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BRIEF REPORT

Tenofovir Alafenamide in Multimorbid HIV-Infected Patients With Prior Tenofovir-Associated Renal Toxicity

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Although the use of tenofovir alafenamide (TAF), a new prodrug of tenofovir, was safe and efficacious in clinical trials, real-world data from multimorbid individuals are scarce. Among 10 persons living with HIV with previous tenofovir disoproxil fumarate–induced nephrotoxicity, renal function remained stable, and proteinuria decreased in several patients after the switch to TAF.

Keywords. antiretroviral therapy; chronic kidney disease; drug nephrotoxicity; tenofovir alafenamide.

As HIV-infected populations are aging, noncommunicable diseases and long-term toxicity of antiretroviral therapy (ART) emerge as important determinants of HIV clinical management [1]. The use of tenofovir disoproxil fumarate (TDF) is associated with a loss in bone mineral density (BMD) and the development of proximal tubular renal dysfunction, with the potential progression to Fanconi syndrome characterized by phosphaturia, glucosuria, tubular proteinuria, and proximal renal tubular acidosis [2–5]. Tenofovir alafenamide (TAF), a new tenofovir (TFV) prodrug, leads to reduced TFV plasma levels, while maintaining high intracellular TFV concentrations in target cells, decreasing the risk for renal toxicity. TAF offers a safe and effective therapeutic option for both treatment-naïve and -experienced HIV/hepatitis B virus (HBV)–coinfected [6] and HIV-monoinfected patients [7, 8]. In patients with renal impairment, the prevalence of significant proteinuria decreased from 42% to 11% 1 year after the switch to TAF [9]. However, despite improvements in renal tubular markers and BMD with TAF, no study has shown a relevant improvement in glomerular filtration. Although serum lipids improve with TDF, this is not the case with TAF [10]. In a recent meta-analysis, TAF was associated with a 1% greater risk of being started on lipid-lowering therapy over 48 weeks of follow-up [11]. However, these changes in lipid profile have not been linked to an elevated cardiovascular risk to date.

Despite recent evidence on the safety and efficacy of TAF in large clinical trials, real-world safety data from cohorts of heavily treatment-experienced, multimorbid patients are scarce [12–14]. We present the first cases of persons living with HIV (PLHIV) with TDF-associated renal toxicity in whom TDF was replaced by TAF in a single center in Switzerland.

ILLUSTRATIVE CASE

In 2007, a 54-year-old HIV/HBV/hepatitis C virus (HCV)-coinfected woman previously exposed to all antiretroviral drug classes, developed phosphaturia with hypophosphatemia, worsening estimated glomerular filtration rate (eGFR) and osteoporosis on a TDF-containing regimen (Table 1, patient 1, and Figure 1). After TDF was stopped, she remained virologically suppressed on etravirine, ritonavir-boosted darunavir and raltegravir, but her medical history was complicated by recurrent cerebral vasculitis and severe osteoporosis. After TDF was stopped, HBV infection was treated with lamivudine monotherapy for 4 years, until viral failure occurred, with documented resistance to lamivudine and entecavir (L80V, L180M, M204I, 184S). Therefore, TDF was reintroduced in 2014, but had to be stopped shortly thereafter due to acute renal failure (eGFR drop from 71 to 41 mL/min/1.72 m^2) with proteinuria, phosphaturia, hypophosphatemia and hypokalemia, suggesting generalized proximal tubular dysfunction. In the context of the worsening cerebral vasculitis, a potential extrahepatic manifestation of HBV and HCV, F/TAF was initiated and the HBV viral load decreased from 9.39 log10 to 2.42 log10 copies/mL over 32 months. Incomplete virological response after years of TDF treatment has been reported in previous studies of HIV/HBV-coinfected patients [15, 16]. Concurrent HCV infection was successfully treated with sofosbuvir and ledipasvir. Despite a minimal decline in kidney function in the first two weeks after the introduction of TAF, it remained stable thereafter and the proteinuria resolved. Furthermore, no recurrence of the cerebral vasculitis was observed. In summary, the introduction of TAF in this patient with prior severe TDF toxicity was safe and offered treatment for her multidrug-resistant HBV infection.

METHODS

We included all PLHIV who switched to a TAF-containing regimen due to prior TDF-induced renal toxicity with a follow-up time on TAF of at least 12 months at Bern University Hospital,

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Table 1. Patient Characteristics at the Time of Switch from TDF to TAF

Patient	Sex, Age, y	Mode of HIV Aqcuisition	Year of Diagnosis	CD4+ Count/μL	HIV-RNA, cp/mL	Chronic HBV (Yes/No) and Resistance	CV Comorbidities	Renal Comorbidities	CKD Stage (KDIGO)	Bone Disease (Therapy)	Antiviral Therapy Before Switch to TAF	Antiviral Therapy After Switch to TAF
1	F, 53	IDU	1986	85	<20	Yes L80V, L180M, M204I, 184S	Hypertension, vasculitis, stroke	Proximal tubulopathy, prior Fanconi syndrome	G2A3	Osteoporosis (Zoledronat)	ETR+RAL+DRV/r	ETR+RAL+DRV/r+ FTC/TAF
2	M, 62	MSM	1992	1056	<20	Yes L180M, M204V	Generalized atherosclerosis with coronary heart disease	Prior Fanconi syndrome	G3bA3	Osteoporosis with fracture (planned)	ETR+DRV/r+DTG Entecavir	DRV/r +DTG + FTC/TAF
3	M, 76	HET	2002	443	<20	No	Metabolic syndrome	Proximal tubulopathy, renal stones	G3aA3	No	EFV+FTC/TDF	EFV+FTC/TAF
4	M, 52	IDU	1992	436	<20	No	Vasculitis	Proximal tubulopathy	G3aA1	No	ETR+RAL+3TC	DTG+FTC/TAF
5	M, 55	MSM	1985	831	<20	No	None	Renal phosphate leak	G2A1	Osteopenia	DRV/r+FTC/TDF	DRV/r+FTC/TAF
6	M, 54	HET	1993	582	<20	No	Stroke, HCV-associated porphyrea cutanea tarda	Proximal tubulopathy	G2A2	Osteopenia	DRV/r +ETR+ FTC/TDF	DTG+FTC/TAF
7	M, 53	MSM	2007	817	<20	No	None	Proximal tubulopathy	G3aA2	No	EVG/c+FTC/TDF	EVG/c+FTC/TAF
8	M, 54	IDU	2003	438	27	No	Peripheral artery occlusive disease	Renal phosphate leak	G2A2	Osteoporosis (Zoledronat)	DRV/r+DTG+3TC	DRV/r+DTG+ FTC/TAF
9	M, 80	HET	1996	795	<20	Yes L180M, M204V	Coronary artery disease	Proximal tubulopathy	G2A3	Osteoporosis (Zoledronat)	DTG+FTC/TDF	DTG+FTC/TAF
10	M, 72	MSM	1986	1032	<20	No	Dyslipidemia	Proxmial tubulopathy	G3aA3	Osteopenia	ETV+DRV/r+RAL+FTC/TDF	ETR+ DRV/r+RAL+ FTC/TAF

Abbreviations: 3TC, lamivudine; CKD, chronic kidney disease; CV, cardiovascular; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirin; EVG/c, elvitegravir/cobicistat; F, female; FTC, emtricitabin; HBV, hepatitis B virus; HCV, hepatitis C virus; HET, heterosexual; IDU, intravenous drug user; KDIGO, kidney disease: improving global outcome; M, male; MSM, men who have sex with men; NA, not applicable; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

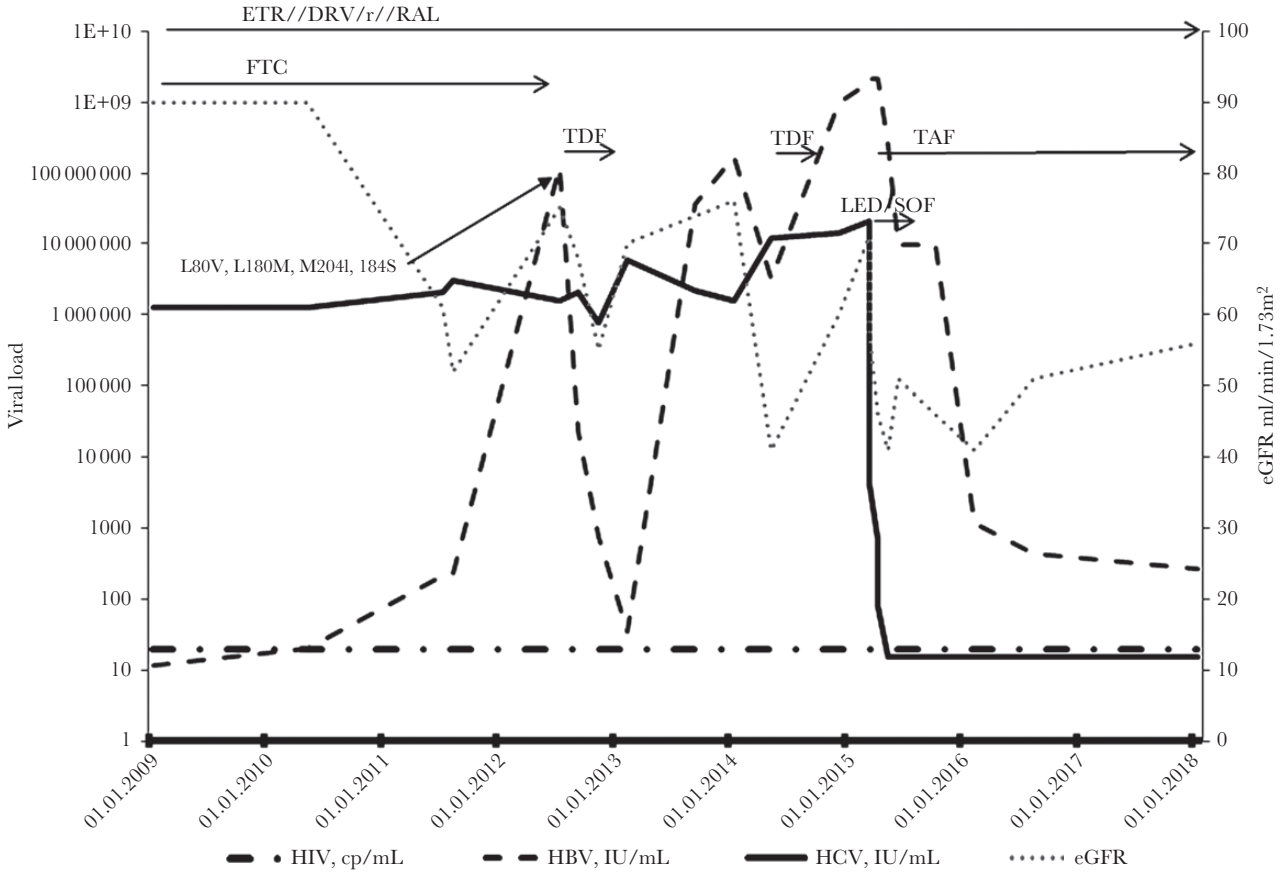

Figure 1. Virologic and renal parameters: HIV, HCV, and HBV treatment history before and during TAF treatment. Abbreviations: DRV/r, darunavir/ritonavir; eGFR, estimated glomerular filtration rate; ETR, etravirin; FTC, lamivudine; HBV, hepatitis B virus; HCV, hepatitis C virus; LED/SOF, ledipasvir/sofosbuvir; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

a site of the Swiss HIV Cohort Study (SHCS; www.shcs.ch). Medical charts were reviewed, and clinical and laboratory information, including HIV and HBV viral loads (VLs), serum lipid profile (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides), renal function (inorganic phosphate as well as creatinine and protein in serum and urine to calculate the urine protein to creatinine ratio [UPCR]), and results from bone mineral density (BMD) testing, was retrieved. Estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and significant proteinuria was defined as a UPCR of >20 mg/mmol. Generalized proximal tubular dysfunction (Fanconi syndrome) was defined as the presence of renal glucosuria, proteinuria, and phosphaturia with concomitant hypophosphatemia, with or without signs of proximal renal tubular acidosis. No statistical analysis was performed due to the small sample size. All patients were participants of the SHCS and signed an informed consent to participate. Before licencing of F/TAF in Switzerland in May 2017, the drug was obtained through a compassionate use program from Gilead Sciences. For each patient, approval by the Swiss Medical Agency (Swissmedic; www.swissmedic.ch) was obtained.

RESULTS

At the time of data analysis, 17 patients had switched from TDF to TAF. Of these, 10 patients with prior contraindications to TDF had at least 1 year of follow-up and were included in this analysis. The median age (interquartile range [IQR]) was 55 (53–70) years (Table 1). At the time of switch to TAF, all patients had a suppressed HIV VL, and the median CD4 cell count (IQR) was 688 (437–828) cells/μL. Participants were heavily treatment-experienced (median time on ART, 19 years) and had numerous changes of drug classes due to virological failure, side effects, and potential long-term toxicity. Nine patients had significant, mostly cardiovascular comorbidities, and 7 had more than 3 comedications. Osteoporosis was documented in 4 patients at baseline, and osteopenia was documented in 3. Three patients had concomitant chronic HBV infection, and 2 had a chronic HCV infection. The reason for switching to TAF was the presence of Fanconi syndrome (2/10), proximal renal tubulopathy (elevated phosphate excretion fraction (FE-Pi) with or without proteinuria) (7/10), and progressive chronic kidney disease with proteinuria (1/10). Six patients were directly switched from TDF to TAF, whereas in 4 patients TDF had to be stopped earlier (median, 13 months before TAF initiation). In the 3 patients with HBV coinfection, TAF was the only HBV active drug: 2 individuals

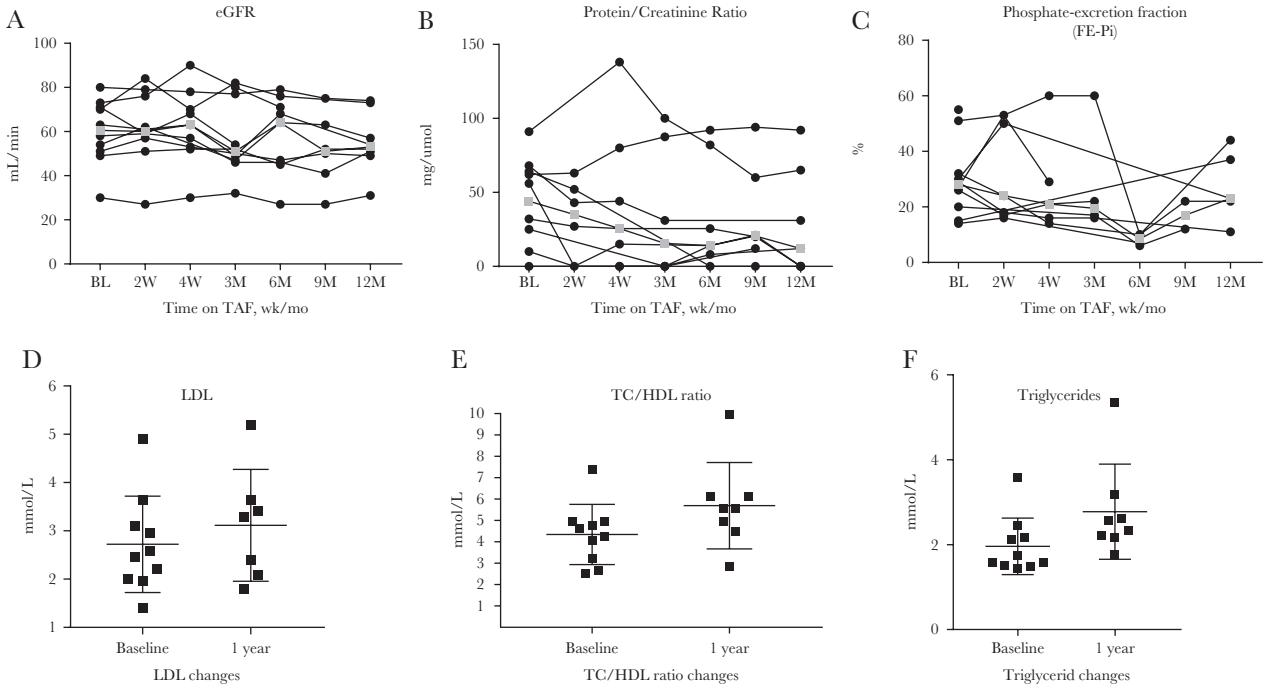

Figure 2. Trends of eGFR (A), urinary protein/creatinine ratio (B), and phosphate-excretion fraction (C) during the first 12 months after introduction of TAF in 10 patients with prior TDF toxicity. Each line represents an individual patient; gray dots indicate means. D–E, Serum lipid profile before and after 12 months of TAF therapy. Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

had intermediate resistance to entecavir (L180M, M204V), and 1 was fully resistant (L80V, L180M, M204I, 184S). All patients had impaired renal function (median eGFR [IQR], 61 [52–71] mL/min). Eight had a phosphate excretion fraction (FE-Pi) >20%, of whom 7 had hypophosphatemia. Proteinuria was found in 7 patients (5/6 currently on TDF), and the median UPCR (IQR) was 28 (22–32) mg/mmol.

During follow-up, patients remained HIV-suppressed, except for a single blip (69 copies/mL) in 1 patient, and HBV VL was undetectable in 2 of 3 coinfected patients. In the third patient, HBV VL decreased but remained detectable (see the case report above). Renal glomerular function remained stable, with a median change in eGFR (IQR) at 12 months of –0.5 (–3 to +3) mL/min (Figure 2A). No Fanconi syndrome or other acute kidney injury was observed during the first year of TAF. Only small changes in tubular markers were seen (Figure 2C), and the proportion of patients with a significant proteinuria (>20 mg/mmol) decreased from 70% to 30% (Figure 2B). Consequently, CKD stage improved in 4 of 10 patients (3 of them directly switched from TDF to TAF; for the fourth patient, see the case report above). Nearly all patients experienced a rise in serum LDL (median level at switch: 2.5 mmol/L [96.78 mg/dl], at 1 year: 3.29 mmol/L [127.22 mg/dL]), total cholesterol/HDL ratio (median ratio at switch: 4.45, at 1 year: 5.55) and serum triglycerides (median level at switch: 1.7 mmol/L [65.73 mg/dL], at 1 year: 2.5 mmol/L [96.78 mg/dL]) during the study period (Figure 2D–F). There were no adverse events attributed to TAF, and no cardiovascular events occurred. One patient died during follow-up for reasons not related to the ART regimen.

DISCUSSION

In our case series of 10 multimorbid patients switched to TAF with prior TDF-associated kidney injury, renal function remained stable over the first year, whereas proteinuria improved in several patients. Our findings support the use of TAF in HIV-monoinfected and HIV/HBV-coinfected patients with severe TDF-related toxicity, but prospective, long-term studies in similar populations are needed to confirm our findings.

The reversibility of TDF-associated kidney injury remains uncertain: recovery of kidney function (eGFR) after TDF cessation is generally reported in patients with acute, but not chronic, kidney disease [17–19]. Changes in eGFR usually occur late in the context of TDF-associated proximal tubulopathy and might represent irreversible injury [17, 18]. Importantly, as many other comorbidities contribute to CKD (eg, hypertension, dyslipidemia), the interruption of TDF alone might be insufficient to improve renal function. Nevertheless, the proportion of patients with significant proteinuria dropped from 70% at baseline to 30% after 1 year of TAF in our study. As a consequence, CKD stage improved in 4 of 10 patients, which is more than previously reported [9]. In 1 patient (see the case report) who initiated TAF years after TDF cessation, proteinuria resolved with concomitant HCV treatment, emphasizing the importance of the elimination of other factors potentially

contributing to renal injury. Although 2-year follow-up data from a study of patients who switched to TAF with prior renal impairment were reassuring [20, 21], its long-term safety profile remains uncertain. Interestingly, 2 cases of acute nephrotoxicity in cirrhotic patients receiving an ART regimen including TAF and cobicistat were recently reported [22, 23]. Although these findings suggest that TAF could potentially be associated with the occurrence of acute nephropathy, no patient in our series developed renal injury despite their high-risk profile.

The lipid profile worsened in most patients after the switch to TAF. However, the impact of this change on cardiovascular risk in these multimorbid patients remains unclear. Surprisingly, the effect was also seen in 3/4 patients who had interrupted TDF months before the introduction of TAF, which argues against the protective effect of TDF as the only cause for the changes in lipid values.

In conclusion, in this case series of multimorbid HIV-infected patients with contraindications to TDF, TAF was well tolerated and led to a reduction in proteinuria in several patients. We observed no improvement in glomerular function and no consistent changes in other tubular markers during the first year of therapy. Long-term effects of TAF on renal function and BMD, as well as on plasma lipids, need to be evaluated in dedicated long-term prospective studies.

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