Tenofovir disoproxil fumarate associated Fanconi syndrome in an HIV uninfected man receiving HIV pre-exposure prophylaxis

M. Philip Dubé[1], Connie A. Funk[1], Katya Corado[2], Sheldon Morris[3]

[1] University of Southern California Keck School of Medicine, Los Angeles, CA, USA; [2] Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Los Angeles CA, USA; [3] University of California at San Diego School of Medicine, San Diego CA, USA. For the California Collaborative Treatment Group Study 595 Team

ABSTRACT

Objectives: Renal dysfunction due to tenofovir disoproxil fumarate (TDF) is rare among individuals without HIV infection. We report an HIV uninfected man who developed reduced renal function and features of Fanconi syndrome while receiving TDF with emtricitabine (FTC) for HIV pre-exposure prophylaxis (PrEP).

Methods: Case report from a prospective study of PrEP with TDF-FTC (CCTG Study 595, NCT01761643). Eligible subjects were men who had sex with men or transgender women who were at increased risk of acquiring HIV infection. Individuals were excluded who had calculated creatinine clearance (CrCl) less than 60 mL/min by the Cockcroft-Gault formula, active hepatitis B, proteinuria 2+ or greater by dipstick, or use of other nephrotoxic drugs. Routine monitoring of serum creatinine was performed at entry, week 4, week 12, then every 12 weeks.

Results: A 49 year old white man with a history of kidney stones 7 years earlier and no ongoing medical problems or medication use initiated daily PrEP with TDF-FTC and had no subjective complaints while on drug. Routine monitoring at week 12 of treatment showed 25% fall in CrCl. Additional testing at week 12 revealed hypophosphatemia with renal phosphate wasting, consistent with Fanconi syndrome. TDF-FTC was discontinued and 4 weeks later there was improvement in CrCl with resolution of phosphate abnormalities. By week 24 (12 weeks off TDF-FTC), CrCl 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).

Discussion: Randomized trials have not documented an increase in renal tubular toxicity with TDF-FTC based PrEP compared to placebo. However, we report a clear and significant reversible impairment in renal function accompanied by hypophosphatemia and renal phosphate wasting in an HIV uninfected man receiving TDF/FTC. Clinicians should be aware that this complication may still occur when TDF is used in HIV uninfected individuals

BACKGROUND

- TDF can cause renal tubular dysfunction and reduced renal function[1]
- In its fully developed form, this condition 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
- Rarely, TDF has caused reversible Fanconi syndrome in hepatitis B mono-infected individuals[2]
- No signal for increased risk of renal tubular toxicity with TDF-FTC has been detected in large placebo controlled trials of PrEP[3]
- To our knowledge, this is the first well-documented case of Fanconi syndrome in an HIV-uninfected person receiving TDF-FTC for PrEP

CASE REPORT

A 49 year old white man with a history of kidney stones 7 years earlier and no ongoing medical problems or medication use initiated daily PrEP with TDF-FTC and had no subjective complaints while on drug. There was no history of renal parenchymal disease and no recent symptoms or findings of nephrolithiasis.

Routine monitoring at week 12 of treatment showed 25% fall in CrCl (Table). Additional testing at week 12 revealed hypophosphatemia with renal phosphate wasting, consistent with Fanconi syndrome.

TDF-FTC was discontinued and 4 weeks later there was improvement in CrCl with resolution of phosphate abnormalities. By week 24 (12 weeks off TDF-FTC), CrCl 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.

TABLE

	Screen	Week 4	Week 12	STOP TDF-FTC	Week 16	Week 18	Week 21	Week 24
Est. CrCl mL/min*	79.9	68.7	58.9		69.1	66.6	71.0	74.0
Serum Phos. mg/dL (normal 2.7-4.5)	--	--	1.8		2.7	3.2	2.6	2.8
FePi† % (normal 10-20)†	--	--	26.6		12.2	--	--	--

*Estimated creatinine clearance by Cockcroft-Gault formula
† Fractional excretion of phosphate

DISCUSSION

- This HIV uninfected man presented an unambiguous renal tubular toxicity due to TDF that was rapidly reversible
- In iPrex, a carefully performed renal substudy[3] showed no excess renal tubulopathy (including hypophosphatemia, proteinuria, glycosuria, and fractional excretion of urate or phosphorus) among TDF-FTC recipients compared to placebo for PrEP
- There was only a minor decrease in estimated creatinine clearance which averaged ~1-2 mL/min over the 144 weeks of study with TDF-FTC compared to placebo, which normalized upon drug discontinuation[3]
- Significant renal toxicity has been rarely been reported during treatment of hepatitis B[2], a disease with established potential for renal damage
- Although rarely reported, periodic renal monitoring is a reasonable recommendation in individuals receiving TDF-FTC for PrEP

REFERENCES

1. Gupta SK, Anderson AM, Ebrahimi R, et al. Fanconi syndrome accompanied by renal function decline with tenofovir disoproxil fumarate: a prospective, case-control study of predictors and resolution in HIV-infected patients. *PLoS ONE* 2014;9(3):e92717.

2. Vigano M, Brocchieri A, Spinetti A, et al. Tenofovir-induced Fanconi syndrome in chronic hepatitis B monoinfected patients that reverted after tenofovir withdrawal. *J Clin Virol*. 2014;61(4):600-603.

3. Solomon MM, Lama JR, Glidden DV, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. *AIDS*. 2014;28(6):851-859.