

Original Article

INCIDENCE AND RISK FACTORS OF RENAL IMPAIRMENT IN HIV-1 INFECTED PATIENTS RECEIVING TENOFOVIR BASED ANTIRETROVIRAL THERAPY IN A SOUTH INDIAN HOSPITAL

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ABSTRACT

Objective: To identify the incidence and risk factors of tenofovir (TDF) induced nephrotoxicity among People Living with HIV/AIDS (PLHA) receiving TDF-based anti-retroviral therapy (ART) in a South Indian Hospital.

Methods: A retrospective cohort study was conducted among HIV-infected ART naïve patients taking TDF as part of either a first-line or second-line ART between July 2013 and June 2015 at Asha kirana Hospital Mysore, India.

Results: A total of 380 patients have been initiated on TDF-based ART. Out of these, 335 patients were on tenofovir+lamivudine+efavirenz, 30 patients were on the tenofovir+lamivudine+nevirapine regimen and 25 patients were on tenofovir+lamivudine+atazanavir/ritonavir regimen. Renal impairment was documented for 35 patients with 9.21% incidence. 34% of renal impaired patients had a severe impairment with eGFR<30 ml/min. Elderly patients (>61 y) had higher chances of developing TDF toxicity compared to adult patients (P=0.0018). Other possible risk factors for TDF-induced renal impairment was CD4>200 (P=0.003). TDF was withdrawn and substituted with Nucleoside Reverse Transcriptase Inhibitor (NRTI) drug following the diagnosis of renal impairment.

Conclusion: TDF-associated renal impairment was not uncommon in real-life practice and considered as a frequent complication during treatment with TDF. Risk factors for developing renal impairment include increasing age and CD4>200 cells.

Keywords: Tenofovir, Renal impairment, Antiretroviral therapy, HIV

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INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue reverse transcriptase inhibitor (NtRTI) approved by the US food and drug administration (FDA) in 2001 for the management of HIV. Its potency, low toxicity profile and favourable pharmacokinetic properties compared to other NtRTIs and a convenient once a day dosing has granted TDF as a preferred backbone agent for HIV/AIDS patients [1]. However, along with other structurally similar nucleotide analogues such as adefovir and cidofovir, the use of TDF has been associated with a risk of renal impairment [2].

Initial post-marketing data supported the renal safety of the TDF but multiple case reports, case-control studies and randomized trials have shown a modest decline in renal function with TDF use [3]. In clinical practice, the occurrence of renal failure in HIV-infected patients is generally multifactorial and identification of TDF toxicity as the aetiology of renal dysfunction can be difficult. Risk factors that have been linked with TDF-associated renal impairment include low body weight, advanced age, high pre-treatment serum creatinine levels, co-morbidities (such as hypertension, diabetes and hepatitis C) as well as advanced HIV infection [4]. Renal function usually recovers after withdrawing the drug but incomplete recovery and chronic kidney disease (CKD) can remain as a long-term sequela [5].

Approximately 20–30% of the TDF is excreted in the urine unchanged, via active secretion by the proximal tubular cells. The free drug is taken up actively by the organic anion transporter (OAT-1) receptor located at the basolateral surface of the tubular cells and concentrated in the cytosol [6]. TDF is excreted into the tubular lumen via the multi-drug resistant proteins (MRP-2 and 4) located at the luminal surface. Although the exact mechanism of TDF-induced nephrotoxicity remains uncertain, it is proposed that TDF inhibits mitochondrial DNA γ -polymerase and thus exerts its mitochondrial toxicity and leads to caspase-mediated proximal tubular cell injury.

The long-term effect of the damage to the proximal tubular cells leads to a variety of nephrotoxic features, which includes chronic renal failure, acute renal failure and fanconi syndrome etc. The incidence of TDF-induced renal dysfunction comes mostly from the case series, however, the true incidence and clinical characteristics remains unclear [7].

Even though TDF has been reported to cause proximal renal tubulopathy Eg: fanconi syndrome, other related nephrotoxicities includes calcium and phosphorous dysregulation with bone disease; diabetes insipidus and reduction in glomerular function have also been documented. In few cases, histopathological changes in renal toxicity showed the proximal tubular injury and varying degrees of chronic tubulointerstitial scarring and also in few cases prominent eosinophilic inclusions within proximal tubular cell cytoplasm and changes in mitochondrial structure and function were observed [8-10].

More recently, two animal studies support the notion that TDF causes mtDNA depletion and mitochondrial dysfunction. A study in HIV+transgenic mice was examined ultrastructure and mtDNA levels with TDF and didanosine exposure. Only renal proximal tubules from HIV+transgenic mice exposed to tenofovir showed ultrastructural mitochondrial abnormalities and decreased mt DNA levels, which paralleled the ultrastructural mitochondrial abnormalities [11, 12].

Continuous evaluation and monitoring of the harm and benefit of ART will help to achieve the ultimate goal of making safer and more effective treatment available to patients at all levels of health care system [13, 14]. Considering the significant number of people living with HIV/AIDS (PLHA) being initiated on TDF-based antiretroviral therapy (ART) in India, and lack of data on TDF-induced nephrotoxicity, we aimed to evaluate the incidence and risk factors of TDF-induced renal impairment among PLHA in a South Indian hospital.

MATERIALS AND METHODS

A retrospective cohort study was conducted among HIV-infected patients taking TDF as part of their first-line or second-line antiretroviral regimen between July 2013 and June 2015 at asha kirana hospital, Mysore, India. The study was approved by an institutional ethical committee of the study site (reference number: AK-IEC 009/2014). Confidentiality of the information was assured in a way that no disclosure of any name of the patient or health care provider in relation to the finding was made. Patients initiated on ART with TDF-based regimen were identified from the database of the hospital and the data regarding the concurrent use of antiretroviral drugs, lab values, opportunistic infections and other prescribed drugs to any other disease condition were collected from the medical records. All patients receiving 300 mg/day of TDF with adherence >80% per month and who were followed after initiation with TDF to identify renal impairment (acute renal failure (ARF), chronic renal failure (CRF) or fanconi syndrome) were included into the study. The final decision regarding whether an adverse event occurred with TDF was taken from the attending physician note in the medical record.

The *start date of treatment* was defined as the date when the patients initiated TDF or a TDF-containing regimen for the first time and the *end date of therapy* was defined as the date of TDF discontinuation or the last documented HIV follow-up visit with a physician, a nurse practitioner, or a pharmacist even if the patients were receiving.

The primary outcome of interest was estimated glomerular filtration rate (eGFR) on every follow-up after the onset of TDF use. The eGFR was calculated by using cockcroft gault formula. Estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) may be a better estimate of renal function than serum creatinine. For this study, CrCl was estimated by the Cockcroft-Gault equation, $\{CrCl = [(140 - \text{age}) \times \text{weight (kg)}] / (\text{serum creatinine} \times 72) (\times 0.85 \text{ for females})\}$. ARF was defined as an onset of any clinical symptoms of ARF, CRF was defined as the asymptomatic measurement of GFR and fanconi syndrome with glycosuria. Serum creatinine value at the time of diagnosis of renal impairment was used for analysis. The severity of CRF was

considered based on eGFR obtained and was classified as mild (>60 ml/min), moderate (30-60 ml/min) and severe (0-30 ml/min).

Categorical variables were described using relative frequencies, whereas the standard deviation and mean were used for continuous variables. Multivariate logistic regression analysis was carried out to identify risk factors associated with renal toxicity. All analyses were carried out using SPSS software version 21.0 (SPSS). A *p*-value <0.05 was considered statistically significant.

RESULTS

A total of 380 patients were initiated on TDF-containing ART. Renal impairment was documented among 35 patients with 9.2%. Of these 380 patients, 335 patients were on tenofovir+lamivudine+efavirenz (T+L+E) regimen, 30 patients were on tenofovir+lamivudine+nevirapine (T+L+N) regimen and 25 patients were on tenofovir+lamivudine+atazanavir/ritonavir (T+L+A/r) regimen.

Out of 35 patients who developed renal impairment, 9 were diagnosed with acute renal failure, 20 with chronic renal failure and 6 with fanconi syndrome. Patients with fanconi syndrome had abnormal urine examination reports mainly seen with glycosuria. Regarding the renal function 34% (12) of patients had an eGFR between 0 to 30 ml/min, 60% (21) of patients had eGFR between 30 to 60 ml/min and 6% (2) had eGFR between 60 to 90 ml/min.

The mean age of the study subjects who developed renal impairment was 45.77 (S. D 13.01; Range 27 to 77) at the time of diagnosis and the mean estimated creatinine clearance among them was 37.29 (S.D 14.68). The mean serum creatinine value was 1.95 (S.D 1.01) and the mean CD4 was found to be 248 (S. D 156.6).

The details of gender, BMI and OI's have been shown in table 1 in comparison to the study subjects who didn't develop renal impairment. Elderly patients (>61 y) had higher chances of developing TDF toxicity compared to adult patients (*P*=0.0018). The possible risk factors associated in the study group was CD4>200 (*P*=0.003); further details on risk factors were shown in table 2.

Table 1: Patient characteristics

Patient demographic characteristics	Total number of patients (N=380)	Patients with renal impairment (n= 35)	Patients without renal impairment (n=345)
Age (Mean+/-SD)	37.17 (11.5)	45.77 (13.01)	36.30 (11)
BMI (Mean+/-SD)	20.86 (3.92)	20.47 (3.94)	20.90 (3.92)
CD4 (Mean+/-SD)	223.7 (181.9)	248 (156.6)	221 (184.3)
Gender %	Male-56.8%	Male-51.4%	Male-57.3%
OI's %	Yes-49.2%	Yes-54.2%	Yes-48.6%

BMI-Body Mass Index, CD4-Cluster of differentiation 4, OI's-Opportunistic Infections

Table 2: Risk factors among study population

Patient characteristic	Category	No. of patients (n=380)	ADR		Odds ratio (95% CI)	<i>p</i> value
			Yes	No		
Age	(0-20 y)	22	-	22	0.229 (0.013-3.883)	0.308
	(21-60 y)	345	30	315	1 (reference)	
	(>61 y)	13	5	8	6.56 (2.01-21.32)	
Gender	Male	216	18	198	1 (reference)	0.498
	Female	164	17	147	1.27 (0.63-2.55)	
CD4 count (cells/ml)	<200 cells/μl	285	17	268	1 (reference)	0.0003
	>200 cells/μl	95	18	77	3.68 (1.81-7.49)	
BMI	</=20	160	13	147	1 (reference)	0.282
	21-25	162	19	143	1.50 (0.71-3.15)	
	>/=26	58	3	55	0.616 (0.169-2.24)	
OI's	Yes	187	19	168	1 (reference)	0.529
	No	193	16	177	0.799 (0.39-1.60)	
WHO Clinical stage	I and II	227	17	210	1 (reference)	0.160
	III and IV	153	18	135	1.64 (0.82-3.30)	

BMI = Body Mass Index, OI's = Opportunistic Infections, *P*<0.05 shows statistically significant

DISCUSSION

The 9.2% of occurrence of renal impairment to TDF is high compared to earlier published reports of 6.5% by Patel *et al.* from India [15]. Patients with raise in serum creatinine were largely asymptomatic, however patient with acute renal failure had presented with weakness, body pain and vomiting. Due to the availability of generic medicine and efficacy-safety profile, TDF usage has increased in most of the developing countries. However many studies need to be conducted to assess the renal impairment with TDF.

Although TDF is generally well tolerated, the potential for renal toxicity exists. TDF is not metabolized by CYP450 enzymes but is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure, declining renal function and Fanconi syndrome, have been reported in association with the use of tenofovir by Rifkin and Perazella study [16]. The present study demonstrates decreases in eGFR in patients receiving tenofovir. Previous reports have shown the onset of TDF-associated nephrotoxicity is relatively common by Zimmermann *et al.* [17]. A previous large dataset evaluating the safety of tenofovir showed the incidence of serious renal adverse events was 0.5% from Nelson *et al.* study whereas it was observed to be 2.3% in our study [18].

Renal impairment due to diseases was usually excluded from the clinical study. Concomitant administration of ritonavir-boosted atazanavir may have enhanced TDF toxicity; markedly increases in the area under the curve and concentrations for TDF when the drug is used concurrently with ritonavir-boosted Protease Inhibitors (PIs) have been described by Pruvost *et al.* [19]. In the present study, five patients receiving ritonavir-boosted PI and TDF developed renal toxicity. TDF is principally secreted in the urine via multidrug resistance protein MRP2, which is located on the apical surface of proximal cells of the renal tubules. Ritonavir is a potent inhibitor of MRP2-mediated transport Miller *et al.* 2001 [20]. Thus, ritonavir can potentially increase proximal tubular concentrations of TDF and promote its toxicity by decreasing its apical efflux.

The mechanism of renal toxicity is not well understood. The majority of these cases occur in patients with underlying systemic or renal dysfunction, in patients having a low CD4 cell count or having a low body weight was stated by many studies conducted earlier in contrary to the data from our study which shows having high CD4 as a risk for developing the toxicity [4, 20-22]. Previously reported risk factors associated with nephrotoxicity include concurrent administration of other nephrotoxic medications; comorbidities associated with nephrotoxicities, such as hypertension and diabetes, chronic pain and the presumed use of non-steroidal anti-inflammatory drugs, current and even previous use of a protease inhibitor, and having a history of opportunistic infections.

There was no significant relationship between gender and the occurrence of Renal Impairment. Some authors have reported female gender as a cause of higher concentrations of TDF [23]. However, a European population study did not find female gender as a predictor of renal damage [24]. Age was associated with renal toxicity in similarity with other studies [18, 25]. It is well known that there is a strong relationship between increased age and presence of a low baseline creatinine clearance, which gradually decreases with age [26].

There were few limitations in the present study. First, some selection bias may have taken place due to the nature of a retrospective study. Second, the confounding factors related to alteration of eGFR may not have been controlled. Third, the patient observation was not uniform, thus, a long-term study is needed. Fourth the incidences of proteinuria and hypophosphatemia were not reported because serum phosphorus levels and urinalyses were not monitored in a huge proportion of patients which should be performed in equal intervals among all the patients, and also we did not evaluate genetic factors. However, some authors have suggested associations between certain polymorphisms of multidrug resistance protein 2 and 4 transporters (MRP4 and MRP2) and renal toxicity of TDF [20, 27]. The expression of these transporters could establish the accumulation of TDF in the tubular epithelial cells,

modulating the extent of renal damage [28]. Some ABCC2 gene polymorphisms and such as haplotype "CATC" or CC genotype at position 24 have been associated with a higher rate of patients with renal failure due to tubular damage associated with TDF [29].

The spectrum of TDF-associated renal impairment spans all levels of severity from acute renal failure to chronic renal failure and fanconi syndrome. Although discontinuation of TDF results in renal recovery in the majority of the cases, some patients experience chronic kidney disease. This information should be useful for a clinician to diagnose TDF-associated renal toxicity early and manage its severe forms with associated morbidity. Clinicians are advised to monitor renal function insistently by calculating creatinine clearance and doing a urine examination, potassium and phosphate levels at baseline and on all follow-ups.

CONCLUSION

In conclusion, TDF-associated renal impairment was not uncommon in real-life practice and considered as a frequent complication during treatment with TDF. Risk factors for developing renal impairment includes increasing age and CD4>200. Prompt withdrawal of TDF and adequate management leads to complete reversal of renal functions and urinary abnormalities. In any case, a close follow-up of renal function is needed in order to optimise the risk-benefit balance of TDF.

CONFLICTS OF INTERESTS

Declared none

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