**Polymorphisms of Tenofovir Disoproxil Fumarate (TDF) transporters and risk of kidney tubular dysfunction in HIV positive patients**

**(Genetics of Tenofovir transporters)**

**Abstract**

**Background**

The association between single nucleotide polymorphisms (SNPs) of genes encoding transport proteins involved in the bio-disposition of Tenofovir disoproxil fumarate (TDF), and kidney tubular dysfunction (KTD) in HIV positive patients was examined in this study.

**Patients and methods**

Fifty-eight patients who received TDF were screened for KTD using retinol-binding protein (RBP) concentration in urine. We defined KTD as the top quartile of urinary RBP/creatinine ratio (> 17 μg/mmol), regardless of estimated glomerular filtration or proteinuria. Genotyping of transport proteins involved in the disposition of TDF was undertaken using validated *Taqman* 5’ nuclease assays.

**Results**

Patients with KTD (N=15) had higher current CD4 cell counts, lower eGFR, and were less likely to possess the genotype *CC* at position 24 of the *ABBC2* (MRP2, rs717620) gene. In multivariate analysis, genotype *CC* at position 24 of the *ABBC2* gene was significantly associated with KTD (odds ratio =0.05, 95% confidence interval = 0.003-0.7, P = 0.027).

**Conclusion**

Genotype *CC* at position 24 of the *ABBC2* (MRP2 rs717620) gene was significantly associated with a reduced risk of elevated urinary RBP in HIV positive patients exposed to TDF.

**Background**

Since the advent of anti-retroviral therapy (ART), there has been a substantial reduction in morbidity and mortality due to HIV infection [1]. While numerous studies have confirmed the efficacy and safety of ART, concern remains about potential toxicity of a number of currently used drugs including the effects of Tenofovir disoproxil fumarate (TDF) on the kidney [2-5]. However, the exact phenotype (clinical and laboratory) as well as genetic and non-genetic determinants of TDF induced kidney injury in HIV positive patients has remained a matter of debate [2]. Single nucleotide polymorphisms (SNPs) of genes encoding transport proteins involved in the disposition of tenofovir such as *ABCC2* (MRP2; rs717620) [6-8] *ABCC4* 4976 (rs1059751) [9], and *ABCC10* (MRP7; rs2125739, rs9349256) [10] have recently been associated with kidney tubular dysfunction (KTD) in HIV positive patients exposed to TDF. While KTD is emerging as one of the clinical phenotypes from recent reports [6, 7], various criteria have been applied to define it. In these studies, KTD has been defined by a composite of urinary and serum parameters which highlights the variable clinical phenotype and which may preclude its easy applicability in clinical practice. Conversely, there has been increasing interest in the potential utility of low molecular weight proteinuria (LMWP) as more reliable and early markers of kidney tubular injury. These include Kidney injury molecule 1 (KIM-1), retinol-binding protein (RBP), neutrophil gelatinase associated lipocalin (NGAL), and L-type fatty acid binding protein (L-FABP) amongst others [11-16]. Retinol-binding protein (RBP) is a low molecular weight (LMW) protein that is excreted in increased amounts in patients with KTD [15]. In a large clinical trial, patients randomised to TDF experienced significant increases in urinary RBP excretion [14]. In a recent cross sectional study, patients exposed to TDF (when administered with a ritonavir-boosted protease inhibitor) were more likely to have substantially elevated urinary RBP concentrations [15]. Whether KTD as defined by LMW proteinuria correlates with SNPs of genes encoding transporter proteins involved in the disposition of TDF is unknown. We examined such an association for previously reported SNPs in the *ABCC2 (MRP2)*, *ABCC4 (MRP4)*, *ABCC10 (MRP7)*, *SLC22A6 (OAT1)* and *SLC22A11 (OAT4)* genes.

**Patients and methods**

**Study population**

The demographic features of the study population have been described previously [15]. Briefly HIV-positive patients attending King’s College Hospital, London, United Kingdom, were invited to participate in a cross sectional study to examine the prevalence of kidney disease and its associated factors. Clinical information was obtained, as well as blood and urine samples collected and stored at -70°C until use. RBP was quantified by enzyme-linked immunosorbent assay (ELISA; Immundiagnostik, Bensheim, Germany; reference range 0.01-0.54 mg/L) and expressed as ratio to creatinine concentration (RBPCR). KTD was defined by an RBPCR value in the top quartile (>17 µg/mmol), regardless of estimated glomerular filtration or proteinuria. The study was reviewed and approved by the NHS research ethics committee.

**Selection of Single Nucleotide Polymorphisms and Genotyping**

Seven SNPs were selected for mutational screening of genes encoding transport proteins involved in the disposition of Tenofovir disoproxil fumarate. All seven SNPs selected in this study have previously been associated or tested for their association with KTD. Evaluated SNPs include *ABCC2* (MRP2; rs717620), *ABCC4* 3463 (MRP4; rs1751034), *ABCC4* 669 (MRP4*;* rs899494*), SLC22A11* (OAT4; rs11231809), *SLC22A6* (OAT1; close to accession numberAJ249369), *ABCC10* (MRP7; rs9349256, rs2125739). Genomic DNA was extracted from stored serum samples using the QIAamp DNA extraction kit. Mutational screening, and genotyping was carried out by allelic discrimination with made-to-order primers and probes using *Taqman 5’ nuclease* genotyping assays with standard protocol (*TaqMa*n SNP Genotyping Assays; Applied Biosystems, 850 Lincoln Centre Drive, Foster City, California 94404, USA.).

**Statistical analysis**

Genotypic frequencies in the study population were compared by Fisher’s exact test. All SNPs were tested for deviation from the Hardy-Weinberg equilibrium (HWE) by Chi squared test using Haploview software (Broad Institute, Cambridge, Massachusetts, USA). Both bivariate and multivariate analyses were carried out to identify predictor variables. Co-variates with p<0.1 in univariate analysis were entered into multivariate logistic regression models. P values <0.05 were considered statistically significant. All other data analyses were carried out using StatsDirect version 2.7.9 (StatsDirect Ltd, Altrincham, Cheshire, UK).

**Results**

**Patient characteristics**

Eighty-one (81) of the 317 patients in the cross sectional cohort received TDF at the time of sampling. Of these, 23 had missing RBPCR values and were not included in analyses. Of the remaining 58, 15 (25.9%) had KTD, whilst the remaining 43 (74.1%) patients served as controls. The median duration of TDF exposure was 583 (IQR 195, 1035) days. Patients with KTD had higher current CD4 cell counts, lower estimated glomerular filtration rates (eGFR), and higher albumin creatinine ratios (ACR) (Table 1).

**Association of KTD and SNPs of Tenofovir transporter genes**

The distributions of genotypes of the studied SNPs are shown in Table 2. There was a lower expression of the genotype *CC* at position 24 of the *ABBC2* (MRP2, rs717620) gene in patients with KTD compared with *CT* and *TT* genotypes (odds ratio [OR] 0.29; 95% confidence interval [CI] 0.08-0.96, p= 0.04). There was a trend towards reduced risk of KTD with the intronic *G* allele of *ABCC10* (MRP7, rs9349256; OR = 0.4, 0.2-1.0, P = 0.08), and increased risk with the *A* allele of the influx transporter *SLC22A11* (OAT 4, rs11231809, OR 2.3, 0.9-5.8, P = 0.07).

**Independent predictors of KTD**

Table 3 shows factors associated with KTD in HIV positive patients exposed to TDF. Univariate odds ratios were calculated for each of the SNPs of interest. Possession of the *CC* genotype at position 24 of the *ABCC2* gene (MRP2, rs717620) was the only SNP significantly associated with KTD. This SNP remained significantly associated with KTD after adjustment for age and eGFR, (adjusted OR= 0.05; 0.003-0.71, P=0.027).

**Haplotype analyses**

We carried out exploratory haplotype analyses of the *ABCC2-ABCC4* SNPs; no significant association with KTD was observed.

**Discussion**

A number of genes encoding transport proteins involved in the disposition of TDF have been known to be polymorphic [6, 7, 10]. This is the first study exploring the potential relationship between SNPs of genes encoding transport proteins involved in the biodisposition of TDF and risk of kidney tubular injury in HIV infected patients as defined by LMW proteinuria (RBPCR). Since its approval in 2001, TDF have found extensive use across a broad range of HIV and Hepatitis B patient cohorts, with its efficacy and safety well established by a number of studies[14, 17]. Nonetheless, a small proportion of patients develop severe renal tubular toxicity (Fanconi syndrome), and about 6-22% of patients reportedly have subclinical KTD [18-20]. Previous studies have suggested possession of genotype *CC* at position 24 of the *ABCC2* (MRP2, rs717620) gene [6-8], *ABCC10* (MRP7, rs9349256, and rs2125739**)** [10] including the extended haplotype *ABCC10-ABCC2* (GGC-CGTC) [10] in addition to age , and low body weight as potential determinants of KTD in HIV positive patients exposed to TDF. In these studies, KTD was defined by a composite of serum and urinary parameters, based around estimated glomerular filtration rate, and tubular proteinuria. Another recent study carried out exclusively in a prospective Japanese cohort of HIV positive patients failed to establish any association between the *ABCC2 24CC* (rs717620) SNP, and risk of KTD. It is noteworthy that this study utilised eGFR (<60mls/min/1.73m2) as a diagnostic marker for kidney dysfunction [21].

In contrast, we observed that subjects with elevated urinary RBP were less likely to carry *ABCC2 24CC*. A number of factors could have accounted for this discrepancy, including the limited size of our study. Most importantly, KTD has previously been defined using different surrogate markers of tubular injury, whereas we elected to study urinary RBP ratio (which has potential benefits as a putative tubular biomarker). How the mode of characterisation of KTD explains the difference in outcome between our report and previous studies is uncertain. Mechanistic studies[22-24] have established MRP4 (*ABCC4*) and MRP7 (*ABCC10*) [10] but not MRP2 (*ABCC2*) as efflux transporters of TDF. However, previous pharmacogenetic studies including ours have observed associations between *ABCC2* (MRP2, rs717620) and not *ABBC4* (MRP4) genotypes and KTD in TDF-exposed patients. Suggested explanations for this paradox include the fact that *ABCC2* (MRP2) may be in linkage disequilibrium with *ABCC4* (MRP4)[7]; possession of the *ABBC2* 24 CC (MRP2) genotype may lead to less efficient tenofovir excretion from tubular cells [7]with the potential for TFV accumulation within kidney tubular cells; possession of *ABCC2* 24 CC (rs717620) genotype may influence the transport of a yet to be identified factor that impacts on TDF induced KTD [7].

Recently, Likanonsakul reporting in an exclusive cohort of Thai patients showed significant association between possession of the *C* allele of the *ABCC4 T4976C* (rs1059751) SNP, and risk of KTD. The novelty of this report includes its utility of a threshold of β-2 microglobulin as a diagnostic marker of KTD, and in classification of patient cohorts into cases and controls. Additionally, this represent the only report to date to demonstrate any significant association between ABCC4 *T4976C* (rs1059751) SNP, and risk of KTD in HIV positive patients exposed to TDF [9].

Kidney tubular dysfunction comprises a spectrum with Fanconi syndrome representing the most extreme phenotype and its definition to date has relied on a composite of several urine and serum parameters [7]. The use of RBP as a single diagnostic marker may provide a convenient mode of assessing KTD in clinical practice [14], but this will need exploration by future prospective studies .

**Limitations**

As has been the case with recent pharmacogenetic reports, although our study showed significant correlation between other evaluated SNPs of TFV transport proteins and markers of kidney function in this population, we had limited power to demonstrate an independent association with KTD. Additionally our study is limited by lack of comparison between traditional composite urinary and serum marrkes of KTD and LMWP in adjudication of our cases and control. Incorporating this in the design of future prospective studies will improve case ascertainment. Owing to these limitations there will be need for further prospective work in this area to ascertain the exact relationship between these LMWP and KTD, as well as any clinically relevant association with SNP’s encoding TFV transporters.

**Conclusion**

In conclusion we have demonstrated that possession of genotype *CC* at position 24 of the *ABCC2* (MRP2 rs717620) gene was significantly negatively associated with the risk of elevated urinary RBP in HIV positive patients exposed to TDF.

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**Declarations**

The corresponding author has no relevant conflict of interest to declare.

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**Tables**

**Table 1: Characteristics of the study population (N = 58)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristics |  | All patients |  KTD a*(N =15)* | Controls*(N = 43)* | *p* |
| Age (years) | *Mean (SDb)* | 42.2 (8.2) | 46 (8.3) | 41.3 (8.5) | 0.06 |
| Gender (Male) | *N (%)* | 60 (73.2) | 12 (80) | 31 (72.1) | 0.55 |
| Ethnicity (White) | *N (%)* | 41 (50) | 10 (66.7) | 19 (44.2) | 0.079 |
| Hepatitis C co-infection(Positive) | *N (%)* | 7 (8.5) | 1 (6.7) | 5 (11.6) | 0.57 |
| CD4 cell count (cells/mm3) | *Median (IQRc)* | 398 (246, 526) | 491 (417, 598) | 361 (227, 492) | 0.006 |
| HIV RNA (copies/mL) | *Median (IQR)* | <50 | <50 | <50 | 0.59 |
| Duration on Tenofovir (Days) | *Median (IQR)* | 583 (195, 1035) | 794 (210, 1370) | 576 (175, 1022) | 0.35 |
| Co-exposure to protease inhibitors (PI) | *N (%)* | 29 (35.4) | 8 (53.3) | 13 (30.2) | 0.11 |
| Weight (Kilograms) | *Median (IQR)* | 73 (66, 81.8) | 76.7 (53-123) | 74.4 (-55-121) | 0.57 |
| Hypertension (Yes) | *N (%)* | 6 (7.3) | 2 (13.3) | 4 (9.3) | 0.75 |
| eGFR (mL/min/1.73m2) | *Median (IQR)* | 85.7 (75.5, 94.6) | 78.2 (50.6, 87.9) | 88.9 (77.8, 100.7) | 0.006 |
| Urine PCRd (mg/mmol) | *Median (IQR)* | 9.4 (6.9, 15.9) | 11.2 (6.9, 21.1) | 11.1 (1.8, 31.9) | 0.112 |
| Urine ACRe (g/mmol) | *Median (IQR)* | 1.1 (0.7, 2.1) | 2.8 (0.16, 12.6) | 1.35 (0.094, 6.31) | 0.019 |
| Serum phosphate (mmol/L) | *Median (IQR)* | 0.96 (0.84, 1.1) | 0.92 (0-1.35) | 0.98 (0.65-1.36) | 0.09 |
| TmPO4/GFRf | *Median (IQR)* | 1.0 (0.9, 1.1) | 80.8 (62.4-94.6) | 87.8 (66.9-98.3) | 0.08 |

Data presented are median (interquartile range) for quantitative variables and number of patients (percentage) for qualitative variables as appropriate.

*a: Based on RBPCR > or < 17* µg/mmol*; b: Standard deviation; c: Inter-quartile range; d: urine protein creatinine ratio; e: urine albumin creatinine ratio; f: Tubular maximum capacity for renal phosphate re-absorption to glomerular filtration rate (GFR) ratio*

**Table 2: Allelic frequencies in HIV positive patients exposed to tenofovir with and without kidney tubular dysfunction (KTD)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SNPb ID | Patients with KTD a*n* = 15 | Patients without KTD*n* = 43 | *OR (95% CI)* | *P*-value |
| *ABCC2 24*  (rs717620) MRP2 (Chromosome 10) |  |  | T allele = 3.4 (1.03-11.1)C allele = 0.29 (0.08-0.96) | **0.04** |
| TT | 1 (6.7) | 0  |
| CT | 5 (33.3) | 7 (16.3) |
| CC | 9 (60.0) | 36 (83.7) |
| C | 23 (76.7) | 79 (91.9) |
| T | 7 (23.3) | 7 (8.1) |
| *ABCC4 3463* (rs1751034) MRP4 (Chromosome 13) |  |  | C allele 1.6 (0.6-4.2) | 0.2 |
| TT | 8 (57.1) | 26 (60.4) |
| CT | 3 (21.4) | 15 (34.9) |
| CC | 3 (31.4) | 2 (4.7) |
| T | 19 (67.9) | 67 (77.9) |
| C | 9 (32.1) | 19 (22.1) |
| *ABCC4 669* (rs899494) MRP4 (Chromosome 13) |  |  | T allele 1.18 (0.31-5.6) | 0.8 |
| CC | -- | -- |
| CT | 3 (20) | 10 (23.3  |
| TT | 12 (80) | 33 (76.7) |
| C | 3 (10) | 10 (11.6) |
| T | 27 (90) | 76 (88.4) |
| *SLC22A11* (OAT 4) rs11231809 (Chromosome 11) |  |  | A allele 2.3 (0.9-5.8) | **0.07** |
| TT | 8 (53.3) | 30 (69.8) |
| AT | 3 (20) | 9 (20.9) |
| AA | 4 26.7) | 4 (9.3) |
| T | 19 (63.3) | 69 (80.2) |
| A | 11 (36.7) | 17 (19.8) |
| *SLC22A6 453 GA (OAT1)* c (Chromosome 2) |  |  | A allele 0.48 (0.1-1.6) | 0.29 |
| GG | 12 (80) | 29 (67.4) |
| AG | 3 (20) | 12 (27.9 |
| AA | 0 | 2 (4.7) |
| G | 27 (90) | 70 (81.4) |
| A | 3 (10) | 16 (18.6) |
| *ABCC10* (rs9349256) MRP7 (Chromosome 6) |  |  | A allele = 2.1(0.9-4)G allele = 0.4 (0.2-1.0) | **0.08** |
| AA | 7 (46.7) | 8 (19) |
| AG | 3 (20) | 17 (38.1)  |
| GG | 5 (33.3) | 18 (42.9) |
| A | 17 (56.7) | 33 (38.4) |
| G | 13 (43.3) | 53 (61.6) |
| *ABCC10* (rs2125739) MRP7 (Chromosome 6) |  |  | C allele 0.79 (0.26-2.2) | 0.6 |
| TT | 6 (54.5) | 9 (29.0) |
| CT | 3 (27.3) | 17 (54.8) |
| CC | 2 (18.2) | 5 (16.1) |
| T | 15 (68.2) | 39 (62.9)  |
| C | 7 (31.8) | 23 (37.1) |

*Note: Data are number of patients with percentages in bracket)*

a: As defined by RBPCR >17 µg/mmol; *b. Single nucleotide polymorphisms; c. Relative to accession no: AJ249369;*

**Table 3: Factors predicting kidney tubular dysfunction(KTD) a in HIV infected patients exposed to Tenofovir a**

|  |  |  |
| --- | --- | --- |
| Parameter | Univariate analysis | Multivariate analysis |
| OR (95% CI) | *P* | OR (95% CI) | *P* |
| Age (Years) | 0.9 (0.99-1.0) | 0.07 | 1.0 (0.91-1.1) | 0.53 |
| *e*-GFRb (ml/min/1.73m2) b | 0.94 (0.89-0.9) | 0.007 | 0.96 (0.9-1.0) | 0.32 |
| *ABCC2 24CC (MRP2)* rs717620 | Genotype CC 0.24 (0.06-0.93) | 0.04 | 0.05 (0.003-0.71) | **0.027** |
| *ABCC10* (rs2125739) MRP7 | C allele 3 (0.54-16.8) | 0.21 | -- | -- |
| *ABCC10* (rs9349256) MRP7 | *G allele* 0.42 (0.1-.1.7) | 0.2 |  |  |
| *ABCC4 669* (rs899494) MRP4 | T allele 0.83 (0.19-3.5) | 0.78 | -- | -- |
| *ABCC4 3463* (rs1751034) MRP4 | *C allele 2.5 (0.31-20.4)**T allele 2.1 (0.29-14.7)* | 0.390.46 | -- | -- |
| *SLC22A11* (OAT 4) rs11231809 | A allele 0.28 (0.03-1.31) | 0.11 | -- | -- |
| *SLC22A6 453 GA (OAT1) c c* | A allele 1.93 0.46-7.9 | 0.36 | -- | -- |

*a: As defined by retinol binding protein/creatinine ratio >17* µg/mmol

*b: As determined by the 4-variable MDRD equation*

*c: Relative to accession no: AJ249369*