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Short Communication: Resolution of Tenofovir Disoproxil Fumarate Induced Fanconi Syndrome with Switch to Tenofovir Alafenamide Fumarate in a HIV-1 and Hepatitis B Coinfected Patient

Maile Young Karris

Abstract

Fanconi syndrome is a rare adverse effect of tenofovir disoproxil fumarate (TDF). Tenofovir alafenamide fumarate (TAF) is a novel prodrug with less nephrotoxicity. We report resolution of Fanconi syndrome in a HIV and hepatitis B coinfected patient switched from TDF to TAF.

Keywords: HIV, hepatitis B, tenofovir alafenamide, Fanconi syndrome

Introduction

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir (TFV) that is approved for the chronic management of HIV and Hepatitis B virus (HBV). In most persons with HIV and HBV coinfection, TDF is not only highly efficacious but also very well tolerated.[2] In persons living with HIV and HBV, TDF has been associated with a small increased risk of nephrotoxicity that in rare circumstances progresses to a severe renal tubulopathy that is characterized by phosphaturia and subsequent hypophosphatemia, renal glucosuria, aminoaciduria, tubular proteinuria, and proximal renal tubular acidosis (Fanconi syndrome).[1] TDF mediated nephrotoxicity is thought to be due to accumulation of TDF in proximal tubules of the kidneys resulting in local mitochondrial toxicity.[3] This effect appears exacerbated by increased plasma TFV concentrations.[4]

In persons living with HIV, the new prodrug tenofovir alafenamide fumarate (TAF) demonstrates an equivalent *in vivo* potency to TDF at 30-fold lower the dose resulting in 91% lower plasma TFV concentrations.[5] This results in a more favorable safety and tolerability profile of TAF containing regimens compared to TDF.[6] Pozniak *et al.* recently published a study evaluating HIV infected persons with mild to moderate renal impairment (estimated creatinine clearance or CrCl 30–69 ml/min) who switched from variable antiretroviral therapy (ART) regimens (65% on TDF, 22% on abacavir, and 5% on a nucleos(t)ide-free regimen) to daily TAF coformulated with cobicistat, elvitegravir, and emtricitabine (EVG/COBI/FTC/TAF).[7] In the participants enrolled, there was minimal change in estimated glomerular filtration rate (eGFR), but significant improvements in proteinuria, albuminuria, and bone mineral density. Despite the growing body of literature supporting the safer profile of TAF compared to TDF in HIV, less is known about the safety and efficacy of TAF in persons coinfected with HIV and HBV or in those with history of TDF-associated renal disease in real-world experiences. In this study we describe an experience with TAF in a patient with HIV and HBV who developed TDF associated renal tubulopathy.

Case Report

A 61-year-old man with HIV and HBV coinfection and chronic kidney disease stage 3 was transferred to our clinic in April 2014 on ritonavir-boosted fosamprenavir and lamivudine/abacavir with an undetectable HIV viral load and CD4 T cell count 320 cells/μL (36%). He was diagnosed with HIV in 1984 and started on zidovudine monotherapy followed by didanosine+dideoxycytidine and other regimens that he could not specifically recall. In this first visit, he reported the recent discontinuation of TDF due to kidney injury. He was treated with TDF in 2008 and recalled it caused kidney injury then as well. Initial laboratory evaluation revealed serum creatinine (Cr) of 1.81 mg/dl (normal range 0.67–1.17 mg/dl) and eGFR of 41.5 ml/min (by Cockcroft–Gault equation). Urinalysis was positive for 1+ protein, 2+ glucose (in the setting of normal serum glucose), and HBV DNA 278 IU/ml.

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Table 1. Laboratory Tests and Medications from April 2014 to June 2016

Laboratory tests	*March 2014*	*April 2014*	*May 2014*	*August 2014*	*September 2014*	*January 2015*	*August 2015*	*September 2015*	*November 2015*	*December 2015*	*March 2016*	*June 2016*	*Medications*
													FPV/r+3TC/ABC
													TDF
													FTC/TAF
													DRV/r+DTG
Creatinine (0.67–1.17 mg/dl)		1.81	1.84	1.66	1.91	1.74	2.1	1.43	1.93	1.66	1.74	1.82	
eGFR[a] ml/min by Cockcroft–Gault equation		41.5	40.8	44.9	39.1	40	33	60	42	42	40	41	
Alkaline phos. (40–129 U/liter)		57	57	104	53	54	54	61	56	49	71	51	
ALT (0–41 U/liter)		30	27	251	42	39	22	18	37	31	36	17	
AST (0–40 U/liter)		29	26	119	29	24	23	23	27	31	27	17	
Phosphorous (2.7–4.5 mg/dl)				3.9		3				2.4	4	3.3	
Hepatitis B DNA		278		$>3\times10^6$	1×10^5	132	<20	3920	<20	<20	UD	UD	
HIV viral load[b] copies/ml		UD		UD		UD	<20	<20	<20			UD	
Dipstick protein		1		1	1	1	1	tr	1	1	neg	neg	
Dipstick glucose		2		neg	neg	small	neg	tr	neg	neg	neg	neg	
Urine Protein: Cr		0.57	0.55	0.21		0.29				0.27	0.18	0.19	
Urine β2: Cr (0–300 μg/g Cr)			49,950									15,822	

Time on medications indicated by shading. Normal laboratory reference ranges in parenthesis. Blank values indicate tests not performed at that interval.

[a]eGFR calculated by Cockcroft–Gault equation.

[b]Laboratory reports HIV viral load as undetectable when there is no signal and <20 when a positive signal exists but cannot be quantified.

3TC, lamivudine; ABC, abacavir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DRV, darunavir; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; FPV, fosamprenavir; FTC, emtricitabine; Neg, negative; r, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; tr, trace; UD, undetectable.

Liver enzymes were normal. HBV genotype suggested resistance to lamivudine and entecavir, but sensitivity to TFV and adefovir [drug resistance mutations L180M, S202G, and M204V of the HBV polymerase region (Pol/RT)].

Nephrology evaluation confirmed that his presentation was consistent with Fanconi syndrome likely due to TDF after ruling out other possible causes and recommended avoidance of future TDF use. He was also not deemed a candidate for adefovir given chronic renal dysfunction and the ongoing risk of renal tubulopathy and hepatology consultation expressed concern that interferon therapy may result in hepatic decompensation. Thus the patient remained off TDF for the next 5 months with close monitoring. Off TDF his kidney function slightly improved to Cr 1.67 mg/dl (GFR 45.6 ml/min) with urinalysis demonstrating 1+ protein but no glycosuria. However his HBV DNA increased to over 3×10^6 IU/ml accompanied by a rise in alanine aminotransferase (ALT) from 29 to 251 U/liter and aspartate aminotransferase (AST) from 19 to 119 U/liter. Hepatology evaluation confirmed cirrhosis with HBV flare and determined he was not a candidate for liver transplant due to intermittent methamphetamine use and a lack of social support. Given the risk of death due to HBV-associated liver disease, TDF coformulated with emtricitabine (FTC/TDF) was resumed at a renally adjusted interval (thrice a week) with a plan to eventually transition to chronic hemodialysis.

At this point, compassionate use of TAF was pursued. On April 1, 2015 the U.S. Food and Drug Administration approved a single patient investigational new drug application (No. 126033). The patient gained access to TAF in the form of FTC/TAF September 2015 after approval from the local institutional review board.

While awaiting access to TAF, a GenoSure Archive (Monogram Biosciences, San Francisco, CA) was performed that demonstrated class-wide nucleos(t)ide reverse transcriptase inhibitor drug resistance. He was switched to ritonavir-boosted darunavir (DRV/r), with the addition of dolutegravir (DTG) and continued on FTC/TDF thrice a week. As expected on TDF, his kidney dysfunction slowly progressed with Cr 2.1 mg/dl (GFR 35 ml/min) accompanied by low grade proteinuria and glycosuria, but liver function tests normalized in December 2014 and HBV became undetectable in August 2015 (Table 1 and Fig. 1). On August 31, 2015 the patient stopped all HIV medications, including FTC/TDF, in response to acutely worsening kidney function and in anticipation of imminent FTC/TAF start. Laboratory tests ordered while off all antiretrovirals, including TDF and just before start of TAF, revealed improved kidney function (Cr 1.43 mg/dl and GFR 61 ml/min with detectable trace proteinuria and glycosuria) but detectable HBV (3,920 IU/ml). He restarted DRV/r+DTG and initiated daily FTC/TAF (200 mg of FTC and 10 mg of TAF) on September 20, 2015.

On F/TAF, he demonstrated a slight improvement in his GFR (40–46 ml/min) and 9 months after switching had improvement of proteinuria (by urinalysis and quantitative protein to creatinine and $\beta 2$ microglobulin to creatinine ratios) and resolution of glycosuria. Of note urine protein to creatinine and $\beta 2$ microglobulin to creatinine ratios were used in concert with urinalysis as a more accurate assay for proteinuria and renal tubular damage. He did not complain of any notable adverse effects with TAF initiation. HBV became quickly undetectable and he did not experience another HBV flare.

Discussion

This case represents the first published experience of use of TAF in a HIV and HBV coinfected patient with TDF induced renal tubulopathy. FTC/TAF was well tolerated and did result in both HIV and HBV virologic control. As consistent with TAF use in persons with chronic kidney disease, the

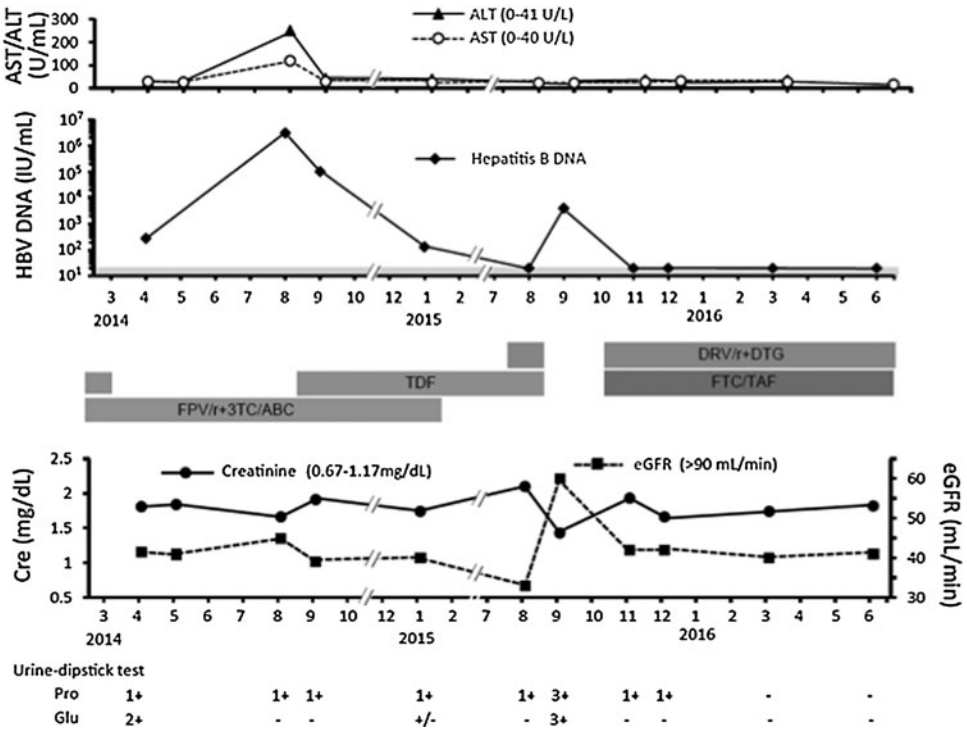

FIG. 1. Graphical representation of the patients' laboratory tests and timing of antiretrovirals. Months are represented by number (i.e., March is 3). 3TC, lamivudine; ABC, abacavir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; DRV, darunavir; DTG, dolutegravir; eGFR, estimated glomerular filtration rate calculated by Cockcroft–Gault equation; FPV, fosamprenavir; FTC, emtricitabine; Glu, glucose; HBV, hepatitis B virus; Pro, protein; r, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

eGFR did not significantly change with switch to TAF, but tubular damage did improve as evident by glycosuria (by urinalysis) and proteinuria (by urinalysis and protein to creatinine ratios).[7]

TAF is believed to have an improved safety profile due to (1) equivalent efficacy at significantly lower plasma levels of TAF and subsequently plasma TFV and (2) unlike TDF, TAF does not appear to be a substrate of organic anion transporters that are thought to contribute to the accumulation of TFV in the proximal tubules.[8] In a recent study evaluating virologically suppressed patients with renal impairment, a small proportion of patients (2% [5/242]) discontinued EVG/COBI/FTC/TAF due to decreased creatinine clearance, but none had evidence of proximal tubulopathy. However, these cases are confounded as all had a secondary reason for progression such as uncontrolled hypertension. Interestingly, in this study, two participants with a history of TDF induced Fanconi syndrome demonstrated stable eGFR and had reductions in proteinuria.[9] This study, our experience, and previously reported case reports of TAF use in the setting of Fanconi syndrome suggests that TAF may have a particularly beneficial role in persons with TDF-induced renal tubular disease.[10,11] However, one limitation in the translatability of this patient's experience is that he had access to FTC/TAF dosed at 200/10 mg due to concurrent dosing with r/DRV. Whether the FDA-approved dosage of FTC/TAF at 200/25 mg provides similar benefit to persons with tubular nephropathy when combined with a boosted protease inhibitor remains unknown.

The ability of TAF to control HBV replication also supports the use of this antiviral in persons coinfected with HIV and HBV. In fact, in our patient, the use of TAF was purely to control HBV as he had essentially maintained virologic control of HIV with DRV/r+DTG (due to widespread nucleos(t)ide resistance on GenoSure Archive). TAF at 25 mg has demonstrated similar efficacy to TDF in monoinfected HBV with significantly less bone and renal toxicity up to week 48 of use.[12] One ongoing clinical trial is evaluating the impact of simplification to EVG/COBI/FTC/TAF from TDF-based ART regimens in HIV and HBV coinfected persons. Similar to our experience, persons that transitioned to EVG/COBI/FTC/TAF maintained HBV viral suppression, improved eGFR, and bone turnover markers.[13]

Conclusion

In clinical trials of persons living with HIV, TAF demonstrates efficacy and a favorable safety and tolerability profile even in persons with mild to moderate kidney dysfunction. Ongoing research will elucidate whether long-term use of TAF in HBV mono and HBV/HIV coinfected persons will continue to be efficacious, safe, and well tolerated. However, in one patient coinfected with HIV and HBV, we demonstrate that switching from TDF to TAF did result in improved markers of renal tubulopathy and sustained virologic control of HIV and HBV.

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