J AIDS HIV Treat. 2022;4(1):1-5.

Journal of AIDS and HIV Treatment | Short Communication

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

Marja Bernardo-Buensalido[1,#], Cybele Lara R. Abad[1,2,#*]

[1]Department of Medicine, Section of Infectious Diseases, The Medical City, Ortigas Avenue, Pasig City, Philippines

[2]Department of Medicine, Section of Infectious Diseases, University of the Philippines Manila-Philippine General Hospital, Taft Ave, Manila, Philippines

[#]The authors contributed equally to this manuscript

[*]Correspondence should be addressed to Cybele Lara R. Abad, cybelemd@yahoo.com; crabad@up.edu.ph

Received date: November 11, 2021, **Accepted date:** February 10, 2022

Citation: Bernardo-Buensalido M, Abad CLR. Incidence of Nephrotoxicity among People Living with Human Immunodeficiency Virus on Tenofovir Treatment in a Tertiary Hospital in the Philippines. J AIDS HIV Treat. 2022;4(1):1-5.

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 20.4 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; CKD 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/mm^3 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 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.

Results

Medical charts of HIV patients seen during the study period were screened. Only 654 were included in the study (*Supplementary Figure 1*). Baseline demographic and clinical data are summarized in Table 1. Males comprised 98.6%. The median (± SD) age was 29 (range 18-69) years. Overall median body mass index (BMI) was 21 (range 12.4 -33.5 kg/m^2). Majority had no comorbidities (631/654, 96.5%), with only a small percentage with hypertension (2%) or diabetes (1%). Most common infections were tuberculosis (40%), *Pneumocystis jirovecii* pneumonia (PJP) (17%), and hepatitis B (15%). The major nephrotoxic drugs included trimethoprim

sulfamethoxazole (TMP-SFX) (49.1%) and anti-tuberculosis (TB) medications (38.1%).

Table 1: Baseline characteristics of HIV patients on tenofovir.

Characteristic, N= 654	**Median (Range); Frequency (%)**
Age, years	29 (18–69)
Gender, Male	645 (98.62)
Body mass index, kg/m^2 (n=506)	21.05 (12.40–33.45)
Body weight, kg (n=596)	58.90 (33–100)
Height, m (n=534)	1.68 (1.48–1.85)
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 m^2	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 (20–4848007)
Initial antiretroviral regimen	
3TC+TDF+EFV	648 (99.08)
3TC+TDF+NVP	5 (0.76)
3TC+TDF+LPV/R	1 (0.15)
Advanced HIV/AIDS	439 (67.13)

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 m^2, 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).

	Adjusted Hazard Ratio (95% CI)	**p-value**
P. jirovecii pneumonia	1.191 (0.88–1.61)	0.255
TMP-SMX only	0.987 (0.75–1.30)	0.927
Baseline CD4 count (n=653)	**0.999 (0.998–0.999)**	**0.028**
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/mm^3. 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.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. WHO. Preparing people living with HIV for ART in Clinical Guidelines: Antiretroviral Therapy. Chapter 4.1 https://www.who.int/hiv/pub/arv/chapter4.pdf. 2016; 71-190.

2. Gupta SK, Eustace JA, Winston JA, Boydstun II, Ahuja TS, Rodriguez RA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clinical Infectious Diseases. 2005 Jun 1;40(11):1559-85.

3. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Performance of GFR equations in Japanese subjects. Clinical and Experimental Nephrology. 2013 Jun;17(3):352-8.

4. Scherzer R, Estrella M, Yongmei LI, Deeks SG, Grunfeld C, Shlipak MG. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS (London, England). 2012 Apr 24;26(7):867.

5. Elias A, Ijeoma O, Edikpo NJ, Oputiri D, Geoffrey OB. Tenofovir Renal Toxicity: Evaluation of Cohorts and Clinical Studies—Part One.

Pharmacology & Pharmacy. 2013 Dec 6;4(09):651.

6. Crum-Cianflone N, Ganesan A, Teneza-Mora N, Riddle M, Medina S, Barahona I, et al. Prevalence and factors associated with renal dysfunction among HIV-infected patients. AIDS Patient Care and STDs. 2010 Jun 1;24(6):353-60.

7. Mugomeri E, Olivier D, van den Heever-Kriek E. The effect of tenofovir in renal function in HIV-positive adult patients in the Roma health service area, Lesotho, southern Africa. Journal of the International AIDS Society. 2014 Nov;17:19681.

8. Kinai E, Hanabusa H. Progressive renal tubular dysfunction associated with long-term use of tenofovir DF. AIDS Research and Human Retroviruses. 2009 Apr 1;25(4):387-94.

9. Chaisiri K, Bowonwatanuwong C, Kasettratat N, Kiertiburanakul S. Incidence and risk factors for tenofovir-associated renal function decline among Thai HIV-infected patients with low-body weight. Current HIV research. 2010 Oct 1;8(7):504-9.

10. Nishijima T, Kawasaki Y, Mutoh Y, Tomonari K, Tsukada K, Kikuchi Y, et al. Prevalence and factors associated with chronic kidney disease and end-stage renal disease in HIV-1-infected Asian patients in Tokyo. Scientific Reports. 2017 Nov 6;7(1):1-8.

11. Suzuki S, Nishijima T, Kawasaki Y, Kurosawa T, Mutoh Y, Kikuchi Y, et al. Effect of tenofovir disoproxil fumarate on incidence of chronic kidney disease and rate of estimated glomerular filtration rate decrement in HIV-1–infected treatment-naïve Asian patients: results from 12-year observational cohort. AIDS Patient Care and STDs. 2017 Mar 1;31(3):105-12.

12. Philippines Department of Health. HIV/AIDS and ART registry of the Philippines (HARP) report. June 2016.

13. Garg AX, Devereaux PJ, Yusuf S, Cuerden MS, Parikh CR, Coca SG, et al. Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. JAMA. 2014 Jun 4;311(21):2191-8.

14. Andrassy KM. Comments on 'KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease'. Kidney International. 2013 Sep 1;84(3):622-3.

15. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. American Journal of Kidney Diseases. 2014 May 1;63(5):713-35.

16. Kovesdy CP, Coresh J, Ballew SH, Woodward M, Levin A, Naimark DM, et al. Past decline versus current eGFR and subsequent ESRD risk. Journal of the American Society of Nephrology. 2016 Aug 1;27(8):2447-55.

17. Phair J, Palella F. Renal disease in HIV infected Individuals. Current Opinion in HIV and AIDS. 2011 Jul;6(4):285.

18. Franceschini N, Napravnik S, Eron Jr JJ, Szczech LA, Finn WF. Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. Kidney International. 2005 Apr 1;67(4):1526-31.

19. Gayet-Ageron A, Ananworanich J, Jupimai T, Chetchotisakd P, Prasithsirikul W, Ubolyam S, et al. No change in calculated creatinine clearance after tenofovir initiation among Thai patients. Journal of Antimicrobial Chemotherapy. 2007 May 1;59(5):1034-7.

20. Barrios A, García-Benayas T, González-Lahoz J, Soriano V. Tenofovir-related nephrotoxicity in HIV-infected patients. AIDS. 2004 Apr 9;18(6):960-3.

21. Wikman P, Safont P, Palacio MD, Moreno A, Moreno S, Casado JL. The significance of antiretroviral-associated acute kidney injury in a cohort of ambulatory human immunodeficiency virus-infected patients. Nephrology Dialysis Transplantation. 2013 Aug 1;28(8):2073-81.

22. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. The Journal of Clinical Investigation. 1950 May 1;29(5):496-507.

23. Cao Y, Han Y, Xie J, Cui Q, Zhang L, Li Y, et al. Impact of a tenofovir disoproxil fumarate plus ritonavir-boosted protease inhibitor-based regimen on renal function in HIV-infected individuals: a prospective, multicenter study. BMC Infectious Diseases. 2013 Dec;13(1):1-8.

24. Gallant JE, Moore RD. Renal function with use of a tenofovir-containing initial antiretroviral regimen. AIDS (London, England). 2009 Sep 24;23(15):1971.

25. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clinical Journal of the American Society of Nephrology. 2010 Jun 1;5(6):1003-9.