acidosis or determined by a nephrologist evaluation). For the acute kidney injury group, we calculated the absolute and percentage change in creatinine and GFR between the value that prompted HLA testing and the previous most recent recorded value. This was used to estimate the number of patients who actually met the Acute Kidney Injury Network (AKIN) criteria of abrupt increase in creatinine ≥ 0.3 mg/dL or a ≥ 50% increase in the serum creatinine concentration [16]. Baseline demographics, comorbidities (history of hypertension, diabetes mellitus, chronic kidney disease defined as GFR ≤ 60 ml/min, and hepatitis C based on documented positive antibody test) and clinical values (CD4 cell count and HIV-1 Plasma Viral Load [PVL]) were recorded at the time a TDF-containing antiretroviral regimen was started. Use of nephrotoxic drugs included documented active use of ACE inhibitors, diuretics, chemotherapeutics, antibiotics (sulfa, amphotericin B, beta-lactams) and intravenous injection drugs at the time of HLA B*5701 testing.

Our primary study outcome was recovery of renal function, defined as an increase in GFR to a value that was higher than the value that prompted HLA testing (values equal or higher to the pre-HLA testing value were considered complete recovery), qualitative or quantitative improvement of the degree of proteinuria, or normalization of parameters defining Fanconi syndrome. These outcome measures were evaluated at 3, 6 or 12 months (±1 month) after discontinuing TDF or after HLA testing among patients in whom TDF was continued. Additional work up to determine the cause of the renal dysfunction such as antinuclear antibody testing, serum complement levels, serum protein electrophoresis, urinary sediment, renal ultrasound and renal biopsy were recorded in some cases but not routinely performed. Virologic suppression was defined as plasma VL ≤ 75 copies/mL. The evaluation was done at baseline, at the time of HLA testing and at 3, 6 and 12 months (±1 month) following the start of a new antiretroviral regimen.

Data analysis

Categorical variables are reported in numbers and percentages, whereas continuous variables are represented in mean or medians according to their distribution. Pearson's X2 and Kruskal-Wallis were used to assess the relationship between improvement of renal function and categorical and continuous variables, respectively. Fisher's exact test was used when expected variable value was less than 5. We used a multivariate logistic regression analysis to assess the associations between exposure variables and the recovery of renal function at 12 months. In addition to the use of TDF, covariates adjusted for the logistic regression analysis included weight (kg), change in serum creatinine ≥ 0.3 (mg/dL), history of diabetes mellitus, hypertension, and use of nephrotoxic drugs. A p-value<0.05 was considered statistically significant. All statistical analyses were done using SAS v9.2.

Results

Eighty patients were identified with possible TDF nephrotoxicity. Individuals were predominantly men (84%), African American (74%) with a median age of 55 years (IQR: 47-61), median weight of 75 kg (IQR: 65-88.5) and a median baseline GFR of 90 ml/min (IQR: 74-111).The median length of TDF use was 122 weeks (IQR: 67-225) and in 64% of patients the initial TDF based regimen included a protease inhibitor (PI).

Sixty-nine (86%) cases were categorized as acute kidney injury with a median increase in serum creatinine of 0.3 mg/dl (IQR: 0.1-0.4). Thirty nine (57%) of those met AKIN definition; 9 (13%) patients had proteinuria alone and 2 (3%) had Fanconi syndrome. TDF was discontinued in 49 (61%) patients. Baseline demographics and clinical characteristics among patients that discontinued TDF were comparable to those that continued TDF (Table 1). Ten patients (12%) in our cohort had underlying CKD; 6/10 patients had GFRs below 50 ml/min and TDF dose was adjusted appropriately in 3 of those patients.

Characteristics	**TDF Stopped**		
	Yes (N=49)	**No (N=31)**	**P value***
Age in years, median (IQR)	55 (47-61)	55 (47-61)	0.7
Weight in kg, median (IQR)	75 (67-85)	76 (64 -93)	0.86
Race, n (%)			
Non Hispanic – White	9 (18)	6 (19)	NA
Non Hispanic – Black	38 (76)	21 (68)	
Other	2 (4)	4 (13)	
Gender, n (%)			
Female	6 (12)	7 (23)	0.22
Male	43 (88)	24 (77)	
Baseline sCr in mg/dl, median (IQR)[2]	1 (1-1)	1 (1-1)	0.13
Baseline GFR in ml/min, median (IQR)[2]	90 (70-107)	87 (79-119)	0.7
sCr in mg/dl before HLA test, median (IQR)[3]	1 (1-2)	1 (1-1)	0.02
GFR in ml/min before HLA test, median(IQR)[3]	67 (57-86)	83 (66 -96)	0.05
sCr in mg/dl at HLA testing, median (IQR)[4]	1.7 (1.4-2)	1.6 (1.3-2)	0.26
GFR in ml/min at HLA testing, median (IQR)[4]	52 (44-61)	60 (50-74)	0.06
Recovered Renal Function, n (%)			
Yes	37 (76)	17 (55)	0.3
No	12 (24)	14 (45)	
Chronic Kidney Disease, n (%)			
Yes	8 (16)	2 (6)	0.3
No	41 (84)	29 (94)	

HCV Antibody status, n (%)			
Positive	12 (24)	8 (26)	0.89
Negative	37 (76)	23 (74)	
Diabetes Mellitus, n (%)			
Yes	9 (18)	3 (10)	0.35
No	40 (82)	28 (90)	
Hypertension, n (%)			
Yes	23 (47)	12 (39)	0.46
No	26 (53)	19 (61)	
Nephrotoxic Drugs, n (%)			
Yes	26 (53)	16 (52)	0.9
No	23 (47)	15 (48)	
HIV-1 PVL at HLA test, n (%)			
≥ 75 log10 copies/ml	10 (21)	9 (31)	0.31
< 75 log10 copies/ml	38 (79)	20 (69)	
CD4 cell count at HLA test, n (%)			
≤ 200 cells/uL	9 (19)	7 (24)	0.6
> 200 cells/uL	38 (81)	22 (76)	

Table 1: Participant Demographics and Clinical Characteristics by TDF Discontinuation (n=80)[1]. [1]Due to missing values for some variables, not all rows add up to total n=80; [2] Value before starting TDF; [3] Value preceding HLA test; [4] Value at HLA test; *Chi-square was used to examine the relationship between serum creatinine and categorical variables, whereas the non-parametric Kruskal-Wallis test was used to examine the difference between continous variable. Fisher's Exact test was used where expected cell value was less than. TDF: Tenofovir; IQR: Interquartile Range; sCr: Serum Creatinine; GFR: Glomerular Filtration Rate (Cockroft-Gault); HCV: Hepatitis C Virus; PVL: Plasma Viral Load.

Recovery of renal function was seen in a total of 54 (67.5%) patients, thirty seven (68%) of whom were in the TDF discontinuation group. Differences in renal function recovery among patients that discontinued vs. continued TDF were demonstrated at 12 months (83% vs. 57% p=0.03), with more than 70% of renal function parameters recorded at each time point. Among the patients that showed improvement of their renal function with TDF cessation, 32/37 (86%) had complete recovery. One of the two patients with Fanconi syndrome recovered after discontinuation. Only 2 patients progressed to severe chronic kidney disease (persistent GFR<30 ml/min for at least 3 months) despite stopping TDF. Both patients had underlying diabetes and baseline CKD. In crude analysis (Table 2), CKD was negatively associated with renal function recovery (OR: 0.16 95% CI: 0.04 - 0.68, p=0.01).While the association between renal function recovery and TDF discontinuation was not significant in crude analysis (OR: 2.54, 95% CI: 0.97 – 6.64, p=0.06), after controlling for possible confounding variables, we found that those who stopped TDF had 3.76 (95% CI: 1.26-11.27, p=0.02) higher odds of renal function recovery compared to those who did not stop the drug (Table 2). We did not observe any significant differences in virologic suppression or immunologic status after switching the antiretroviral regimen at any time point, however all laboratory values were not available for each time point. Abacavir was the most common NRTI used alternatively to TDF (87.8%).

Discussion

TDF is the most widely prescribed NRTI for the treatment of HIV. Overall, the incidence of serious renal adverse events with TDF use has been reassuring with reports of 0.5% cases per 1000 patient-years and a risk of acute kidney injury of 0.7% (95% CI 0.2-1.2%) demonstrated in a meta-analysis [15,17,18]. However, in clinical practice the development of this complication remains a concern, particularly when patients suffer a decline in GFR and clinicians have to decide if switching TDF to an alternative antiretroviral agent is appropriate.

Identification of TDF associated renal toxicity can be challenging as there is no standardized definition or gold standard diagnostic test. We decided to use HLA-B*5701 testing as surrogate marker for TDF nephrotoxicity. HIV care providers at the Ruth Rothstein Core Center do not order this test routinely and reserve it for cases where abacavir is considered as an alternative NRTI. This can be due to baseline resistance, underlying renal failure or side effects related to other antiretrovirals. We do acknowledge that patients switched to non-abacavir based regimens could be missed. Nonetheless a cohort of patients with possible TDF nephrotoxicity were successfully identified with the use of HLA-B*5701 from an estimated population of 5500 HIV positive patients in the Chicago metropolitan receiving care at the Ruth Rothstein Core Center by 2011; the majority who were receiving TDF as part of their antiretroviral regimen.

Variable	**Crude Analysis**		**Adjusted Analysis***	
	Odds Ratio (95% CI)	**P value**	**Odds Ratio (95% CI)**	**P value**
Age in years	1.0 (0.95-1.04)	0.8	-	-
Race/Ethnicity				
Non-hispanic white	Reference	-	-	-
Non-hispanic black	1.52 (0.47-4.9)	-	-	-
Other	1.33 (0.18-9.73)	0.78	-	-
Weight in Kg	0.99 (0.97-1.01)	0.33	0.99 (0.96-1.01)	0.24
Gender				
Male	Reference	-	-	-
Female	0.5 (0.15-1.66)	0.26	-	-
TDF stopped				
No	Reference	-	-	-
Yes	2.54 (0.97-6.64)	0.06	3.76 (1.26-11.27)	0.02
Increase in sCr ≥0.3 mg/dl	1.00 (0.87-1.15)	0.97	0.75 (0.45-1.23)	0.25
Baseline CKD[1]				
No	Reference	-	-	-

Yes	0.16 (0.04-0.68)	0.01	-	
HCV Antibody				
Negative	Reference	-	-	-
Positive	2.32 (0.69-7.81)	0.18	-	-
Diabetes Mellitus				
No	Reference		Reference	
Yes	0.63 (0.18-2.2)	0.46	0.29 (0.06-1.48)	0.14
Hypertension				
No	Reference		Reference	
Yes	1.09 (0.42-2.81)	0.86	1.59 (0.45-5.66)	0.47
Nephrotoxic drugs				
No	Reference		Reference	
Yes	1.16 (0.46–2.96)	0.76	1.34 (0.43-4.21)	0.61
HIV-1 PVL[2]				
≤75 log_{10} copies/ml	Reference			
>75 log_{10} copies/ml	0.52 (0.18-1.54)	0.24		
CD4 cell count[2]				
≤200 cells/μL	Reference			
>200 cells/μL	0.86 (0.33-2.21)	0.75		

Table 2: Crude and Adjusted Analysis: Factors Associated with Renal Function Recovery. [1]Adjusted not performed given small number of cases (n = 10); [2]At time of HLA test; *Observations with missing data were excluded from analysis. TDF: Tenofovir; sCr: Serum Creatinine; HCV: Hepatitis C Virus; PVL: Plasma Viral Load.

The most common manifestations of renal toxicity with TDF use include tubular dysfunction with or without decline in GFR, diabetes insipidus and acute tubular necrosis [17-19]. In our cohort a decline in GFR was the most common manifestation captured. Even minor declines in GFR of 6.5 ml/min triggered physicians to consider a TDF switch. A published metanalysis reported that the risk of acute kidney injury associated with TDF is small (0.7%, 95% IC: 0.2-1.2), however, discrepancies with our data might be due to variable definitions of AKI used in other studies and uncertainty of exact timing of renal function changes as they are usually captured during scheduled laboratory monitoring [17]. Routine monitoring of phosphorus levels and urinalysis were not performed by HIV practitioners, a phenomenon that could explain the seldom number of tubular dysfunction alone captured in our population.

Recognized risk factors for TDF nephrotoxicity include increased age, low body weight, low $CD4^+$ cell count, preexisting CKD, concurrent use of nephrotoxic medications, and combination therapy with a PI [10]. In our population of mostly older African American men with suspected TDF induced renal dysfunction, we did not find any association between weight, history of diabetes, hypertension, use of nephrotoxic drugs or concomitant use of a PI, and failure to recover renal function. Although CKD seems to be negatively associated with renal function recovery, the small number of patients with underlying renal failure in our population limited the inclusion of CKD in multivariate analysis. In addition, appropriate TDF dosing according to GFR values was only done in half of the patients with CKD highlighting the importance of clinician's vigilance and awareness of dose adjustment to avoid irreversible renal damage.

Improvement of renal function with TDF discontinuation has been previously reported [9,12,20,21]. However, rates and timing of reversibility are variable and progression to end stage renal disease after discontinuation of the drug can happen [5,22]. In addition, recognizing TDF as the etiology for development of renal injury in HIV infected patients is a challenge, given that most of these patients tend to have multiple other factors that may contribute to the development of renal dysfunction. In our study, potential concomitant risk factors for renal failure were identified in some cases and the causality of TDF and nephrotoxicity could not be precisely determined in each case. Fifty-five percent of patients that continued TDF recovered their renal function suggesting that the etiology of their renal dysfunction was likely multifactorial and possibly additional interventions unrelated to TDF were effective. It is unclear to us why physicians decided to stop TDF in some patients but not in all. Although clinical characteristics including changes in serum creatinine and GFR were comparable among patients that stopped and continued TDF, we could hypothesize that either higher number of patients with baseline CKD, persistence of renal impairment on serial chemistries or a greater drop in GFR prompted physicians to stop the drug. Nonetheless, we found that discontinuation of TDF was independently associated with improvement of renal function at 12 months. In the majority of our patients, the renal injury reversed after cessation of TDF, but only partial recovery occurred in the presence of other potential aggravating factors such as underlying diabetes, hypertension, obstructive staghorn calculus, concomitant use of nephrotoxic drugs and biopsy proven focal segmental glomerulosclerosis (FSGS). Patients that progressed to severe CKD despite TDF discontinuation suffered from diabetes and had underlying CKD. Prior small studies in mostly white older HIV infected men have shown time to resolution as early as 4 weeks with a median time to maximum improvement of 5 months [15]. Most of our patients showed improvement of their renal function during the first 3 months after TDF cessation.

Viral suppression at the time of stopping TDF was 79%, raising concerns of virologic failure related to either ART resistance or suboptimal adherence. However, the majority of the patients with unsuppressed viral loads had low level viremia (below 500 copies/ml) and information is not available to make categorical conclusions about this observation. Even in patients in whom TDF was switched to an abacavir based regimen, we did not observe any difference in viral suppression rates suggesting that abacavir is an equally effective antiretroviral agent as previously described [23].

Our study is limited by its retrospective design, hence we were unable to control for definition of TDF-associated renal dysfunction or standardize evaluations or interventions considered in each case. Small number of events, such as CKD, might have lead to a failure in identifying significant associations with renal function improvement. Although our study represents the largest population studied on reversibility of TDF induced renal toxicity, it is possible that we did not capture all potential patients with nephrotoxicity using HLA-B*5701 and therefore cannot calculate the true incidence in our

population. In addition, the inconsistent record of laboratory values during follow up limited our ability to make conclusions on specific predicting factors for renal function recovery or assess exact timing of reversibility.

Conclusions

In this mostly African American male population, discontinuation of TDF for suspected renal dysfunction was strongly associated with renal function recovery at 12 months after cessation. No difference in virologic suppression was seen after switching TDF to an alternative NRTI.TDF induced nephrotoxicity seems to be an uncommon event with most patients exhibiting reversibility. Early detection of signs of tubular dysfunction or progressive decline in GFR are key to avoid irreversible renal damage and progression to severe CKD, particularly in patients with other risk factors. Our study reinforces the importance of following current guidelines for the management of CKD in HIV infected patients which recommends that all patients on TDF be monitored with biannual GFR and urine protein assessment [24]. Prompt discontinuation of TDF is encouraged in patients with unexplained declines in GFR.

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