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

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

**Running title: Risk factors for severe renal tubulopathy with tenofovir**

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## Abstract

**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, 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/1·73m$^2$/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 (28). PRT was defined by the presence of at least 2 of the following: normoglycaemic glycosuria ($\geq$1+ on dipstick), hypophosphataemia (serum phosphate <1.98 mg/dl), proteinuria ($\geq$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 (29)), 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(30). 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) (31). 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 mean slope was unduly influenced by eGFR reductions just prior to stopping TDF. Assumptions for multivariate models were tested graphically. We compared the proportions of subjects with and without renal tubulopathy who experience rapid eGFR decline (defined as a mean decline in eGFR >3 or >5 ml/min/1·73m$^2$/year) or incident CKD while receiving TDF using Chi squared tests. All analyses were performed using STATA version 12 (StataCorp LP, College Station, Tx).

**Results**

*Baseline characteristics*

Between October 2002 and June 2013, 15983 patients received at least four weeks of TDF-containing antiretroviral therapy (ART). During a median follow up of 4·1 (IQR 1·8, 6·7) years, treatment-limiting renal tubulopathy was diagnosed in 69 (0·4%) subjects, of whom 60 (87%) were included in the present analyses; 48 met the case definition of PRT and 12 had ATI on renal biopsy (including four with sufficient data to confirm the presence of PRT). Nine subjects were excluded as they had <2 markers of PRT and no histological evidence of ATI.

*Factors associated with renal tubulopathy*

Renal tubulopathy was diagnosed after a median of 44·1 (IQR 20·4, 64·4 months; range 3·9 months to 11·0 years) months of TDF exposure. The subjects who were diagnosed with renal tubulopathy were older at TDF initiation and more likely to be male, of white ethnicity, and to have initiated TDF in earlier years than those who did not develop renal tubulopathy. The renal tubulopathy cases also had lower nadir CD4 cell counts, more often a prior AIDS diagnosis, and greater prior ART exposure at TDF initiation, and they were more likely to have initiated TDF with ddI or a PI. By contrast, patients with and without renal tubulopathy did not differ by HBV or HCV status, current CD4 cell count or eGFR at baseline (Table 1). At renal tubulopathy diagnosis, the majority (n=54, 90%) of patients received an ART regimen that contained a PI [lopinavir (LPV) in 37%, atazanavir (ATV) in 39%, darunavir (DRV) in 13%, other PI in 11% of subjects], and 18 (30%) subjects received ddI (15 as part of a PI-containing regimen). Normoglycaemic glycosuria was present in 37/46 (80%), hypophosphataemia in 41/55 (75%), proteinuria in all 55 (100%), hypokalaemia in 3/44 (7%) and metabolic acidosis in 7/22 (32%) subjects with data. Nine subjects had diabetes mellitus; all diabetics with glycosuria had a paired plasma glucose measurement within the normal range. In addition, 33/59 patients (56%) had raised serum alkaline phosphatase concentrations (with normal hepatic transaminases) suggestive of osteomalacia. The median eGFR at renal tubulopathy diagnosis was 52·7 (IQR 44·5, 71·5) mL/min/1·73m$^2$, an eGFR reduction of >25% from baseline was observed in 34/57 (60%) of subjects. The clinical characteristics of the PRT and ATI cases were indistinguishable (Table 2).

In univariate regression analysis, age, gender, ethnicity, CD4 cell count, having initiated TDF in earlier calendar years and with a more prolonged ART history, and receipt of ddI and PI were associated with renal tubulopathy (Table 3). Due to interaction between ddI and PI use (p<0·001), ART was categorised in the model as no ddI/no PI, ddI/no PI, no ddI/PI or ddI/PI. In multivariate analysis, age, ethnicity, calendar year, CD4 cell count, and ddI and PI use remained significantly associated with renal tubulopathy (Table 2). Similar results were obtained when the analysis was restricted to the 52 PRT cases (data not shown). The incidence rates of renal tubulopathy on LPV, ATV and DRV were

similar (0·21 [95% CI: 0·13, 0·32], 0·18 [0·12, 0·27] and 0·10 [0·05, 0·22] per 100 person-years respectively); the incidence of renal tubulopathy with ATV or DRV did not differ significantly from LPV (p>0·05 for all).

*eGFR slopes on and post TDF*

We included 15764 patients in the eGFR slope analysis. In the renal tubulopathy cases, the mean [95% confidence interval] crude eGFR slope while receiving TDF was -5·55 [-6·47, -4·63] mL/min/1·73m$^2$/year, as compared with -0·19 [-0·24, -0·13] mL/min/1·73m$^2$/year in those without renal tubulopathy (p<0·0001). After adjustment for age, ethnicity and time updated PI use, CD4 cell count and viral load, the eGFR slopes of subjects who developed renal tubulopathy remained significantly worse (-6·60 [-7·70, -5·50] vs. -0·34 [ -0·43, -0·26] mL/min/1·73m$^2$/year, p<0·0001), even if eGFR data for the last six months of TDF exposure were excluded (-5·93 [ -7·04, -4·82] vs. -0·22 [-0·30, -0·13] mL/min/1·73m$^2$/year, p<0·0001). The mean eGFR slope in the renal tubulopathy cases improved following TDF discontinuation (+13·21 [9·85, 16·58] during the first six months, +1·26 [0·20, 2·33] mL/min/1·73m$^2$/year thereafter). Adverse eGFR patterns were more common among those who developed renal tubulopathy than those who did not develop renal tubulopathy: rapid eGFR decline >3 mL/min/1·73m$^2$/year was noted in 69·6% and 7·9% (p<0·0001), rapid eGFR decline >5 mL/min/1·73m$^2$/year in 55·4% and 3·5% (p<0·001), and incident CKD (eGFR <60 mL/min/1·73m$^2$ for >3 months) in 43·5% and 9·5% (p<0·0001) of patients respectively.

**Discussion**

This study describes the largest cohort of TDF-associated renal tubulopathy cases to date. Consistent with previous case series, the majority of patients who developed renal tubulopathy were older, white men. Renal tubulopathy was associated with TDF use in earlier calendar years when TDF was more commonly used in PI-containing salvage ART regimens in a setting of limited appreciation of the potential for renal toxicity and little if any monitoring for renal complications. Many of these early patients had a history of severe immunodeficiency and prolonged ART exposure; TDF was not

infrequently co-administered with ddI, and the most commonly used PI in this era was lopinavir, giving the impression that perhaps this PI predisposed patients to developing renal tubulopathy (19). The introduction of routine renal monitoring advocated by HIV management guidelines may have contributed to the decline in the incidence of renal tubulopathy as patients with reduced eGFR were identified earlier and switched to alternative ART (32). Interestingly, the propensity for TDF to cause renal tubulopathy appears undiminished as several cases were reported in recent clinical trials in which patients (with relatively high CD4 cell counts and preserved eGFR) received TDF together with emtricitabine plus cobicistat/elvitegravir or ritonavir/atazanavir (33, 34).

The pathogenesis of TDF-induced renal tubulopathy remains poorly understood. Proximal tubular cells are highly metabolically active and renal histology of patients with tubulopathy has revealed structural abnormalities of mitochondria (14-16). Relatively high CD4 cell counts argue against opportunistic infection, and given that most cases had an undetectable HIV viral load, a direct action of HIV appears unlikely. Boosting agents such as ritonavir and cobicistat increase systemic TFV exposure by approximately 30% (35, 36). Increased TFV exposure and PI co-administration have been associated with greater eGFR decline (37-39). Organic anion transporters on the basolateral membrane of proximal tubular cells allow efficient uptake of TFV while ritonavir or cobicistat are potent inhibitors of apical membrane transporters involved in the extrusion of TFV from these cells; high intracellular TFV concentration may affect mitochondrial function and thereby the absorptive capacity of renal tubular cells (40). Of note, particularly high intracellular TFV concentrations have been reported in a patient with renal tubulopathy (41).

Consistent with previously reported cases (21-24), we observed a strong association between renal tubulopathy and TDF/ddI co-administration. Exposure to ddI (without TDF or PI) appears to be sufficient to induce renal tubulopathy (42-45). Didanosine has been shown *in vitro* to be more toxic to renal tubular cells than TFV, causing profound depletion of mitochondrial DNA and cytochrome oxidase II mRNA (46). These effects of ddI were enhanced in the presence of tenofovir, which may

be the result of TFV-mediated inhibition of purine nucleoside phosphorylase, the enzyme responsible for ddI phosphorylation and degradation (21, 47).

The majority of our patients who developed renal tubulopathy had received TDF for several years. Interestingly, the mean eGFR slope during TDF exposure was significantly worse in cases as compared to comparators, suggesting that sub-clinical renal tubular toxicity had been present throughout this time. This potentially affords opportunities for early diagnosis. The role of renal tubular biomarkers has been advocated but their clinical utility remains unclear (48). By contrast, plasma creatinine and urinalysis for proteinuria and glycosuria are routinely available. Our data suggest that patients who develop rapid eGFR decline or incident CKD while receiving TDF may be particularly at risk of developing renal tubulopathy. Such patients should be switched off TDF, or closely monitored if TDF is continued. The biomarker profile of tenofovir alafenamide (TAF) suggests that this may be a safer option for such patients (49, 50).

The strong ethnic association observed in this study is consistent with population-specific genetic susceptibility factors for renal tubulopathy as described for sub-clinical renal tubular dysfunction (4-9). TDF is increasingly used in sub-Saharan Africa where the population is at risk of HIV-associated nephropathy (HIVAN) (51) and regular monitoring of renal function may not be possible. Our observation that black patients were at approximately 80% lower risk of developing renal tubulopathy suggests that severe renal toxicity may be less frequent in this setting, especially if TDF is used in a relatively young population as part of first line ART that does not include a PI. Of note, no individuals of black ethnicity in our cohort who received TDF without a PI were diagnosed with severe tubulopathy.

Strengths and limitations

The strengths of this study include the relatively large number of cases, the robust case definition, and the large (and for the UK representative) population used to study the risk factors for renal tubulopathy. However, some limitations need to be acknowledged. Case ascertainment was

retrospective, which is likely to have resulted in under-ascertainment. The UK CHIC study has limited information on the reasons for ART discontinuation; some subjects may have been misclassified as comparators where in fact they discontinued TDF for renal tubulopathy. In addition, there was no information in the comparator subjects on acute clinical events, concomitant medications such as nephrotoxic drugs or creatine supplements and other risk factors for renal disease such as hypertension and diabetes. We were unable to include these in our model and this may have introduced unmeasured confounding. Our study was also affected by incomplete data which precluded assessment of the full PRT phenotype in each subject, and nine cases had to be excluded for insufficient data.

## Conclusions

Our study indicates that older age, white ethnicity, immunodeficiency, and co-administration of TDF with ddI and PI are important risk factors for renal tubulopathy in HIV positive patients. Although severe renal tubulopathy may manifest within weeks of TDF exposure, the median time to overt renal toxicity in our patients was more than 3.5 years. Sub-clinical renal tubular dysfunction, as manifested by rapid eGFR decline or incident CKD, preceded renal tubulopathy in the majority of patients. Patients who develop these adverse eGFR patterns while receiving TDF should be considered for alternative therapy or carefully monitored if they are maintained on TDF. With the availability of tenofovir alafenamide (50, 52), a pro-drug with 90% reduced plasma tenofovir exposure, the incidence of severe renal tubulopathy is likely to decline. A clinical trial (EudraCT 2016-003345-29) is currently evaluating whether patients with a history of severe renal tubulopathy on TDF can be safely managed with tenofovir alafenamide (53).

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### 1.2 Author contributions:

Study design: LH, BMH, CAS, FAP; Data Collection: LH, JWB, AH, MR, AB, DIW, PH, RJ, DRC, MJ; Data analysis: LH, SJ, CAS, FAP; First draft of the manuscript: LH, FAP; All authors contributed to the data interpretation, final version of the manuscript and approved the submission.

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**Table 1: Baseline characteristics of renal tubulopathy cases and controls**

| | | RT cases [N=60] | Controls [N=15,914] | p-value* |
|---|---|---|---|---|
| **Age [Years]** | **Mean [SD]** | **45·6 [10·1]** | **40·7 [9·5]** | **0·0001** |
| **Sex [Male]** | **N [%]** | **55 [91·7]** | **12,689 [79·7]** | **0·02** |
| **Ethnicity [White/Other]** | **N [%]** | **56 [93·3]** | **11,739 [73·8]** | **0·001** |
| Exposure [MSM] | N [%] | 46 [78·9] | 9,819 [58·8] | 0·06 |
| **Calendar year at TDF start** | | | | |
| **1996-2003** | **N [%]** | **17 [28·3]** | **1,178 [7·4]** | **<0·0001** |
| **2004-2007** | **N [%]** | **28 [46·7]** | **5,022 [31·6]** | |
| **2008-2010** | **N [%]** | **9 [15·0]** | **5,014 [31·6]** | |
| **2011-2014** | **N [%]** | **6 [10·0]** | **4,700 [29·5]** | |
| ART naïve at TDF start | N [%] | 39 [65·0] | 9038 [56·8] | 0·20 |
| **Years on ART at TDF start** | **Median [IQR]** | **4·2 [0·0, 7·5]** | **0·0 [0·0, 5·5]** | **0·0006** |
| **ddI co-administration** | **N [%]** | **18 [30]** | **600 [3·79]** | **<0·0001** |
| **PI co-administration** | **N [%]** | **37 [61·7]** | **5,491 [34·5]** | **<0·0001** |
| **Previous AIDS event** | **N [%]** | **24 [40·0]** | **4,095 [25·7]** | **0·01** |
| HBcAb positive | N [%] | 3 [8·1] | 640 [6·0] | 0·60 |
| HCV Ab positive | N [%] | 1 [2·9] | 1,035 [2·9] | 0·22 |
| **Nadir CD4 cell count** | **Median [IQR]** | **119 [29, 185]** | **190 [91, 284]** | **0·0001** |
| CD4 cell count | Median [IQR] | 361 [198, 470] | 364 [237, 528] | 0·37 |
| HIV RNA [$\log_{10}$ copies] | Median [IQR] | 2·24 [1·70, 3·44] | 2·18 [1·70, 3·13] | 0·44 |
| eGFR [mL/min/1·73m$^2$] | Mean [SD] | 93·6 [16·9] | 96·2 [16·4] | 0·26 |

*level of significance set at p=0·05/15=0·003

RT: renal tubulopathy, MSM: men who have sex with men, TDF: tenofovir disoproxil fumarate, ART: antiretroviral therapy, ddI: didanosine, PI: protease inhibitor, HBV: hepatitis B core antibody, HCV Ab: hepatitis C antibody, eGFR: estimated glomerular filtration rate

**Table 2: Characteristics of PRT and ATI cases**

| | | PRT cases [n=48] | ATI cases [n=12] | P value* |
|---|---|---|---|---|
| **At baseline** | | | | |
| Age [Years] | Mean [SD] | 45·8 [10·0] | 44·6 [11·0] | 0·71 |
| Sex [Male] | N [%] | 44 [91·7] | 11 [91·7] | 0·69 |
| Ethnicity [White/Other] | N [%] | 45 [93·8] | 11 [91·7] | 0·60 |
| Exposure [MSM] | N [%] | 37 [77·1] | 9 [75·0] | 0·84 |
| Calendar year at TDF start | | | | 0·10 |
| 1996-2003 | N [%] | 16 [33·3] | 3 [8·3] | |
| 2004-2007 | N [%] | 20 [41·7] | 7 [66·7] | |
| 2008-2010 | N [%] | 6 [12·5] | 7 [25·0] | |
| 2011-2014 | N [%] | 6 [12·5] | 0 [0·0] | |
| ART naïve at TDF start | N [%] | 19 [39·6] | 2 [16· 7] | 0·12 |
| Years on ART | Median [IQR] | 3·9 [0·0, 9·3] | 4·69 [1·6, 6·5] | 0·88 |
| ddI co-administration | N [%] | 15 [31·3] | 3 [25·0] | 0·67 |
| PI co-administration | N [%] | 29 [60·4] | 8 [66·7] | 0·48 |
| Previous AIDS event | N [%] | 19 [39·6] | 5 [41·7] | 0·57 |
| HBcAb positive | N [%] | 3 [10·3] | 0 [0·0] | 0·22 |
| HCV Ab positive | N [%] | 1 [3·6] | 0 [0·0] | 0·80 |
| Nadir CD4 cell count | Median [IQR] | 110 [25, 185] | 156 [75, 242] | 0·32 |
| CD4 cell count | Median [IQR] | 317 [169, 459] | 470 [335, 635] | 0·11 |
| Viral Load [$log_{10}$copies] | Median [IQR] | 2·47 [1·70, 3·57] | 1·70 [1·70, 2·36] | 0·32 |
| eGFR [ml/min/1·73$m^2$] | Mean [SD] | 93·1 [17·2] | 94·9 [16·5] | 0·76 |
| **At RT diagnosis** | | | | |
| Duration of TDF exposure | months | 44·1 | 43·4 | 0·39 |
| PI/r co-exposure | N [%] | 38 (79·2) | 11 (91·7) | 0·30 |

*level of significance set at p=0·05/15=0·003

PRT: proximal renal tubulopathy, ATI: acute tubular injury, MSM: men who have sex with men, TDF: tenofovir disoproxil fumarate, ART: antiretroviral therapy, ddI: didanosine, PI: protease inhibitor, HBV: hepatitis B core antibody, HCV Ab: hepatitis C antibody, eGFR: estimated glomerular filtration rate

**Table 2: Factors associated with developing renal tubulopathy**

| | Univariate | | | Multivariate [$] | | |
|---|---|---|---|---|---|---|
| | RR | 95% CI | P | RR | 95% CI | P |
| **Age (per 5 year increase)** | **1·30** | **(1·15, 1·47)** | **<0·0001** | **1·35** | **(1·19, 1·55)** | **<0·0001** |
| Sex | | | | | | |
| Male | 1 | | | | | |
| Female | 0·38 | (0·15, 0·94) | 0·04 | | | |
| **Ethnicity** | | | | | | |
| **White/Other** | **1** | | | **1** | | |
| **Black** | **0·21** | **(0·08, 0·57)** | **0·002** | **0·19** | **(0·07, 0·51)** | **0·001** |
| Calendar year at TDF start | | | | | | |
| 1996-2003 | 1 | | | | | |
| 2004-2007 | 0·46 | (0·26, 0·81) | 0·007 | 0·78 | (0·42, 1·45) | 0·43 |
| 2008-2010 | 0·31 | (0·15, 0·63) | 0·001 | 0·73 | (0·29, 1·84) | 0·51 |
| 2011-2014 | 0·39 | (0·15, 0·97) | 0·04 | 1·36 | (0·46, 4·03) | 0·57 |
| Antiretroviral naïve at TDF start | 1·03 | (0·61, 1·76) | 0·90 | | | |
| **Time on TDF (per year increase)*** | **1·08** | **(0·98, 1·19)** | **0·13** | **1·15** | **(1·03, 1·27)** | **0·01** |
| Years on antiretrovirals at TDF start | 1·06 | (1·00,1·12) | 0·03 | 0·97 | (0·91, 1·04) | 0·40 |
| **ARV regime*** | | | | | | |
| **No PI / no ddI** | **1** | | | **1** | | |
| **No PI / ddI** | **17·62** | **(6·39, 48·59)** | **<0·0001** | **17·09** | **(5·86, 49·84)** | **<0·0001** |
| **PI / no ddI** | **8·67** | **(4·01, 18·72)** | **<0·0001** | **8·87** | **(4·08, 19·28)** | **<0·0001** |
| **PI / ddI** | **22·07** | **(8·88, 54·87)** | **<0·0001** | **24·57** | **(9·19, 65·69)** | **<0·0001** |
| Previous AIDS event | 1·48 | (0·88, 2·48) | 0·14 | | | |
| Hepatitis B status* | | | | | | |
| Negative | 1 | | | | | |
| Positive | 1·27 | (0·46, 3·53) | 0·65 | | | |
| Hepatitis C status* | | | | | | |
| Negative | 1 | | | | | |
| Positive | 0·37 | (0·09, 1·52) | 0·17 | | | |
| Nadir CD4 cell count (per 50 cell ↓)* | 0·89 | (0·80, 1·00) | 0·05 | | | |
| **CD4 cell count (per 50 cell increase)*** | **0·91** | **(0·85, 0·96)** | **0·001** | **0·91** | **(0·86, 0·97)** | **0·002** |
| HIV Viral load (per 1 log increase)* | 0·74 | (0·44, 1·23) | 0·24 | | | |
| Baseline eGFR (per 10ml/min decrease) | 0·90 | (0·76, 1·08) | 0·26 | | | |

*Time updated

TDF: tenofovir disoproxil fumarate; ARV: antiretroviral, PI: protease inhibitor, ddi: didanosine, AIDS: acquired immune deficiency syndrome, eGFR: estimated glomerular filtration rate; RR: relative risk

[$] adjusted for fixed covariates: age, ethnicity, years on ARVs prior to TDF start, time updated covariates: DDI use, PI vs. NNRTI use, time on TDF and CD4 cell count

Highlights

- Severe renal proximal tubulopathy (Fanconi syndrome) was only rarely seen with tenofovir disoproxil fumarate (TDF) exposure
- Being older, of white ethnicity, with more advanced HIV and co-administration of protease inhibitors or didanosine increased the risk of developing severe proximal tubulopathy
- Rapid eGFR decline or incident CKD often preceded overt tubulopapthy and if detected should prompt consideration of alternative therapy or careful monitoring if remaining on TDF