Tenofovir alafenamide nephrotoxicity: a case report and literature review

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Abstract

Background: Tenofovir alafenamide (TAF), a novel prodrug of tenofovir (TFV), has become the preferred drug for the treatment of HIV-1 and chronic hepatitis B infection in clinical practice. Results from clinical trials showed that it had better renal and bone mineral outcomes compared to tenofovir disoproxil fumarate (TDF). However, as we have seen with TDF, side effects from the new medication can be more prevalent and recognized after extensive use in real world situations. Sporadic cases of acute kidney injury in patients using TAF have started to emerge.

Case presentation: We report a case of 49-year-old Thai, HIV treatment-experienced female with hypertension presented with worsening renal function after switching her antiretroviral regimen from TDF, emtricitabine (FTC), and lopinavir/ritonavir (LPV/r) to TAF, FTC and dolutegravir (DTG) for 3 months. Kidney biopsy showed distinctive picture of tenofovir nephrotoxicity with acute tubular injury and mitochondrial injury. The possible causes of acute kidney injury and nephrotoxicity from TAF for this patient were discussed. We have extensively reviewed all published case reports of TAF-associated nephrotoxicity and summarized the essential information in this article.

Conclusion: Although TAF has less nephrotoxicity compared with TDF; renal function should always be monitored after the initiation of both drugs. Future large cohort studies are required to identify the risk factors of TAF-associated nephrotoxicity and to design an effective preventive strategy.

Keywords: Tenofovir alafenamide, Acute kidney injury, Nephrotoxicity, Renal pathology, Mitochondria, HIV, Antiretroviral therapy, Case report

Introduction

Tenofovir (TFV) has become one of the backbone antiretroviral therapies (ART) in this era. However, the nephrotoxicity profile which is caused by cytoplasmic and intra-mitochondrial accumulation of TFV and results in the messenger ribonucleic acid (mRNA) depletion, mitochondrial deoxyribonucleic acid (DNA) depletion, and oxidative respiratory chain dysfunction, eventually contribute to proximal renal tubular abnormalities and renal insufficiency, limit its use in clinical practice [1, 2]. Tenofovir alafenamide (TAF) is a novel prodrug of TFV. It has a more favorable renal and bone safety profiles than its predecessor tenofovir disoproxil fumarate (TDF). Since 2015, TAF was approved by the U.S. Food and Drug Administration (FDA) as the first-line treatment of HIV in adults and adolescents. It is recommended as the preferred nucleotide analogue reverse transcriptase inhibitor (NRTI) backbone of the ART in the current HIV treatment guidelines [3, 4]. Since TAF has become more widely available, sporadic cases of acute kidney injury in patients using TAF is increasing [5–9]. Here we present a patient with TAF-containing ART regimen who came to our hospital with kidney injury.
Case presentation
The patient was a 49-year-old Thai female with HIV infection, hypertension, and dyslipidemia. She was diagnosed with HIV infection since 1997 and had been exposed to multiple antiretroviral medications. In October 2001, she finally achieved undetectable viral load (<50 copies/mL). In November 2015, she started to use TDF-based ART, which was TDF, emtricitabine (FTC), and lopinavir/ritonavir (LPV/r). Her serum creatinine and estimated glomerular filtration rate (eGFR) by CKD-EPI were stable at <1 mg/dL and >80 ml/min/1.73m² since then.

In October 2019, her regimen was switched to a once daily, fixed dose combination pill containing TAF 25 mg, FTC 200 mg, and dolutegravir (DTG) 50 mg (TAF/FTC/DTG). Three months after she had changed her regimen (January 2020), serum creatinine increased from baseline of 1.05 mg/dL to 1.47 mg/dL. At 6 months follow-up (April 2020), her serum creatinine continuously increased to 2.30 mg/dL which prompted further investigation as described below.

Other concomitant medications included amlodipine 5 mg/day for hypertension and atorvastatin 20 mg/day for dyslipidemia. However, in January 2020, her hypertension was not well controlled and amlodipine was increased to 10 mg/day.

Investigations
The patient’s baseline serum creatinine was within 0.8–1.0 mg/dL and eGFR (CKD-EPI) was within 70–85 mL/min/1.73m² as shown in Fig. 1. Retrospective review of the medical record showed that she had persistent red blood cells (RBC) within the range of 3–5 cells/high power field (HPF) in urine and 1+ proteinuria for nearly eight years.

After starting of TAF/FTC/DTG, her serum creatinine was rapidly increased to 2.30 mg/dL and eGFR declined to 24 mL/min/1.73m². Creatine phosphokinase (CPK) was within the normal range. Ultrasonography revealed a mild dilatation at the left pelvicalyceal system and mild hydronephrosis which could not be responsible for the significant deterioration of the patient’s renal function.

A kidney biopsy was then performed. From the light microscopic examination of the specimen, glomeruli with mild mesangial expansion and mesangial hypercellularity were detected (Fig. 2A). Some tubules showed apical blebs and disrupted brush border (Fig. 2B). Apoptotic tubular cells were occasionally seen (Fig. 2B). Eosinophilic intracytoplasmic inclusions in the proximal tubular epithelial cells resembled to megamitochondria were identified in a few tubules (Fig. 2C). Immunofluorescence study showed granular staining of IgA 3+ and C3 1+ in the mesangium. The pathological findings were compatible with IgA nephropathy (Oxford classification M1 E0 S1 T1 C0) with acute tubular injury suspected to be from drug toxicity (tenofovir).

Treatment and outcome
Since the patient’s renal function continuously declined, TAF/FTC/DTG was discontinued. Lopinavir/ritonavir and low dose lamivudine were prescribed thereafter. After TAF/FTC/DTG was discontinued for 2 months, her serum creatinine decreased to 1.82 mg/dL and

![Graph](image-url)

**Fig. 1** The patient’s serum creatinine and eGFR (CKD-EPI creatinine equation) before and after starting TAF/FTC/DTG
eGFR improved from 24 to 32 mL/min/1.73m². Her renal function was stabilized within the eGFR range of 35–40 mL/min/1.73m² during the next 6 months. The patient had no hypophosphatemia or hypokalemia. After renal function was steady, amlodipine was switched to losartan to reduce proteinuria and control the blood pressure. Patient’s proteinuria was stable at 1.5–2 g/day during the follow-up periods after the initiation of losartan. Urine RBCs was persistently positive for 1–5 cells/HPF. After discussed with the patient regarding eGFR, proteinuria, and hypertension, kidney biopsy will be reperformed if these parameters are worsened, and corticosteroid is planned if there is a significant progression of IgA nephropathy.

**Discussion**

This article presented a case report of the HIV-infected patient who had an acute kidney injury while receiving TAF/FTC/DTG. Her renal function had been stable for many years with the TDF-containing ART, before switching to the culprit regimen. Many possibilities are needed to be discussed of how her renal function was deteriorated.

First, the pathological findings suggested that the patient had a significant acute tubular injury which could have been caused by tenofovir toxicity. Tenofovir (TFV)- associated nephrotoxicity have long been described. It is more well-known with TDF which is a prodrug of TFV. TDF is converted to TFV in plasma and can damage the
mitochondria of the proximal tubular cells [10]. Conversely, TAF is another TFV prodrug that is more stable in the plasma and is converted to TFV intracellularly [11]. Previous studies showed that therapeutic dose of TAF has a better renal safety profile compared with TDF, due to the fact that the level of TFV in the plasma is lower, hence lessens the exposure of proximal tubular epithelial cells to TFV [12–14]. However, TFV from TAF is still renally excreted and may cause tubular injury [15–17]. A pharmacokinetic study of a single-dose TAF administered to severe renal impairment participants with eGFR 15–29 mL/min/1.73m² resulted in higher TAF and TFV plasma levels compared to the matched normal healthy controls with eGFR ≥ 90 mL/min/1.73m² [18]. As a result, one can postulate that in patients with baseline renal insufficiency, the regular dose of TAF could result in higher plasma TFV level and lead to higher risk of kidney injury, compared with the normal eGFR patients. Case reports of TAF-associated nephrotoxicity were reviewed and shown in Table 1. [5–9]. Most of the cases had either underlying renal abnormalities or concurrent use of nephrotoxic medications. These renal diseases and co-medications possibly put the patients at risk of kidney injury in this patient. However, the combination of both, had an effect on the patient’s renal function.

Second, DTG can inhibit organic cation transporter 2 (OCT2) at the basolateral membrane of the proximal renal tubular cells which mediates tubular uptake of creatinine, results in decreasing of creatinine clearance and rising of serum creatinine without changing the true glomerular filtration rate [21–23]. From previous studies, estimated decrease in creatinine clearance was approximately 10–14% from baseline, and increase of serum creatinine of less than 0.5 mg/dL [21, 24–27]. The serum creatinine are usually stabilized after 2–4 weeks of DTG initiation [25–27]. It is possible that DTG could partly contribute to the rising of serum creatinine in this patient. However, her renal function continued to decline beyond the threshold of DTG effect, thus it is unlikely that DTG was the sole cause of an acute kidney injury. However, there are still limited information of the pharmacokinetic and drug interaction between DTG and TAF in the Asian population. In a large randomized controlled trial of DTG and TAF conducted in African patients with creatinine clearance higher than 60 mL/min showed that the combination of DTG and TAF had minimal adverse effects [28]. However, pharmacogenomic of DTG and TAF in Asians might be different from Africans. It is possible that this combination might increase the plasma and intracellular TFV to the toxic levels. Additional pharmacokinetics studies of DTG in combination with TAF in Asian population are needed.

IgA nephropathy could have caused the patient’s abnormal urinary sediments and proteinuria for many years before this presentation. IgA nephropathy is the most common primary glomerular disease in Asia and has been associated with various inflammatory and infectious diseases, including HIV infection [29, 30]. This patient might develop IgA nephropathy since 2012 when she started having microscopic hematuria and proteinuria. The pathological findings based on the Oxford (MEST) classification; mesangial hypercellularity (M1), segmental glomerulosclerosis (S1), and tubular atrophy and interstitial fibrosis (T1) were all described as poor prognostic markers for IgA nephropathy [31–35]. Thus, IgA nephropathy could be partly responsible to renal function deterioration in our case. However, the improvement and stabilization of renal function after TAF discontinuation and before the initiation of losartan cannot be exclusively explained by IgA nephropathy.

There are also some limitations in our report. Although there was a pathological evidence of tubular injury from tenofovir from the kidney biopsy, our case did not have other laboratory abnormalities associated with proximal renal tubulopathy such as glucosuria, phosphaturia, hypophosphatemia, hypokalemia, or metabolic acidosis. However, certain group of patients can have tenofovir-associated nephrotoxicity without classical laboratory abnormalities as previously been reported [10, 36]. Since the kidney pathology showed both the characteristics of IgA nephropathy and tenofovir-nephrotoxicity, it is worth to keep in mind that the combination of both, rather than the single entity, had an effect on the patient’s renal function.

In conclusion, the temporal relationship of the event in our case suggested that the cause of acute kidney disease could be multifactorial. However, the evidence from kidney biopsy informed that the possibility of TAF-associated nephrotoxicity could not be omitted. Clinicians should be aware of this adverse effect of TAF, especially when the drug is prescribed in patients with an underlying renal disease. In these patients, renal...
### Table 1  Case reports of acute kidney injury associated with tenofovir alafenamide use

| Clinical feature | Novick TK et al. 2017 [9] | Serota DP et al. 2018 [8] | Alvarez H et al. 2018 [7] | Bahr NC et al. 2019 [6] | Heron JE et al. 2020 [5] | The present case |
|------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-----------------|
| Age (years)      | 58                       | 70                       | 51                       | 54                       | 46                       | 49              |
| Sex              | Male                     | Male                     | Male                     | Male                     | N/A                      | Female          |
| Ethnic           | African American         | N/A                      | Caucasian                | N/A                      | Asian                    | Asian           |
| Co-infection     | HCV                      | HCV                      | HCV                      | None                     | HCV                      | None            |
| Co-morbidities   | Cirrhosis, Diabetes, Drug abuse | Cirrhosis, Alcohol use | None                     | Dyslipidemia, Hypothyroidism | Hodgkin lymphoma | Hypertension, Hypothyroidism, IGA nephropathy |
| Viral load (copies/mL) | 14,000                  | > 1 million              | 38                       | suppressed              | N/A                      | < 50            |
| CD4 (cells/µL)   | 367                      | 100                      | 587                      | N/A                      | N/A                      | 1,096           |
| TDF exposure     | 2 years                  | None                     | 6 years                  | 10 years                 | Yes                      | 4 years         |
| Baseline Cr (mg/dL) | 0.9                     | 1.2                      | 0.59                     | N/A                      | N/A                      | 1.05            |
| Baseline CrCl    | N/A                      | 50 mL/min                | N/A                      | N/A                      | N/A                      | 63.5 mL/min/1.73 m² |
| Baseline proteinuria | UPO 0.27 g/gCr         | N/A                      | N/A                      | N/A                      | Protein 2+               | None            |
| Regimen          | TAF/FTC+DRV/c            | EVG/c/FTC/TAF            | EVG/c/FTC/TAF (intentional overdose) | TAF/FTC+DRV/r+RAL | TAF+FTC+DRV/c | TAF/FTC/DTG |
| Significant concurrent medications | None                    | None                     | None                     | Carboplatin, Gentamicin | None                    | None            |
| Duration of TAF prior to presentation | 2 months                | 3 months                 | 9 months                 | 2 months                 | N/A                      | 3 months        |
| Presentation     | Oliguric acute kidney injury with volume overload | Acute kidney injury with hyperkalemia and non-anion gap metabolic acidosis | Acute kidney injury | Fanconi syndrome | Renal proximal tubulopathy (hypophosphatemia, hypokalemia, glucosuria, and proteinuria) | Acute kidney injury with proteinuria and hematuria |
| Cr at diagnosis (mg/dL) | 4.0                     | 5.2                      | 2.15                     | 5.56                     | 0.76                     | 2.30            |
| Proteinuria      | 24-h urine protein 8.5 g/day | 24-h urine protein 6.3 g/day | No proteinuria | N/A                      | UPCI 1.36 g/g | Protein 3+ |
| Urine sediments (cells/HPF) | RBC 5                   | RBC 3                    | N/A                      | N/A                      | N/A                      | RBC 5–10 |
| Kidney biopsy    | Diabetic nephropathy, focal glomerular hypercellularity, immune complex deposition, and mitochondrial injury | Not done                 | Not done                 | Not done                 | Not done                 | IgA nephropathy, and acute tubular injury with megamitochondria |
| Treatment        | Acute dialysis, TAF-containing regimen was stopped | TAF-containing regimen and ledipasvir were stopped | TAF-containing regimen was stopped | Gentamicin was stopped | TAF-containing regimen was stopped | None            |
| Outcome          | Recovery (4 weeks after discharge, Cr was 0.9 mg/dL) | Recovery (12 weeks after discharge, Cr was 1.32 mg/dL) | Recovery (Cr returned to baseline level after 2 weeks) | Recovery (Cr returned to baseline level after 3 months) | Recovery of tubulopathy | Improvement of Cr (2 months after TAF was discontinued, Cr was 1.82 mg/dL) |
Table 1 (continued)

| Clinical feature | Novick TK et al. 2017 [9] | Serota DP et al. 2018 [8] | Alvarez H et al. 2018 [7] | Bahr NC et al. 2019 [6] | Heron JE et al. 2020 [5] | The present case |
|------------------|---------------------------|---------------------------|--------------------------|-------------------------|-------------------------|------------------|
| Possible explanations | TAF and comorbidities | Drug-drug interaction between Ledipasvir, cobicistat, and TAF | Drug overdose of cobicistat and TAF | TAF | Sepsis and lymphopenia leading to TAF and gentamicin toxicities | TAF and comorbidities |

DRV/c: Darunavir/Cobicistat; DRV/r: Darunavir/Ritonavir; EVG/c/FTC/TAF: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide; RAL: Raltegravir; UPCI: Urine protein creatinine index
function should be closely monitored after the initiation of TAF. Literature reviews of TAF-associated nephrotoxicity are summarized in Table 1, which the general prognosis was good and renal function could spontaneously recover after the withdrawal of the medication.

Abbreviations
ART: Antiretroviral therapy; Cr: Creatinine; CrCl: Creatinine clearance; CPK: Creatine phosphokinase; DRV/c: Darunavir/Cobicistat; DRV/r: Darunavir/Ritonavir; DTG: Dolutegravir; EFV: Efavirenz; eGFR: Estimated glomerular filtration rate; EVG/c/FTC/TAF: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide; FTC: Emtricitabine; HPF: High power field; LPV/r: Lopinavir/Ritonavir; OCT2: Organic cation transporter 2; RAL: Raltegravir; RBC: Red blood cells; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate; TFV: Tenofovir; UPCI: Urine protein creatinine index; WBC: White blood cells.

Acknowledgements
The authors would like to thank June Ohata for English editing of the manuscript. The authors thank to Tuberculosis Research Unit, Faculty of Medicine, Chulalongkorn University for providing the support in this study.

Authors’ contributions
TU prepared the first draft of this manuscript. JS, KI, and SU reviewed the pathology of the specimens and provided images for the manuscript. SC, AA, YA, and SU reviewed and edited the manuscript. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors have read and approved the final manuscript.

Declaration
TU is supported by Second Century Fund (C2F) for post-doctorate researcher, Chulalongkorn University. Funders had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

Availability of data and materials
All data are presented in the manuscript. Additional data are available on reasonable request.

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Received: 7 January 2021   Accepted: 12 August 2021
Published online: 21 August 2021
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