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Tenofovir Disoproxil Fumarate-Associated Fanconi Syndrome in an HIV-Uninfected Man Receiving HIV Pre-Exposure Prophylaxis

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Tenofovir disoproxil fumarate (TDF) has been used worldwide in antiretroviral regimens of human immunodeficiency virus (HIV)-infected patients since being approved by the US Food and Drug Administration in 2001. Tenofovir disoproxil fumarate can cause renal tubular dysfunction and reduced renal function [1]. In its fully developed form, TDF renal dysfunction is associated with hypophosphatemia, renal phosphate wasting, and other features of Fanconi syndrome [1]. Cases of TDF-associated Fanconi syndrome have been reported predominantly among patients with HIV infection [1]. There has been no excess risk of renal tubular toxicity with TDF-emtricitabine (TDF-FTC) detected in large, placebo-controlled trials of HIV pre-exposure prophylaxis (PrEP) [2, 3]. One other well documented likely Fanconi syndrome has been reported in an online supplement to the latter paper [3]. In this study, we report an additional case of this previously described phenomenon.

CASE REPORT

A 49-year-old white man with a single episode of kidney stones 7 years earlier and no ongoing medical problems or medication use initiated daily PrEP with TDF-FTC in California Collaborative Treatment Group (CCTG) study 595 (NCT 01761643). He had no subjective complaints while on the drug. There was no history of renal parenchymal disease and no

recent symptoms or findings of nephrolithiasis, but, as shown in the Table 1, mild renal impairment was present at baseline with an estimated creatinine clearance of 79.9 mL/minute. Baseline testing for hepatitis B virus (HBV) and hepatitis C virus was negative. Routine monitoring at week 12 of treatment showed 25% fall in estimated creatinine clearance (Table 1). Additional testing at week 12 revealed hypophosphatemia with renal phosphate wasting, consistent with Fanconi syndrome. Tenofovir disoproxil fumarate-FTC was discontinued. Four weeks later, there was improvement in creatinine clearance with resolution of phosphate abnormalities. By week 24 (12 weeks off TDF-FTC), creatinine clearance had risen to near baseline levels. He was not rechallenged and remained HIV negative throughout. Neither glycosuria, hematuria, nor proteinuria were detected by dipstick at any time point. No other similar cases were documented in CCTG 595 (N = 400) during 577 person-years of follow up.

DISCUSSION

This HIV-uninfected man presented an unambiguous renal tubular toxicity due to TDF that was rapidly reversible. In the Pre-exposure Prophylaxis Initiative (iPrEx) study of PrEP, a carefully performed renal substudy of 1137 participants [2] showed no excess renal tubulopathy (including hypophosphatemia, proteinuria, glycosuria, and fractional excretion of urate or phosphorus) among TDF-FTC recipients compared with placebo for PrEP. There was a decrease in estimated creatinine clearance that averaged ~1–2 mL/minute over the 144 weeks of the study with TDF-FTC compared with placebo, which normalized upon drug discontinuation [2]. Another randomized, placebo-controlled study of daily PrEP with TDF or TDF-FTC among HIV-uninfected African men and women examined proximal tubule dysfunction, defined as the occurrence of ≥ 2 of the following at the same time point: tubular proteinuria, euglycemic glycosuria, increased urinary excretion of phosphorus, and increased urinary excretion of uric acid. The authors found over a median drug-exposure period of 24 months, tubular damage occurred in <2% of participants [3]. Similar to iPrEx, rates of tubular dysfunction did not differ by treatment arm in that study. As in our study, the authors also suggest that monitoring for tubular dysfunction may be prudent for individuals at increased risk for renal injury. It is worth noting that our patient may have had pre-existing renal dysfunction with a calculated creatinine clearance of 80. This may have predisposed him to TDF-related renal dysfunction as a result.

One limitation of our report is the lack of baseline data on phosphorus/urinary phosphorus levels. Screening for hypophosphatemia is not routine when considering PrEP.

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Table 1. Laboratory Testing

Test	Screen	Week 4	Week 12		Week 16	Week 18	Week 21	Week 24
Estimated creatinine clearance ^a , mL/min	79.9	68.7	58.9		69.1	66.6	71.0	74.0
Serum creatinine, mg/dL	1.15	1.33	1.58		1.28	1.32	1.27	1.20
Serum phosphorus, mg/dL (normal 2.7–4.5)	—	—	1.8	Stop TDF-FTC	2.7	3.2	2.6	2.8
Fractional excretion of Phosphate, % (normal 10–20)	—	—	26.6		12.2	—	—	—

Abbreviations: FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

^aEstimated creatinine clearance by Cockcroft-Gault formula.

However, there was a clear development of significant renal impairment accompanied by a low serum phosphate that resolved upon drug discontinuation. In spite of concurrent hypophosphatemia, the fractional excretion of phosphate was elevated, confirming inappropriate renal tubular function at the time of drug discontinuation.

Renal dysfunction has been reported in other settings with TDF in patients without HIV infection, such as HBV [4, 5]. Overt instances of Fanconi syndrome have been rarely reported [4]. A 60-month retrospective study of renal toxicity compared the effect of TDF-FTC in patients' dual infection with HIV and HBV with those with HBV mono-infection [5]. That study showed a statistically significant decrease of renal function during long-term TDF use in both groups, averaging 9 mL/minute in the coinfecting group and 23 mL/minute in the HBV mono-infecting group ($P < .01$). It is notable that those with HBV alone had a greater proportion (69%) that developed a glomerular filtration rate <90 mL/minute than those with HIV/HBV coinfection (12%). However, the authors believed that the clinical impact was not clinically relevant and no cases of Fanconi syndrome occurred [5].

CONCLUSIONS

Although significant nephrotoxicity has been rarely reported, periodic renal monitoring is a reasonable recommendation in HIV-uninfected individuals receiving TDF-FTC for PrEP and other conditions. This case and others [3] document that, albeit uncommon, a reversible TDF-FTC-associated Fanconi

syndrome may nonetheless occur during PrEP. It is possible that pre-existing renal impairment may have contributed in this instance.

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Potential conflicts of interest. M. P. D. has served as a consultant to Gilead, Theratec, and Astra Zeneca and receives research support through his university from Gilead, Serono, Merck, Theratec, and ViiV.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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