Infect Chemother. 2020 Sep;52(3):381-388
https://doi.org/10.3947/ic.2020.52.3.381
pISSN 2093-2340·eISSN 2092-6448

Infection & Chemotherapy

Original Article

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Recovery of Tenofovir-induced Nephrotoxicity following Switch from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in Human Immunodeficiency Virus-Positive Patients

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OPEN ACCESS

Received: Mar 20, 2020
Accepted: Jul 2, 2020

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ABSTRACT

Background: Tenofovir disoproxil fumarate (TDF)-induced nephrotoxicity is related to high plasma tenofovir concentrations. Tenofovir alafenamide (TAF) is a tenofovir prodrug with 90% lower plasma tenofovir concentrations. The aim of this study was to evaluate changes in tenofovir-induced nephrotoxicity in Human Immunodeficiency Virus (HIV)-positive patients who switched from TDF to TAF.
Materials and Methods: We identified all HIV-positive patients who switched from elvitegravir/cobicistat/emtricitabine/TDF to elvitegravir/cobicistat/emtricitabine/TAF at a tertiary hospital. We assessed tubulopathy and renal dysfunction before TDF administration, at the time TAF was used following at least 3 months of TDF use, and 3 months after TAF administration. Tubulopathy was defined by the presence of at least three abnormalities in fractional excretion of phosphate, fractional excretion of uric acid, urinary β2-microglobulin, urinary N-acetyl-β-D-glucosaminidase, glucosuria or proteinuria. Renal dysfunction was defined as decreased by more than 25% in the estimated glomerular filtration rate (eGFR) relative to baseline.
Results: In 80 patients, the mean eGFR was 96.8 mL/min/1.73 m^2 before administration of TDF, 81.2 (P <0.001) at the time of change to TAF, 90.9 (P <0.001) after TAF administration. Renal dysfunction occurred in 19 patients (23.8%) after TDF use for a median 15 months, 11 (57.9%) of these patients recovered from renal dysfunction after TAF administration. Six patients (7.5%) had tubulopathy before TDF administration, 36 (45.0%) after TDF administration (P <0.001), 12 (15.0%) after TAF administration (P = 0.002).
Conclusion: Tenofovir-induced nephrotoxicity in HIV-positive patients receiving TDF was mostly reversible after changing to TAF. Thus, TAF-containing regimens can be administered safely to HIV-positive patients with tenofovir-induced nephrotoxicity.

Keywords: Renal dysfunction; Tubulopathy; Tenofovir disoproxil fumarate; Tenofovir alafenamide; HIV

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Conflict of Interest
WBP is associate editor of *Infect Chemother*; HBK, NJK are editorial board of *Infect Chemother*; however, they did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported.

Author Contributions
Conceptualization: JWS, KCK. Data curation: JWS, KCK, KIJ, CKK. Formal analysis: JWS, KCK, KIJ, CKK. Investigation: SMM, KHS. Methodology: HBK, SWP. Project administration: PGC, WBP. Resources: NJK, MDO. Software: JHB, ESK. Supervision: PGC, WBP. Validation: HBK, SWP, NJK, MDO. Visualization: JWS, WBP. Writing - original draft: JWS, KCK. Writing - review & editing: PGC, WBP.

INTRODUCTION

Tenofovir disoproxil fumarate (TDF), the first-generation prodrug of tenofovir, is a nucleotide reverse transcriptase inhibitor used for Human Immunodeficiency Virus (HIV) infection since 2001. TDF has been widely used for treatment and prophylaxis in HIV infection [1-3], though safety issues have been reported with TDF, including renal and bone toxicity [4-6].

TDF-induced nephrotoxicity is related to high plasma tenofovir concentrations, and mitochondrial abnormalities during TDF administration [7-12]. Consequently, tenofovir alafenamide (TAF), a new tenofovir prodrug with 90% reduced plasma concentrations and approximately 4 time higher intracellular concentrations, has been developed to optimize renal safety [13]. To date, several phase 2 and 3 randomized controlled trials have shown that TAF has similar antiviral activity, with a significant ability to reduce the risk of renal and bone toxicity compared to TDF [13-15].

However, few studies have examined the changes in renal function when TDF is switched to TAF in patients with tenofovir-induced nephrotoxicity [15]. The purpose of this study was to evaluate changes in tenofovir-induced nephrotoxicity in Korean HIV-positive patients who switched TDF to TAF.

MATERIALS AND METHODS

1. Study design and population

We identified all Korean HIV-positive patients who changed their anti-retroviral treatment regimen from elvitegravir (EVG)/cobicistat (c)/emtricitabine (FTC)/TDF to EVG/c/FTC/TAF between June 2017 and October 2018 at Seoul National University Hospital, Korea. EVG/c/FTC/TAF has been available in Korea since June 2017. We included patients with normal renal function before starting TDF who were taking TDF and TAF for more than 3 months. Patients were excluded if they used a TDF or TAF formulation other than EVG/c/FTC/TDF or TAF, were not followed up for more than 3 months after using TAF, or were not evaluated for nephrotoxicity as routine clinical practice.

2. Data collection and definitions

We evaluated tenofovir-induced nephrotoxicity as tubulopathy and renal dysfunction at three time points: before TDF administration, at the time TDF was switched to TAF, and after TAF administration. Tubulopathy was defined by the presence of at least three abnormalities in the following parameters, suggesting proximal tubular dysfunction like Fanconi syndrome: fractional excretion of phosphate (FEphos) [(urine phosphorus × plasma creatinine)/(plasma phosphorus × urine creatinine) × 100] lower than 10% (normal value: more than 20% among patients with normal serum phosphate levels or more than 10% among patients with hypophosphatemia), fractional excretion of uric acid [(urine uric acid × plasma creatinine)/(urine creatinine × plasma uric acid) × 100] greater than 15% (normal value: less than 10%), β2-microglobulinuria greater than 1 mg daily, urinary N-acetyl-β-D-glucosaminidase greater than 11.5 and glucosuria or proteinuria, defined as at least 1+ on urine dipstick [8, 9, 16].

Renal dysfunction was defined as a more than 25% decrease in the estimated glomerular filtration rate (eGFR) relative to baseline and eGFR was calculated using the equation from the 4-variable Modification of Diet in Renal Disease study [17, 18].

3. Ethics statement

The Institutional Review Board at Seoul National University Hospital reviewed the study protocol, provided study approval, and waived the informed consent (IRB registration number 1510-012-706). This included a waiver of consent, permitting access to identified health data.

4. Statistical analysis

Continuous variables, including eGFR, were compared using the paired *t* test and Wilcoxon signed rank test. McNemar's test and a Kaplan-Meier survival analysis were used to evaluate the incidence and improvement of tubulopathy. The level of significance in two-sided tests was 0.05. All statistical analyses were performed using the Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, a total of 123 patients switched from TDF to TAF. All 123 patients did not have chronic kidney disease, and other acute diseases that could decrease renal function, such as diarrhea and vomiting. Twenty-four patients prescribed other TDF formulations were excluded, and 99 patients changed from EVG/c/FTC/TDF to EVG/c/FTC/TAF. However, 1 patient was taking TDF for less than 3 months, 5 patients were lost to follow-up, and 13 patients did not undergo nephrotoxicity testing; these 19 patients were excluded. Thus, data from 80 patients were analysed (**Fig. 1**).

The median patient age was 44 years. The median body weight and body mass index were 65.2 kg and 22.5 kg/m^2, respectively. Total follow-up duration for EVG/c/FTC/TDF and EVG/c/FTC/TAF was 14.6 months (437 days, interquartile range [IQR] 248 - 544) and 8.7 months (260 days, IQR 196 - 307), respectively (**Table 1**).

These 80 patients had no significant change in GFR from at least a year before the study began, the mean eGFR was 96.8 mL/min/1.73m^2 before administration of TDF, 81.2 mL/min/1.73m^2 (-16.1%, P <0.001) at the time of changing to TAF from TDF, and 90.9 mL/min/1.73m^2 (+11.9%, P <0.001) after TAF administration (**Fig. 2**). Renal dysfunction was detected in 6, 8, 8, and 9 patients at 3, 6, 9, and 12 months after starting TDF, respectively, and a total of 19 (23.8%) patients experienced renal dysfunction just before changing to TAF.

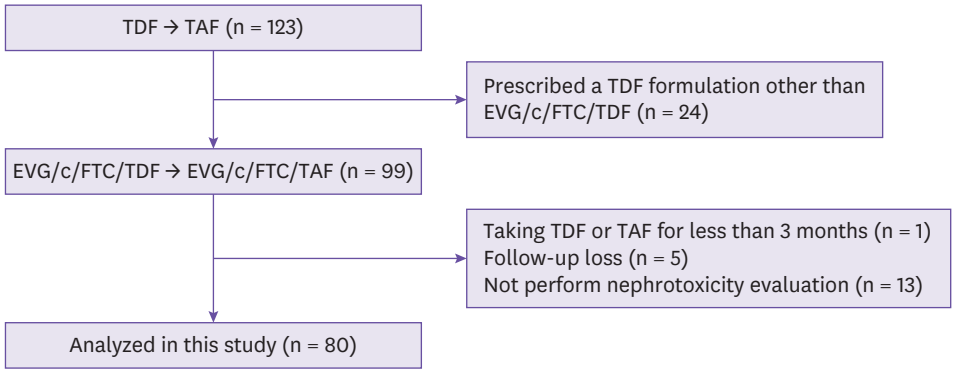

Figure 1. Study flowchart.
TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; EVG, elvitegravir; c, cobicistat; FTC, emtricitabine.

https://doi.org/10.3947/ic.2020.52.3.381

Table 1. Baseline characteristics of patients (N = 80)

Characteristic	Value
Median age, years (IQR)	43 (34.5 – 51)
Sex	
Male	75 (93.8)
Female	5 (6.2)
Korean ethnicity	80 (100)
Median weight, kg (IQR)	65.2 (57.5 – 73.3)
Median height, cm (IQR)	169.8 (166.3 – 173.9)
Median BMI, kg/m^2 (IQR)	22.5 (20.3 – 24.3)
Underlying disease	
Hypertension	4 (5)
Diabetes mellitus	4 (5)
Chronic HBV carrier	3 (3.75)
Chronic HCV carrier	0 (0)
Chronic kidney disease	0 (0)
Median CD4 T cell count, cells/mm^3 (IQR)	
At the start of TDF	572 (313 – 721)
At change from TDF to TAF	643 (493 – 764)
At last follow-up	709 (498 – 850)
Median HIV RNA titer, copies/mL (IQR)[a]	
At the start of TDF	112 (40 – 218)
At change from TDF to TAF	40 (40 – 40)
Last follow-up	40 (40 – 40)
Median baseline eGFR, mL/min/1.73m^2 (IQR)	96.8 (80.7 – 107.2)
Concomitant nephrotoxic drug	
Protease inhibitor (ritonavir-boosted)	12 (15)
Diuretics	3 (3.75)
Trimethoprim/sulfamethoxazole	3 (3.75)
NSAIDs	0 (0)
Median duration of TDF administration, days (IQR)	437 (248 – 544)
Median duration of TAF administration, days (IQR)	260 (196 – 307)

Data are given as number (%) unless otherwise indicated.
[a]Undetectable level was considered 40 copies/mL.
IQR, interquartile range; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; HIV, human immunodeficiency viruses; RNA, ribonucleic acid; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug.

Of these patients, 5, 7, 8, and 10 recovered from renal dysfunction 3, 6, 9, and 12 months after TAF use, respectively. Finally, renal dysfunction recovered in 11 patients (57.9%), and in 5 patients (26.3%) it recovered to above baseline level.

Six patients (7.5%) had tubulopathy before TDF administration, which increased to 36 patients (45%) after TDF administration (P <0.001) and decreased to 12 patients (15%) after TAF administration (P = 0.002, **Fig. 3**, **Supplementary Table 1**). Of these 30 patients (40.5%) who newly developed tubulopathy during TDF use, 26 (86.6%) recovered from tubulopathy at the last follow-up after changing from TDF to TAF.

DISCUSSION

In this study, we observed recovery of renal dysfunction or tubulopathy in HIV-infected Korean patients who developed nephrotoxicity during treatment with TDF by changing the treatment regimen to TAF. TDF has been one of the treatments of choice in HIV infected patients [19-21], particularly as pre- or post-exposure prophylaxis for HIV infection [2, 3]. However, in 2001, the first case of TDF-induced acute nephrotoxicity, which is associated

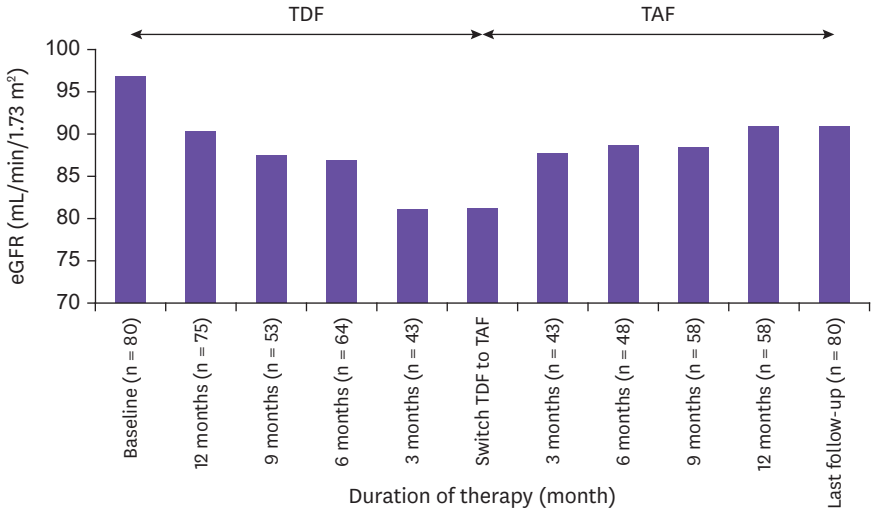

Figure 2. Changes in eGFR over time. Baseline eGFR means the nearest value before starting TDF.
eGFR, estimated glomerular filtration rate; TDF, tenofovir disoproxil fumarate; TAF, Tenofovir alafenamide.

with high plasma concentrations of tenofovir, was reported [7]. Several studies have since reported that, in severe cases, Fanconi syndrome or acute kidney injury develop in the proximal tubule [10-12].

Nephrotoxicity has been reported in approximately 1 - 2% of HIV-positive patients receiving tenofovir [22]. Asians are considered to be more susceptible to tenofovir-induced nephrotoxicity due to their small body stature in general, because low body weight is associated with reduced plasma TDF clearance and high plasma TDF concentrations, which could result in renal tubular dysfunction [18, 23, 24]. This finding has been indirectly supported by a retrospective investigation in Caucasian HIV-infected individuals, which demonstrated a significant association between higher TDF plasma concentration and the development of renal impairment [25]. Eastern HIV-positive patients have lower body weight than Western patients; therefore, there are concerns about tenofovir-induced nephrotoxicity [18].

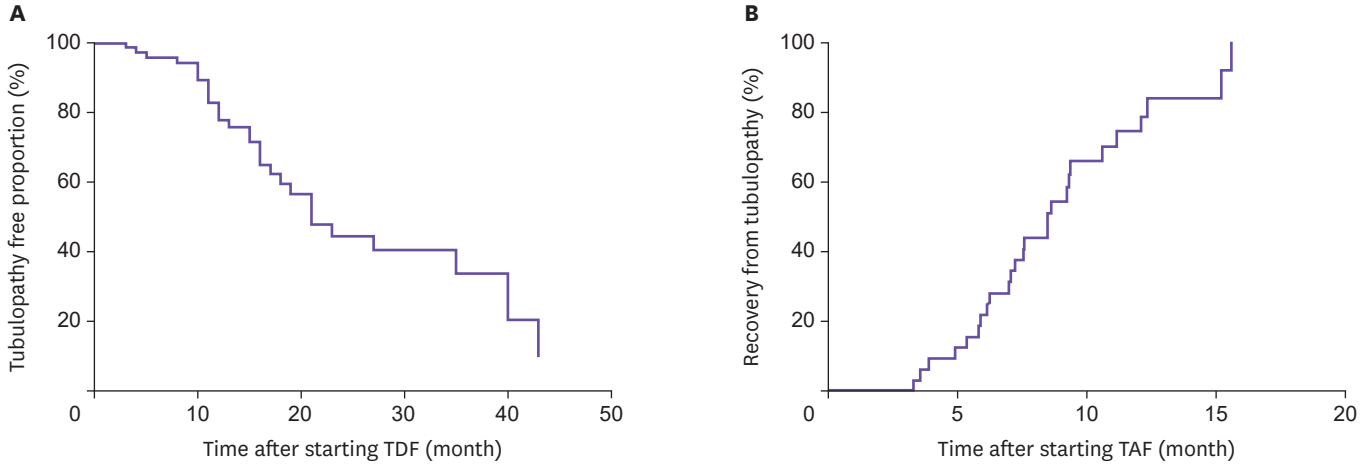

Figure 3. Incidence of tubulopathy. (A) Incidence of tubulopathy following administration of EVG/c/FTC/TDF in patients without tubulopathy (n = 74). (B) Recovery rate of tubulopathy after starting EVF/c/FTC/TAF among patients with tubulopathy related to EVG/c/FTC/TDF (n = 30).
EVG, elvitegravir; c, cobicistat; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; TAF, Tenofovir alafenamide.

https://doi.org/10.3947/ic.2020.52.3.381

Previous studies have shown that the use of TAF-based therapies results in lower plasma level of tenofovir and have less of an impact on kidney safety measurements. These studies were the result of a comparison between the groups administered TDF and TAF [13, 14]. In addition, studies have evaluated changes in renal function after the administration of TAF to HIV-positive patients who had already lost their renal function while taking conventional ART [15]. In this study, there was significant improvement in tubular proteinuria and no deterioration of eGFR for 1 year following the change to EVG/c/FTC/TAF. However, this study has some limitations in the interpretation of the results because patients with renal dysfunction due to causes other than antiretroviral therapy were included, and because various TDF-containing regimens were used. For these reasons, we included patients without underlying renal dysfunction before using TDF, and confined the treatments to tenofovir-containing regimens EVG/c/FTC/TDF and EVG/c/FTC/TAF to minimize the bias caused by different anti-retroviral treatment regimens.

In the present study, nephrotoxicity comprised renal dysfunction and tubulopathy. Renal dysfunction occurred in 24% of patients after TDF administration, and 53% of these patients exhibited a recovery of renal dysfunction within 1 year after TAF administration. In addition, among 30 patients with newly developed tubulopathy after using TDF, 87% patients recovered from tubulopathy 1 year after changing to TAF from TDF. In particular, 7 out of 19 patients (36.8%) with reduced GFR by more than 25% after TDF administration had tubulopathy at the same time, and all of them (100.0%) were recovered together after TAF administration. This may be the basis for suggesting that nephrotoxicity by TDF reduced the rate of filtration of the dune and that the rate of filtration of the dune recovered after TAF administration. These results support restoration of renal dysfunction or tubulopathy in patients with TDF-associated nephrotoxicity by altering the anti-retroviral therapy with a TAF formulation.

Limitations to this study include the duration of TAF administration being relatively short. In addition, other drugs, such as cobicistat, could affect the evaluation of renal function, though cobicistat was used with both TDF and TAF. In addition, it was not possible to measure the exact renal function of the patients in this study, so the calculated renal function may not be the actual renal function, and the definition of renal tubular abnormality might be incomplete because it is not supported by pathologic findings.

In conclusion, tenofovir-induced nephrotoxicity was frequently observed in Korean HIV-positive patients receiving TDF, but was mostly reversible after changing to TAF. Therefore, TAF-containing regimens can be safely administered in HIV-positive patients with tenofovir-induced nephrotoxicity due to TDF.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Details of the parameters for evaluating tubulopathy by period

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https://doi.org/10.3947/ic.2020.52.3.381

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