Prevalence and factors associated with renal dysfunction in patients on tenofovir disoproxil fumarate-based antiretroviral regimens for HIV infection in Southern India

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Abstract

Objectives: Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor commonly used in the treatment of HIV infection. This retrospective study aims to establish the prevalence of abnormal renal function among patients with HIV receiving TDF, and to investigate the risks for TDF-related renal dysfunction in this population.

Methods: Patients at the YRGCARE Medical Centre, Voluntary Health Services, receiving TDF-containing antiretroviral (ART) regimens between January 2002 and March 2017, were assessed for renal dysfunction using creatinine level and eGFR (DAIDS/NIH) during continuum of care. Demographic data and comorbidities were analysed for association with TDF toxicity. Data were obtained from the Natural History Study Database. Other causes of renal dysfunction were excluded.

Results: From the 14,118 patients on ART between 2002 and 2017 seen in the clinic, 7171 (50.8%) were initiated on TDF-containing regimens. Among these, 4400 were on a first-line NNRTI regimen, and 2771 on a second-line PI/r regimen, initiated after failure of first-line therapy. The majority of patients on ART were male, with a median age for the whole sample of 36 years (IQR 30–42). At ART initiation, the median CD4 cell count was 277 cells/mm^3 (IQR 165–421) and the viral load (VL) 31,198 HIV-1 copies/mL (IQR 400–226,690). Median duration of follow-up was 5.1 years (IQR 2.3–9.5). The prevalence of renal dysfunction in patients taking TDF was 5.6%. Increased age, low BMI, low baseline CD4 cell count, hypertension and diabetes were associated with tenofovir toxicity (P<0.05). Concomitant PI use was not associated with increased risk for renal dysfunction (P>0.05).

Conclusions: The prevalence of renal dysfunction associated with TDF in our study population was higher than in other well-resourced settings, suggesting the need for increased renal parameter monitoring in patients in resource-limited settings. Treatment with ART should be initiated earlier and BMI should be maintained ≥18.5 kg/m^2 through adequate nutrition and prevention of opportunistic infections. For patients with multiple comorbidities, tenofovir alafenamide (TAF) should be considered, instead of TDF, to avoid renal dysfunction.

Key words: HIV, tenofovir disoproxil fumarate, toxicity, resource-limited settings, TAF, India

Introduction

Tenofovir disoproxil fumarate (TDF) is a first-line nucleotide reverse transcriptase inhibitor (NRTI) used as a component of antiretroviral therapy (ART) treatment for HIV infection in both high-income and middle-to-low income countries [1]. However, concerns have been raised about the potential renal toxicity of the drug due to its structural similarity to acyclic nucleotide analogues [2]. Meta-analyses of randomised controlled trials and observational studies have concluded that a significant loss of renal function is associated with TDF-containing ART regimens [3]. Additionally, an increasing number of observational studies and case reports have suggested that interactions between TDF and other antiretroviral agents (ARVs) may contribute to the development of renal toxicity [4–5]. In resource-limited settings, ARVs commonly used alongside NRTIs are non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) [1]. Several case reports have found that the majority of cases with TDF-related toxicity are associated with the concomitant use of ritonavir-boosted PI (PI/r) regimens [6]. Studies have also reported that additional factors, such as age, sex, comorbidities, low nadir CD4 T cell count, pre-existing chronic kidney disease (CKD), diabetes and hypertension may also contribute to TDF-related renal toxicity [7–8].

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Treatment guidelines for the use of TDF in HIV infection recommend bi-annual monitoring of renal function, including quantitative measurement of proteinuria when ART is initiated or changed, and more frequent monitoring when additional kidney disease risk factors are present [9–10]. In resource-limited settings, the lack of infrastructure for such regular monitoring can make these recommendations difficult to follow. At present there are limited data available on renal dysfunction among patients receiving TDF in these settings. However, with an increasing patient population with associated comorbidities, and diverse ART regimens with TDF use in clinical practice, it is vital to understand the impact of such factors on TDF-associated renal toxicity, particularly in resource-limited settings.

In this study, we aimed to establish the prevalence of renal dysfunction in patients taking TDF-containing ART, compared it to PI-based versus NNRTI-based ART regimens, and investigated the risk for TDF-associated renal toxicity in patients with other pre-existing comorbidities.

Methods

Setting

This study was carried out at the YRGCARE Medical Centre, Voluntary Health Services, a large HIV tertiary referral care centre in Chennai, India. Since 1996, it has provided medical and psychosocial care to more than 22,000 persons with HIV infection. All patients receive treatment based on the World Health Organization (WHO) treatment guidelines [11].

Subjects

The observational patient cohort in this study was analysed retrospectively using the Natural History Study Database, which has been described previously [12]. Initiated in 1996, this database contains relevant information on individual patients collected and recorded at the time of their visit to the centre. It includes demographics, clinical data on visits, opportunistic infections, admissions, prophylactic and ART regimens, adverse events as well as laboratory results such as CD4 cell count, HIV-1 plasma viral load (VL), and serum creatinine collected at baseline for new enrollees, at 1 month, 6 and 12 months during the first year of ART, and then every 6 months. This database also includes comorbidity data such as diabetes and hypertension, as well as PI exposure. We have included in this analysis subjects ≥18 years and treated with a TDF-containing ARVs between January 2002 and March 2017.

Definitions

First-line therapy administered to ART-naïve patients typically included one NNRTI, commonly efavirenz (EFV) or nevirapine (NVP), plus two NRTIs, either lamivudine (3TC) or emtricitabine (FTC), in addition to TDF. After first-line therapy failed, the second-line consisted of a ritonavir-boosted PI, either atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r), in addition to the aforementioned NRTIs. The majority (83.7%) of the first-line cohort received TDF+3TC+EFV, and 10.1% received TDF+FTC+EFV. The remaining individuals were on NVP-based regimens. The majority (67.3%) of the second-line cohort received TDF+3TC+ATV/r and 17.1% TDF+FTC+ATV/r. The remaining individuals were on LPV/r-based regimens.

Renal function was assessed using serum creatinine level measurement to calculate the glomerular filtration rate (GFR), based on the creatinine clearance calculated with the Cockcroft–Gault Equation [13]. The GFR was graded according to the DAIDS/NIH toxicity grading table [14]. Renal dysfunction at grade 3 or 4 was considered as renal toxicity. Urine protein was not routinely measured.

This study had three aims: (1) to establish the prevalence and incidence of renal dysfunction in patients on TDF-containing regimens; (2) to compare patient renal profiles on first-line and second-line TDF-containing regimens; and (3) to analyse potential associations between toxicities and other baseline demographics and comorbidities. Factors assessed included sex, age, BMI, baseline CD4 T cell count, diabetes and hypertension. For this study and analysis, diabetes was defined as fasting blood glucose >120 mg/dL and 2-hour postprandial glucose >200 mg/dL as per WHO criteria. Hypertension was defined as systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg.

Statistical analysis

Descriptive statistics were calculated with median and interquartile ranges (IQR) for variables influenced by extreme values. The odds ratios (OR) and their confidence intervals (CI) were obtained by using logistic regression analysis. *P* values <0.05 were considered statistically significant. All statistical analyses were performed with SPSS software IBM SPSS STATISTICS Version 24.0 (IBM Corp, New York, USA).

Results

From the 14,118 patients on ART between 2002 and 2017 in the clinic, 7171 (50.8%) were initiated on TDF-containing regimens. Patient demographics are shown in Table 1. The present data analysis includes only patients initiated on TDF-containing regimens. Among these, 4400 were on a first-line NNRTI regimen, and 2771 on a second-line PI/r, initiated after failure of first-line therapy. The majority of patients on ART were male with a median age for the whole sample of 36 years (IQR 30–42). At ART initiation, median CD4 cell count was 277 cells/mm^3 (IQR 165–421) and VL 31,198 HIV-1 copies/mL (IQR 400–226,690).

Median duration of follow-up was 5.1 years (IQR 2.3–9.5). At TDF initiation, the first-line cohort had a baseline median creatinine level of 0.9 mg/dL (IQR 0.7–1.1) and the second-line cohort had a baseline median creatinine level of 0.8 mg/dL (IQR 0.7–0.9). After 1 month of their ART regimen, the first and second-line cohorts had median creatinine values of 0.8 mg/dL (IQR 0.7–1.1) and 1.1 mg/dL (IQR 0.8–2.0), respectively. At 36 months after ART initiation, the first-line and second-line cohorts had median creatinine levels of 0.9 mg/dL (IQR 0.7–1.0) and 1.1 mg/dL (IQR 0.9–1.1), respectively.

The proportion of patients who developed grade 3 or 4 renal dysfunction was 5.6%, with an incidence rate of two cases per 100 person-years. There was no difference in the incidence of tenofovir toxicity between the first- and second-line cohorts. The odds of developing renal dysfunction when taking TDF increased with age, especially when over 60 years (age 50–59 years, OR 0.455, CI 0.292–0.709, *P*=0.001), low BMI (BMI <18.5 kg/m^2, OR 2.764, CI 1.066–7.168, *P*=0.037), a baseline CD4 cell count <200 cells/mm^3 (CD4 <200 cells/mm^3, OR 1.886, CI 1.302–2.732, *P*=0.001), a history of diabetes and hypertension (diabetes, OR

Table 1. Demographic characteristics of study subjects

Sex (*n*, %)	
Male	4600 (64.1)
Female	2551 (35.6)
Transgender	20 (0.3)
Age (years, median, IQR)	36 (30–42)
Age group (*n*, %)	
<20	292 (4.1)
20–29	1262 (17.6)
30–39	3026 (42.2)
40–49	1917 (26.7)
50–59	539 (7.5)
60 and above	135 (1.9)
HIV exposure category (*n*, %)	
Heterosexual	6256 (87.2)
Homosexual (MSM)	57 (0.8)
Blood transfusion	282 (3.9)
Intravenous	23 (0.3)
Vertical	172 (2.4)
Bisexual	82 (1.1)
Others	299 (4.2)
Median duration of follow up (years, IQR)	5.1 (2.3–9.5)
Median CD4 cell count at ART initiation (cells/mm^3, IQR)	277 (165–421)
Median viral load at ART initiation (copies/mL, IQR)	31,198 (400–226,690)

IQR, interquartile range

Table 2. Risk of renal dysfunction by baseline factors from a logistic regression model that includes sex, age, BMI, diabetes, hypertension and CD4 T cell count among all the patients initiated on TDF-containing ART

Factor	OR (CI)	*P* value
Sex		
Male	0.852 (0.704–1.032)	0.101
Female	1.0 (ref)	-
Age group		
<20	0.151 (0.70–0.324)	<0.001*
20–29	0.134 (0.081–0.221)	<0.001*
30–39	0.170 (0.111–0.259)	<0.001*
40–49	0.267 (0.176–0.406)	<0.001*
50–59	0.455 (0.292–0.709)	0.001*
60 and above	1.0	-
BMI		
<18.5	2.764 (1.066–7.168)	0.037*
18.5–24.9	0.975 (0.376–2.531)	0.959
25–29.9	0.893 (0.325–2.459)	0.827
30 and above	1.0	-
Diabetes		
Yes	0.614 (0.457–0.824)	0.001*
No	1.0	
Hypertension		
Yes	0.397 (0.204–0.772)	0.007*
No	1.0	
CD4 cell counts (cells/mm^3)		
<200	1.886 (1.302–2.732)	0.001*
201–350	1.437 (0.968–2.134)	0.072
351–500	0.893 (0.325–2.459)	0.153
>500	1.0	-

* Statistically significant.
OR: odds ratio; CI: 95% confidence interval

0.614, CI 0.457–0.824, *P*=0.001; hypertension, OR 0.397, CI 0.204–0.772, *P*=0.007). The various risk factors for renal dysfunction are shown in Table 2.

Discussion

We found that of the 7171 patients on a TDF-containing regimen in our centre, 5.6% had developed grade 3 or 4 renal dysfunction using the DAIDS/NIH toxicity grading. Some were subsequently switched to another NRTI, such as abacavir (ABC). A case series study from a London, specialist HIV renal clinic found that 1.6% of patients had developed TDF-associated renal dysfunction [15]. In an observational cohort involving 22 treatment centres in 12 countries of varying income levels in Asia, a prevalence of 4.2% was found among patients receiving TDF [16]. Based on our present findings, it appears that the prevalence of renal toxicity attributed to TDF in resource-limited settings may be higher than in well-resourced ones [3,15,16,20], and that frequent monitoring of renal parameters and serum creatinine seems advisable.

Observational cohort studies have reported an increased attributable risk for renal toxicity in patients on PI/r-based regimens that include TDF [17,18,21]. However, our analysis did not identify a significant difference in grade 3 or 4 renal dysfunction between the first- and second-line cohorts. One reason for the discrepancy might be explained by differences in specific treatment regimens in different study populations. In our study population, 67.3% of the second-line group were on atazanavir/r-containing regimens, which corroborates the findings from another study that found no significant risk for renal dysfunction with ATV/r, despite risk from the PI/r group overall [18].

Among the patients who developed TDF renal toxicity, multivariate odds analysis was conducted using their demographics and pre-existing comorbidities. Significant risk for renal dysfunction was found in patients with hypertension, diabetes, older age, low BMI and low CD4 T cell count. The risk for TDF-related renal toxicity increased with age, with the highest risk in the 50–59-years age group. Prior analyses of TDF pharmacokinetics in HIV-infected women have found that an inverse measure of the speed of elimination of the drug increases by an average of 1.21-fold for every decade of age [19]. Our findings are also in accordance with a prior multinational and randomised study, which found an association between the development of adverse renal events and multiple pre-existing factors, including age >40 years, history of diabetes and lower baseline GFR [22]. Low BMI was also associated with increased risk for renal dysfunction in our study population, as in other studies from well-resourced settings [8,19]. Furthermore, a baseline CD4 cell count <200 cells/mm^3 contributed to an increased risk for TDF-related renal toxicity. In resource-limited settings, the risk for TDF-associated renal dysfunction exacerbated by low BMI and decreased numbers of CD4 T cells demonstrates the importance of early HIV diagnosis, with ART initiation at preserved CD4 cell counts, thereby preventing opportunistic infections and HIV-related malignancies that cause body wasting and emphasising the need for adequate nutrition.

Therefore, regular monitoring of renal parameters, including serum creatinine, should be conducted for those on ART taking TDF. Furthermore, as the HIV-infected population grows older, risk factors for TDF-toxicity should be considered, such as comorbidities including diabetes and hypertension, which will increase, leading to a careful choice of ARVs. Earlier ART initiation should also be emphasised, as recommended by the recent WHO treatment guidelines [11], and adequate nutrition and weight monitoring encouraged in order to minimise risk of renal toxicity. Recently, a TDF pro-drug, tenofovir alafenamide (TAF), has been approved for use in several countries. Unlike TDF, it does not interact with the transport proteins that contribute to TDF accumulation in renal proximal tubules and the associated toxicity. It has been shown in recent studies to have an improved renal safety profile as compared to TDF, and may represent, if made available, an alternative to tenofovir [23], in resource-limited settings where regular renal function monitoring may be impractical.

In conclusion, wide use of TDF in resource-limited settings will require regular renal parameter monitoring to prevent the development of severe renal toxicity, particularly in the context of an ageing patient cohort.

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Declaration of interests

The authors have no conflicts of interest.

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