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# Factors associated with increased risk of Tenofovir-related renal toxicity: Case-Control Study

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## Abstract

**Background**
Renal toxicity remains a concern in patients receiving tenofovir (TDF)(1-3). Our previously published studies (4,5) suggested proximal tubular toxicity as a common pathogenic mechanism. We proposed that screening for renal toxicity in patients receiving TDF should include estimation of the urine protein/creatinine (Up/c) and monitoring of serum phosphate. We undertake a case-control study in order to identify factors associated with an increased risk of TDF-renal toxicity.
**Methods**
The cases were defined by presence of tubular proteinuria as a substitute marker for TDF toxicity. Among the cases the earliest data of starting TDF was January 2002 and the latest June 2008.
We identified 22 patients who developed TDF related renal toxicity (cases) and we matched them for the TDF starting date and duration of TDF use (on 1:3 ratio) with patients on TDF treatment but without TDF-related renal toxicity.
**Results**
In the univariate analysis patients with TDF-related renal toxicity were more likely to be older (age-per 10 year increase), to have cardiovascular disease, hypertension, diabetes or cirrhosis or hepatitis co-infection than controls. Diagnosis of chronic renal disease (defined as eGFR<90) prior to TDF start was an independent risk factor for developing TDF-related toxicity. Concomitant use of TDF with a boosted PI-regimen was not associated with increased odds of renal toxicity. Lower CD4 cell count nadir, lower body mass index, prior AIDS diagnosis did not have higher odds of renal toxicity. Association with ethnicity and gender with renal disease previously reported was not observed in our study. In the multivariate analysis patients with TDF-related renal toxicity were more likely to be older (age-per 10 year increase) (OR=3.24, CI (1.45, 7.21), p=0.004), and with previous chronic kidney disease diagnosed (OR 15.11, CI (1.96, 116.1), p=0.009) when compared to controls.
**Conclusions**
Older age, hepatitis co-infection, and past medical history of cardiovascular disease, diabetes, cirrhosis or chronic renal disease were strong determinant of the future risk of TDF associated renal toxicity. Renal toxicity in TDF-treated patients is likely to be related to pre-existing renal pathology, and common risk factors shared with HIV-negative population. With such an expanded use of TDF, screening for the risk factors prior to TDF initiation, and close monitoring of renal function is warranted in patients receiving TDF.

## Objectives

To identify clinical and laboratory risk factors for the development of TDF associated renal toxicity in HIV positive patients treated with ant-retroviral therapy

## Methods

We identified 22 patients who developed TDF related toxicity (cases) and then matched them (1:3) with controls who had not developed TDF renal toxicity, by date of starting TDF and duration on TDF. All started TDF between January 2002 and June 2008.

For the cases TDF renal toxicity was defined as:

1. Elevated total protein creatinine ratio (>30mg/mmol)
2. Renal Proximal tubulopathy: 2 or more of the following
   - Elevated urinary retinol binding protein creatinine ratio (all cases)
   - Decreased fractional phosphate reabsorption capacity
   - Normoglycaemic glycosuria
   - Serum bicarbonate <21 mmol/l, urinary pH >5.5
3. Improvement of renal dysfunction on discontinuation of TDF

Data were collected on demographics, and clinical characteristics including laboratory measures and HIV and non HIV associated co-morbidities (hepatitis, cardiovascular events, hypertension, diabetes). Baseline data was defined as either at time of or within the 6 months prior to starting TDF. Baseline measures were missing for UP/C and plasma inorganic PO4 for some patients .
We used conditional logistic regression in STATA 12 to fit univariable and multivariable regression models for the risk of developing TDF related toxicity in terms of covariates of interest.

## Results

Demographic and clinical characteristics of the cases and the controls are described in table 1. The majority were white homosexual/bisexual men. The median time on tenofovir was 51 months (32-63). Total duration on any ART, exposure to a PI and CD4 count and eGFR prior to starting TDF were similar for the cases and the controls.

Laboratory measures of renal function prior to starting TDF and either at diagnosis of TDF toxicity for the cases or at last follow up for the controls are described in table 2. The cases experienced impairment of renal function and proteinuria. At diagnosis of TDF renal toxicity all cases had markedly elevated urinary RBP / creatinine ratios (Fig 1), median (IQR): 1791 µg/mmol (893-4098), confirming tubular proteinuria and proximal renal tubule dysfunction. The majority also had phosphaturia (fig 2), fractional PO4 reabsorption median (IQR) 0.73 (0.62-0.84)

Factors associated with TDF renal toxicity on univariate analysis are described in table 3. Only age (per 10 year increase) and pre-existing CKD were found to be significantly associated with an increased risk of TDF renal toxicity on multivariate analysis.

**Figure 1: Urinary RBP / Creatinine ratio** in the cases at time of diagnosis of tenofovir renal toxicity. All cases showed marked elevation, confirming tubular proteinuria secondary to proximal renal tubule toxicity. The normal reference range (3.9-32 µg/mmol) has been derived from children age 10-16 years. An adult reference range has not been validated.

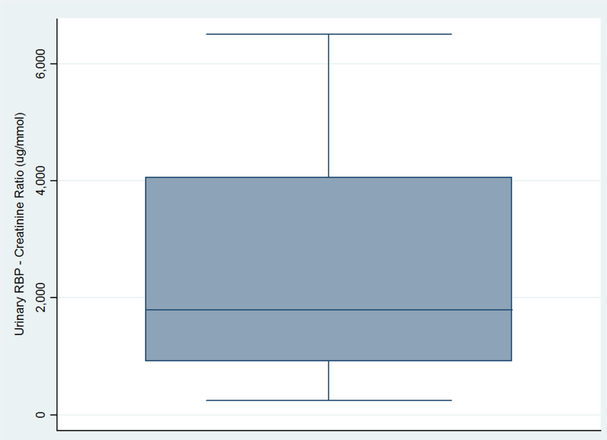


**Figure 2: Fractional phosphate reabsorption** in the cases at time of diagnosis of tenofovir renal toxicity. Values <0.82 mmol/L indicate phosphaturia consistent with proximal renal tubule toxicity.

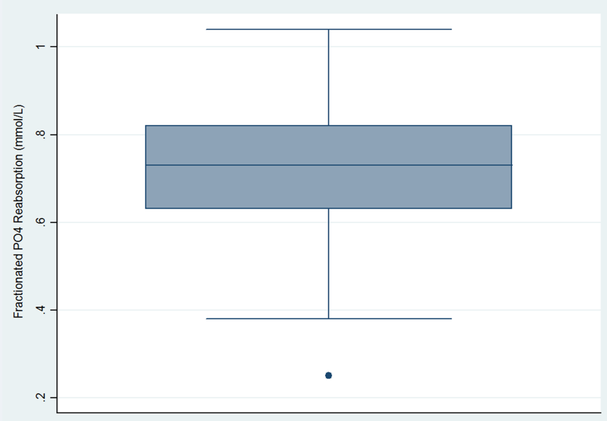


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**Table 1: Demographic and clinical Characteristics** of 86 patients: 22 with TDF Toxicity(cases) and 64 without (controls)

| Demographics | Controls | Cases |
|---|---|---|
| Age in years, median (IQR) age | 40 (36-46) | 46(41-50) |
| Weight (on starting TDF) in Kg, median (IQR) | 72 (65-82) | 70 (61-71) |
| Male gender, No(%) | 55 (86) | 19 (86) |
| Race, ethnicity, No(%) | | |
| *White* | 45 (70) | 17 (77) |
| *Black* | 11 (17) | 2 (9) |
| *Other* | 8 (13) | 3 (14) |
| Route of transmission, No ( %) | | |
| *Homosexual/bisexual* | 49 (78) | 16 (73) |
| *Heterosexual* | 13 (21) | 5 (23) |
| *Intravenous drug use* | 1 (2) | 1 (4) |
| Smoker No(%) | 26 (42) | 8 (36) |
| **ART** | | |
| *Duration on any ART in months, median (IQR)* | 106 (60-154) | 81 (41-145) |
| *Duration on TDF in months, median (IQR)* | 51 (32-63) | |
| *Use of PI at the time of stopping TDF, N(%)* | 24 (38) | 10 (45) |
| *Use of PI at any time whilst on TDF, N(%)* | 27(42) | 10 (45) |
| *Exposure on PI in months, median (IQR)* | 43 (24-57) | 46 (18-54) |
| Time since first positive in months, median (IQR) | 82 (35-147) | 77 (8-188) |
| **Clinical Characteristics, median (IQR)** | | |
| *CD4 start (cells/µL)* | 260 (160-430) | 210 (130-330) |
| *eGFR start (ml/min)* | 104 (92-125) | 100 (89-120) |
| Complications N (%) | | |
| *Hepatitis (B or C )* | 21 (32) | 2 (9) |
| *Co-morbid conditions (CV, hypertension, diabetes, cirrhosis)* | 6(9) | 38(37) |
| *AIDS defining illness* | 7(11) | 8(36) |
| *Chronic Kidney disease* | 2(3) | 4(18) |

**Table 2: Renal characteristics** (Median, IQR) prior to starting TDF and at diagnosis of TDF toxicity (cases) or at last follow-up (controls)

| Variables | Cases | | Controls | |
|---|---|---|---|---|
| | **Baseline** | **Diagnosis** | **Baseline** | **Last follow-up** |
| eGFR (ml/min/1.73 m²) | 100 (89-120) | 66 (55-79) | 104 (92-125) | 98 (78-114) |
| UPC (mg/mmol) | 18 (9-21) | 59 (30-105) | 13 (11-15) | 12 (11-16) |
| Serum Creatinine (µmol/L) | 72 (62-83) | 105 (88-127) | 78 (68-84) | 81 (71-93) |
| Serum PO4 (mmol/L) | 1.06 (0.88-1.18) | 0.95 (0.78-1.11) | 1.01 (0.88-1.18) | 1.04 (0.89-1.16) |

**Table 3: Univariate analysis**

| Variable | OR (CI) | p-value |
|---|---|---|
| Age (per 10 year increase) | 2.24 (1.19,4.23) | 0.013 |
| Ethnicity – Not white | 0.70(0.23,2.12) | 0.531 |
| Gender – female | 0.96 (0.24,3.83) | 0.953 |
| Route of transmission – Not homo/bi-sexual | 1.26 (0.40,3.96) | 0.693 |
| Smoking | 0.79 (0.31, 2.00) | 0.614 |
| Starting weight (per one kilo increase) | 0.98 (0.93,1.04) | 0.489 |
| Time since first positive (per one month increase) | 1.00 (0.99,1.01) | 0.563 |
| eGFR – < 90 ml/min/1.73 m² | 1.19 (0.34, 4.11) | 0.789 |
| Log CD4 count (per one unit increase in the log-cd4 value) | 0.60 (0.29, 1.23) | 0.166 |
| Concurrent use of PI on stopping TDF | 1.35 (0.50,3.65) | 0.527 |
| Exposure on PI (per one month increase) | 0.99 (0.94,1.05) | 0.813 |
| Viral hepatitis co-infection | 0.22 (0.047,1.01) | 0.053 |
| Co-morbid conditions *(CVD, hypertension, diabetes, cirrhosis)* | 4.99 (1.47, 16.8) | 0.010 |
| AIDS defining illness | 4.76 (1.40, 16.2) | 0.012 |
| Chronic kidney disease | 5.63 (1.03,30.86) | 0.046 |

**Multivariate analysis:**
We have also performed multivariate analysis. All significant variables from the univariate analysis were included in a regression model and using a forward stepwise procedure, the variables **CKD [OR 15.11, CI (1.96, 116.1), p=0.009 ] and age 10 [OR=3.24, CI (1.45, 7.21), p=0.004] were found significant .**

## Conclusions

Older age, hepatitis co-infection, and past medical history of cardiovascular disease, diabetes, cirrhosis or chronic renal disease were determinants of the future risk of TDF renal toxicity.

Renal toxicity in TDF-treated patients is likely to be related to pre-existing renal pathology, and common risk factors shared with HIV-negative population. In contrast to previous studies (6) we did not identify concomitant use of a PI/r as a risk factor.

With such an expanded use of TDF, screening for the risk factors prior to TDF initiation, and close monitoring of renal function is warranted in patients receiving TDF.