Incidence of Nephrotoxicity among People Living with Human Immunodeficiency Virus on Tenofovir Treatment in a Tertiary Hospital in the Philippines

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Abstract

Objective: We aimed to determine the incidence and risk factors of nephrotoxicity among Filipino human immunodeficiency virus (HIV) patients on tenofovir disoproxil fumarate (TDF).

Methods: Retrospective cohort study; we reviewed medical records of HIV adults on TDF in the University of the Philippines-Philippine General Hospital (UP-PGH) clinic from January 2004 - December 2016. Nephrotoxicity was defined as at least a 20% decline in estimated glomerular filtration rate (eGFR). Relevant demographic and laboratory data were collected. Statistical analysis was performed to compare characteristics between groups. Kaplan-Meier method was used to determine incidence rate over time, and incidence density rates of nephrotoxicity were calculated.

Results: 654 patients were included, with mean age of 29 years (18-69) and male-female ratio of 72:1. Nephrotoxicity incidence was 51.38% with a density rate of 11.05 per 10,000 person days. Kaplan Meier analysis showed probability of nephrotoxicity of 50% at 20.5 months. Cox regression modeling of covariates revealed low CD4 as a significant covariate for predicting a subsequent 20% eGFR decline.

Conclusion: TDF may contribute to a decline in GFR over time. Half of patients taking TDF developed mild nephrotoxicity by 20.5 months. Clinicians must consider the potential risk of nephrotoxicity with prolonged use especially among young patients with low CD4 counts.

Keywords: HIV/AIDS, Nephrotoxicity, Tenofovir, Philippines

Abbreviations: AIDS: Acquired Immune Deficiency Syndrome; ART: Antiretroviral Therapy; BMI: Body Mass Index; CDK Epi: Chronic Kidney Disease Epidemiology Collaboration; EFV: Efavirenz; eGFR: estimate Glomerular Filtration Rate; HIV: Human Immunodeficiency Virus; LPV/r: Lopinavir boosted ritonavir; MDRD: Modification of Diet in Renal Disease; MSM: Men who have Sex with Men; OI: Opportunistic Infection; PLWHIV: People Living With HIV; PJP: Pneumocystis jirovecii Pneumonia; SAGIP: STD/AIDS Guidance, Intervention and Prevention; TB: Tuberculosis; TDF: Tenofovir Disoproxil Fumarate; TFV: Tenofovir; TMP-SFX: Trimethoprim Sulfamethoxazole; 3TC: Lamivudine; UP-PGH: University of the Philippines-Philippine General Hospital; UPREB: University of the Philippines Research and Ethics Board
Introduction

Tenofovir disoproxil fumarate (TDF) is one of the main antiretroviral drugs of people living with human immunodeficiency virus (PLWHIV) [1]. Despite its efficacy and tolerability, there is conflicting evidence regarding TDF-associated nephrotoxicity, which is proposed to cause injury by accumulation of tenofovir (TFV) within proximal tubular cells leading to mitochondrial injury and tissue hypoxia [2-5]. Incidence of TDF-associated nephrotoxicity ranges from 0.7% to 17% [2,6]. Risk factors often include old age, female gender, African-American ethnicity, diabetes, hypertension, duration of TDF use, and low CD4 count [6,7]. There are now several studies on TDF-induced nephrotoxicity including a meta-analysis [5], but this included only one study from Asia [8] or involved the older age-group [2,4,5,9] which highlights the need for studies inclusive of a younger cohort of patients who will remain on TDF for a prolonged period. Data among young PLWHIV are still just emerging [9-11].

There is an ongoing HIV epidemic of young PLWHIV in the Philippines with an exponential growth particularly among young men who have sex with men (MSM) [12]. We anticipate they will experience complications related to prolonged ART. We aimed to determine the incidence and risk of nephrotoxicity among HIV patients taking TDF.

Material and Methods

Study design and setting

We conducted a retrospective cohort study at the UP-PGH STD/AIDS Guidance, Intervention, and Prevention (SAGIP) clinic. Data were abstracted from 2,313 available patient charts from January 1, 2004 to December 31, 2016.

Study population

Only adult HIV patients’ ≥19 years old upon initiation of antiretroviral therapy (ART) with a normal baseline serum creatinine defined as 0.84 to 1.49 mg/dL prior to TDF exposure were included. Subjects were excluded if they transferred from another treatment hub, were previously on ART, or if they had chronic kidney disease, acute kidney injury, or had an established structural or functional abnormality of the kidneys.

Data collection

Data obtained from medical records included dates of HIV confirmation and ART initiation, age, gender, weight (kg), height (m), comorbidities, nephrotoxic drugs, and opportunistic infections (OI). Advanced HIV or AIDS was defined as absolute CD4< 200 cells/mm³ and/or presence of an AIDS-defining illness. Pertinent laboratory tests including creatinine, urinalysis, CD4 count, and HIV viral load were recorded.

Outcomes

The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) equation. The primary outcome was nephrotoxicity, defined as at least a 20% decline from baseline in eGFR per 1,000 person days while on TDF to capture early decline in eGFR [13]. We also compared nephrotoxicity of at least a 30% from baseline eGFR, the more commonly used cut-off [14-16]. Proteinuria was defined as the presence of proteinuria at baseline, and on at least 1 more subsequent urinalysis.

Statistical analysis

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Independent Sample T-test, Mann-Whitney U test and Fisher’s Exact/Chi-square test were used to determine the difference of mean, median and frequency between groups, respectively. Kaplan-Meier failure function analysis was used to determine the incidence rate of decline in eGFR by at least a) 20% and b) 30% of the patients considering the day of TDF initiation. Cox Proportional Hazard Regression was used to determine the significant covariates that were associated with a) 20% and b) 30% decline in eGFR from baseline. Incidence density rates for nephrotoxicity were generated. All valid data was included in the analysis. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

Ethical considerations

The study adhered to the principles of the Declaration of Helsinki. The UP - Manila Research Ethics Board (UPMREB) approved this study and waived the need for informed consent.

All information obtained was kept securely and access to files was only available to study authors. Patients were de-identified and known only to the primary investigator who reviewed charts from December 1, 2016-March 31, 2017.
sulfamethoxazole (TMP-SFX) (49.1%) and anti-tuberculosis (TB) medications (38.1%).

Table 1: Baseline characteristics of HIV patients on tenofovir.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range); Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>29 (18–69)</td>
</tr>
<tr>
<td>Gender, Male</td>
<td>645 (98.62)</td>
</tr>
<tr>
<td>Body mass index, kg/m² (n=506)</td>
<td>21.05 (12.40–33.45)</td>
</tr>
<tr>
<td>Body weight, kg (n=596)</td>
<td>58.90 (33–100)</td>
</tr>
<tr>
<td>Height, m (n=534)</td>
<td>1.68 (1.48–1.85)</td>
</tr>
</tbody>
</table>

Comorbid disease

- Hypertension: 15 (2.29)
- Diabetes mellitus: 7 (1.07)
- None: 631 (96.48)

Infection history

- Tuberculosis: 263 (40.21)
- P. jirovecii pneumonia: 114 (17.43)
- Hepatitis B: 100 (15.29)
- Syphilis: 23 (3.52)
- Cryptococcal meningitis: 8 (1.22)
- CNS toxoplasmosis: 7 (1.07)
- Hepatitis C: 6 (0.92)
- None: 278 (42.51)

Concurrent nephrotoxic drug

- Trimethoprim-sulfamethoxazole: 321 (49.08)
- Anti-tuberculosis medication: 249 (38.07)
- Amphotericin B: 9 (1.38)
- ACE inhibitor: 4 (0.61)
- NSAID: 0 (0)
- None: 238 (36.39)

Laboratory data

- Serum creatinine, mg/dL: 0.85 (0.42–1.45)
- Estimated GFR, mL/min/1.73 m²: 113.33 (44.57–261.66)
- Proteinuria at baseline (n=448): 119 (26.56)
- Absolute CD4+ cell count, per μL (n=653): 154 (1–1044)
- CD4+ % of total lymphocytes (n=511): 10.07 (0.01–72.18)
- HIV load, copies/mL (n=233): 44.8 (20–484807)

Initial antiretroviral regimen

<table>
<thead>
<tr>
<th>ART regimen</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC+TDF+EFV</td>
<td>648 (99.08)</td>
</tr>
<tr>
<td>3TC+TDF+NVP</td>
<td>5 (0.76)</td>
</tr>
<tr>
<td>3TC+TDF+LPV/R</td>
<td>1 (0.15)</td>
</tr>
<tr>
<td>Advanced HIV/AIDS</td>
<td>439 (67.13)</td>
</tr>
</tbody>
</table>

Patients had low median CD4+ absolute lymphocyte count at 154 [range 1-1044] cells/μL, and majority (67.1%) had advanced HIV/AIDS. The median HIV viral load was 44.8 (range 20-4,848,007) copies/mL. The initial ART regimen was lamivudine (3TC), TDF, and efavirenz (EFV) (99%). Of 448 patients with baseline urinalysis, 119 (26.56%) had proteinuria. The initial serum creatinine and eGFR were 0.85 (0.42–1.45) mg/dL and 113.3 (44.57–261.66) mL/min/1.73 m², respectively.

At least a 20% or 30% drop in eGFR was seen in 51.4% (n=336) and 35.8% (n=234) of patients over time, respectively. The incidence density of having at least 20 or 30% decline in eGFR was 11 per 10,000 and 6 per 10,000 person-days, respectively. Of 178 patients with subsequent urinalysis, 58 (32.6%) had persistent proteinuria (Supplementary Table 1). Time to 20% or 30% decline are in Supplementary Figure 2 and Supplementary Figure 3, respectively.

The time to event of incurring 25%, 50%, and 75% decline in renal function occurred at 5.7, 20.4 and 61 months from the time of TDF initiation (Supplementary Table 2). Cox regression modeling of covariates revealed that only low baseline CD4 was a significant covariate for predicting a subsequent ≥20% (Table 2) or ≥30% eGFR decline (Supplementary Table 3).

Table 2. Cox proportional hazard modeling of time to a decrease in eGFR of at least 20% among HIV patients initiated on tenofovir (n=654).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. jirovecii pneumonia</td>
<td>1.191 (0.88–1.61)</td>
<td>0.255</td>
</tr>
<tr>
<td>TMP-SMX only</td>
<td>0.987 (0.75–1.30)</td>
<td>0.927</td>
</tr>
<tr>
<td>Baseline CD4 count</td>
<td>0.999 (0.998–0.999)</td>
<td>0.028</td>
</tr>
</tbody>
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Pseudo R2: 0.51%; Model p<0.001

Discussion

Our study showed that a young cohort of treatment naïve PLWHIV had a decline in eGFR (51.4%) by 20 months of treatment, with an incidence density rate of 11/10,000 person days. Only low CD4 count was associated with a subsequent decline in eGFR.

Our study confirms the possible association between low CD4, TDF use, and nephrotoxicity [17]. We concede that causes may be multifactorial related to OIs, and use of other drugs [18]. The association between advanced disease, TDF, and the subsequent decline in eGFR makes sense in this context since a patient with a lower CD4 count is more likely to be...
hospitalized, more prone to OIs, and more likely to receive drugs, including potentially nephrotoxic agents, compared to someone with asymptomatic or early HIV.

We did not find an association between BMI and a decline in GFR. The lack of association may be because we were unable to document weight, or calculate the BMI in a good proportion of patients (n = 148, 23%). This is in contrast to other studies, where a lower BMI predisposed to a higher risk of nephrotoxicity [4,9,19]. Low BMI or weight may lead to a higher TDF concentration and increased risk of kidney impairment [20]. Notably, median body weight in this study was 58.90 (range 33-100) kg, which is lighter than the average 70 kg Caucasian male. This suggests that more frequent monitoring of renal function, or even a dose reduction in TDF, may be particularly important among the lighter-weighted Asian population.

Co-infection with PJP was not a risk factor for subsequent nephrotoxicity in our cohort. PJP is an AIDS-defining illness, and often occurs below a CD4 threshold of <200 cells/mm³. Not all patients with a CD4 below this threshold acquire PJP, however, and we hypothesize that PJP is a surrogate marker indicative of advanced HIV or a low CD4 count. Other studies have described it in association with TDF-induced nephrotoxicity [21].

This study showed a lower incidence density rate of TDF induced nephrotoxicity compared to published data [4,5,9]. This can potentially be explained by several factors. First, we have a younger cohort of patients compared with previous studies [4,5,9]. It is known that an older individual's renal function is often more prone to decline, given the physiologic effect of aging on renal function [22]. Second, our cohort had a shorter duration of TDF exposure compared to others [4,9] with majority of the cohort followed only a year (n=338). Third, in comparison to published data [4], few of our subjects had hypertension and diabetes, which contribute to nephrotoxicity [2]. Fourth, we excluded ART-experienced subjects; the higher rate of nephrotoxicity seen among ART-experienced subjects may be due to the cumulative effect of prior ART use, and not necessarily due to TDF alone. This could explain the higher incidence density rate seen in some studies that included ART-experienced subjects [9,19]. Lastly, patients treated with TDF and ritonavir boosted lopinavir (LPV/r) may experience greater nephrotoxicity [6,23,24]. Majority (98%) of our patients were on 3TC, EFV and TDF and only one was given LPV/r in addition to TDF as part of the ART regimen.

Limitations

Our study has limitations inherent to its retrospective nature. Relevant data including BMI over time, and specific doses of TMP-SFX and non-steroidal anti-inflammatory drug use were not documented and could not be captured by chart review. We were also unable to describe the individual anti-TB drugs that may have given insight on the nephrotoxic potential of second line agents (e.g., amikacin, streptomycin). However, 2nd line anti-TB drugs are used in <1% of the SAGIP cohort (unpublished data). We excluded a large proportion of patients on TDF (n=503) as they had incomplete laboratory data, which may have resulted in pre-selection bias. Incomplete laboratory data is not uncommon as many are unable to afford tests that are paid for out-of-pocket. We used the simplified MDRD equation as opposed to the chronic kidney disease epidemiology collaboration (CKD-Epi) for calculating our patient's eGFR as differences in accuracy between MDRD and CKD-Epi are small and are not statistically significant [25] and the former is considered reliable in PLWHIV [2]. Although we included a good-sized number of patients, a larger sample size may have more power to detect relatively small hazard ratios for the risk of TDF-associated nephrotoxicity outcomes per year of exposure. Finally, only a limited number of patients had a urinalysis, and the incidence density rate of proteinuria may be underestimated. Despite these limitations, our study is one of the larger cohorts in a resource-limited setting that adds relevant information regarding TDF among young, treatment naïve, PLWHIV.

Conclusion

In summary, our study shows that TDF may be associated with a modest decline in eGFR over a relatively short period of time (e.g., 20 months), even among a young cohort of treatment-naïve individuals. As such, renal function among patients on TDF should be monitored regularly, especially among those with increased risk, such as those with advanced HIV/AIDS at time of diagnosis.

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References


