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Treatment-limiting renal tubulopathy in patients treated with tenofovir disoproxil fumarate

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Summary *Objectives:* Tenofovir disoproxil fumarate (TDF) is widely used in the treatment or prevention of HIV and hepatitis B infection. TDF may cause renal tubulopathy in a small proportion of recipients. We aimed to study the risk factors for developing severe renal tubulopathy.

Methods: We conducted an observational cohort study with retrospective identification of cases of treatment-limiting tubulopathy during TDF exposure. We used multivariate Poisson regression analysis to identify risk factors for tubulopathy, and mixed effects models to analyse adjusted estimated glomerular filtration rate (eGFR) slopes.

Results: Between October 2002 and June 2013, 60 (0.4%) of 15,983 patients who had received TDF developed tubulopathy after a median exposure of 44.1 (IQR 20.4, 64.4) months. Tubulopathy cases were predominantly male (92%), of white ethnicity (93%), and exposed to antiretroviral regimens that contained boosted protease inhibitors (PI, 90%). In multivariate analysis,

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age, ethnicity, CD4 cell count and use of didanosine or PI were significantly associated with tubulopathy. Tubulopathy cases experienced significantly greater eGFR decline while receiving TDF than the comparator group (−6.60 [−7.70, −5.50] vs. −0.34 [−0.43, −0.26] mL/min/1.73 m^2/year, $p < 0.0001$).

Conclusions: Older age, white ethnicity, immunodeficiency and co-administration of ddI and PI were risk factors for tubulopathy in patients who received TDF-containing antiretroviral therapy. The presence of rapid eGFR decline identified TDF recipients at increased risk of tubulopathy.

Introduction

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir (TFV), a nucleotide reverse transcriptase inhibitor with potent activity against HIV-1 and hepatitis B. Although TDF has a favourable safety profile, the plasma TFV concentrations obtained with TDF exposure have been shown to result in a degree of renal tubular dysfunction.[1,2] Manifestations of renal tubular dysfunction include proteinuria (predominantly low molecular weight proteins) and increased fractional excretion of phosphate and urate.[3] Older age and genetic polymorphisms in the tubular transporters ABCC2, 4 and 10 (encoding multidrug resistant proteins 2, 4 and 7 respectively) have been associated with higher TFV concentrations and renal tubular dysfunction.[4–9] In cohort studies, TDF has also been associated with accelerated decline of estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD).[10–12] Hence, guidelines suggest that renal function should be monitored regularly in patients who receive TDF-containing antiretroviral therapy (ART).[13]

In a small proportion of patients, TDF may cause Fanconi syndrome (a well described proximal renal tubulopathy, PRT) accompanied by acute tubular injury (ATI) on kidney biopsy.[14–24] PRT is characterised by normoglycaemic glycosuria, proteinuria, renal phosphate wasting and metabolic acidosis which may be accompanied by reductions in bone mineral density, osteomalacia and/or fragility fractures.[3,14,25,26] The risk factors for developing PRT have not been studied comprehensively to date. Case reports, case series and a small case-control study have suggested that older age, immunodeficiency, renal impairment and co-exposure to didanosine (ddI) or boosted protease inhibitors (PI) may increase the risk of PRT.[14–20] The purpose of the present study was to describe the clinical phenotype of TDF-induced treatment-limiting PRT using the largest cohort of individuals collected to date, and, using data from the UK CHIC study, analyse the risk factors for developing renal tubulopathy (PRT/ATI).

Methods

A multi-centre study was undertaken in HIV clinics which contribute data to the UK CHIC study, a large multicentre observational cohort study of HIV positive adults in the UK.[27] Cases of treatment-limiting renal tubulopathy were identified retrospectively through searches of electronic databases and physician recall. Clinical and laboratory data were collected on case report forms. The study was approved by the National Health Service Research Ethics Committee.

All cases were reviewed by two clinicians (LH and FAP) and included in the analyses if they had required TDF discontinuation and biochemical evidence of PRT or histological evidence of ATI that was not explained by other aetiologies.[18] PRT was defined by the presence of at least 2 of the following: normoglycaemic glycosuria (≥1+ on dipstick), hypophosphataemia (serum phosphate <1.98 mg/dl), proteinuria (≥1+ on dipstick or protein/creatinine ratio (PCR) >26.5 mg/mg), hypokalaemia (serum potassium <3.0 mEq/l), and metabolic acidosis (serum bicarbonate <19 mEq/l).[19] Reductions in eGFR from baseline were not a prerequisite for inclusion in the study. Comparator subjects were individuals in the UK CHIC study who had attended a centre from which cases were drawn and who had been exposed to a TDF-containing ART regime without having developed RT. Follow up was from the date of starting TDF to either the date of stopping TDF or the last visit (up to 31st December 2013) if TDF was not discontinued.

Baseline variables, including CD4 cell count, HIV viral load (expressed as $\log_{10}$), eGFR (calculated by CKD-Epi[28]), hepatitis B (HBV surface antigen) and hepatitis C (HCV antibody) status, were defined as the most recent measurement prior to starting TDF and compared using Chi squared, Fisher's exact or Wilcoxon rank sum tests, depending on the variable distribution. Poisson regression analysis was used to investigate factors associated with renal tubulopathy.[29] Age, sex, ethnicity (black vs. white/other), AIDS, eGFR at start TDF and year of starting TDF were included as fixed covariates, and hepatitis B and C status, nadir and current CD4 cell count (per 50 cells/mm^3 increase), HIV RNA (per 1 $\log_{10}$ increase), type of ART regimen (ddI or PI containing/sparing) and time on TDF as time-updated covariates. Factors significant in univariate analysis ($p < 0.1$) were taken forward in the multivariable models in a forward stepwise approach. We performed a sensitivity analysis restricted to individuals with PRT.

We analysed eGFR slopes on TDF in the renal tubulopathy cases and the comparators who had ≥3 eGFR values while receiving TDF using mixed effects models in which time was considered as a continuous fixed effect (allowing a random intercept for time) and as a random effect (allowing the slope to vary).[30] Adjusted eGFR slopes were determined using multivariate models; covariates considered for inclusion included demographic and HIV characteristics, including fixed covariates such as ethnicity and time updated covariates such as age, PI use, CD4 cell count and viral load. In additional analyses, the last six months of eGFR results on TDF were excluded to determine if the