Risk Factors of Renal Tubular Dysfunction in Thai People Living with HIV Receiving Tenofovir Disoproxil Fumarate

Angsana Phuphuakrat, MD, PhD1, Ekawat Pasomsub, PhD2, Wasun Chantratita, PhD3, Surakameth Mahasirimongkol, MD, PhD4, Sinee Disthabanchong, MD1, Somnuek Sungkanuparph, MD5, and Sasisopin Kiertiburanakul, MD, MHS1

Abstract
Tenofovir disoproxil fumarate (TDF) associates with renal tubular dysfunction (RTD) in some people living with HIV (PLWH). We studied clinical and genetic factors associated with RTD in Thai PLWH receiving TDF. RTD was diagnosed in 13 of 65 (20%) patients. The median (interquartile range) age and CD4 cell counts were 43.8 (40.4-50.9) years and 554 (437-716) cells/mm³, respectively. The median duration of TDF use was 46.9 (31.5-54.1) months. Univariate logistic regression demonstrated body mass index (BMI), concomitant use of protease inhibitor (PI), hyperlipidemia, and homozygous C/C SNP rs1059751 of ABCC4 gene as predisposing factors of RTD. In multivariate model, concomitant use of PI [adjusted odds ratio (aOR) 11.39; 95% confidence interval (CI), 1.59-81.56; \(P=0.015\)], hyperlipidemia (aOR 8.59; 95% CI, 1.46-50.40; \(P=0.017\)), and BMI (aOR 0.76; 95% CI, 0.59-0.98; \(P=0.037\)) remained associated with RTD in patients receiving TDF. PLWH receiving TDF with the presence of these factors should be closely monitored for RTD.

Keywords
HIV, renal tubular dysfunction, pharmacogenomics, risk factors, tenofovir disoproxil fumarate

Introduction
Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor that is widely used for the treatment of people living with human immunodeficiency virus type 1 (HIV-1). TDF has been recommended as a component of the nucleoside backbone of the preferred HIV treatment regimens in Thailand since 2010. The drug is an orally bioavailable prodrug of tenofovir (TFV). TFV is excreted by glomerular filtration and active tubular secretion. Although TFV is considered safe and tolerable in clinical trials, multiple cases of proximal renal tubulopathy and renal failure have been reported in practical settings. A study in the Asia-Pacific reported TDF-nephrotoxicity with an incidence of 1.75 per 100 person-years.

Although the subsequent more favorable renal safety profile pro-drug formulation, tenofovir alafenamide (TAF), is available, some concerns on weight and metabolic changes, as well as an economic value may limit the use of TAF.

The mechanism of TFV-induced kidney injury is not completely understood. It is suggested that mitochondria are a target of TFV toxicity. Mitochondrial damage in the proximal
renal tubular cells was observed in people living with HIV (PLWH) with renal tubular dysfunction (RTD) receiving TDF.\textsuperscript{11,12} TFV is a weak inhibitor of mitochondrial DNA polymerase-γ, and mitochondrial DNA depletion has been demonstrated in animal models of TFV toxicity.\textsuperscript{13}

Transporter proteins in the renal proximal tubules play a part in controlling the intracellular concentration of TFV and hence alteration in their expression could associate with TFV-related RTD. TFV enters renal tubule epithelial cells through the basolateral membrane and involves organic anion transporters (OATs), OAT1, and OAT3\textsuperscript{14,15} that are encoded by the genes SLC22A6 and SLC22A8, respectively. OAT4, encoded by the gene SLC22A11, is expressed in the apical membrane of renal proximal tubule cells. A polymorphism in this gene (rs11231809) has been shown to interfere with diuretic transport in the proximal tubule cells. A polymorphism in this gene (ABCC2) demonstrated,\textsuperscript{19,20} although the involvement of MRP2 with TFV transport in the proximal tubule cells, intestinal cells, and hepatocytes.\textsuperscript{22-24} P-glycoprotein, encoded by the ABCB1 gene, is a membrane protein expressed on the renal proximal tubular cells, intestinal cells, and hepatocytes.\textsuperscript{22-24} P-glycoprotein transports TDF, therefore the alteration of P-glycoprotein expression in enterocytes could affect TFV exposure.

TFV-associated nephrotoxicity is multifactorial. Genetic polymorphisms of renal tubular cell transporter proteins have been shown to affect the risk of developing TFV-related RTD.\textsuperscript{19,20,25} Clinical factors, including increasing age, low body weight, pre-existing decreased kidney function, coexisting diabetes mellitus, and concomitant use of protease inhibitor (PI) or nephrotoxic drugs are known to be risk factors for nephrotoxicity.\textsuperscript{26-28}

We aimed to study the association between RTD and clinical factors as well as 57 single nucleotide polymorphisms (SNPs) in the ABCC2, ABCC4, ABCC10, SCL22A6, SCL22A11, and ABCB1 genes in Thai PLWH receiving TDF. Characterizing risk factors could guide frequent monitoring of renal tubular function in PLWH with particular risk factors whom TDF is needed or switching to other antiretroviral regimens.

### Methods

#### Study Population

A cross-sectional study was conducted to investigate the association between clinical factors and SNPs in genes encoding renal tubular transporter and TFV-associated RTD in Thai PLWH. Thai adults (age >15 years) living with HIV receiving TDF-containing antiretroviral regimens between September 2012 and January 2013 were invited to participate in this study. PLWH invited were the subset 149 PLWH from the previous study on the association between SNPs and nevirapine-induced rash, who were treated with stavudine, lamivudine, and nevirapine regimen,\textsuperscript{26} and stavudine was switched to TDF. The exclusion criteria included PLWH with fasting plasma glucose >200 mg/dL or diagnosed with diabetes mellitus and those denied to participate in the study. Demographic data were extracted from the medical records.

#### Pharmacodynamic

SNPs in genes encoding tubular transporters were chosen for the study based on their functional significance from previously published literatures.\textsuperscript{20,25} Fifty-seven SNPs in the ABCC2, ABCC4, ABCC10, SCL22A6, SCL22A11, and ABCB1 genes data retrieved from the previous genome-wide association study (GWAS) samples\textsuperscript{29} were collected. GenABEL package\textsuperscript{32} in the R statistical program was used to estimate the significance of candidate SNPs. Bonferroni adjustment was used for the correction of multiple testing. SNPs with complete homozygosity and minimal allele frequency less than 0.05 were excluded for further analysis.

#### Statistical Analysis

Median (interquartile range, IQR) and frequencies (%) were used to describe characteristics of PLWH. Chi-square test or Fisher’s exact test and Mann-Whitney U test were used to compare categorical variables and continuous variables between the two groups, respectively. Associations between clinical factors, alleles, and RTD were tested by univariate and multivariate logistic regression analyses. Variables that presented $P<0.1$, were considered in a multivariate logistic regression model with forward and backward stepwise logistic regression. Odds ratio (OR) and adjusted odds ratio (aOR) and their 95% confidence interval (CI) were calculated. A $P$-value of $<0.05$ was considered statistically significant. The receiver operating characteristic (ROC) curve and the Youden
The statistical analyses were conducted using Stata statistical software version 17.0 (StataCorp, College Station, TX, USA).

Ethical Approval and Informed Consent

The protocol of this study was reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA2012/217). All participants provided written informed consent prior to enrollment in the study.

Results

A total of 65 PLWH who were able to provide blood and urine samples and fulfilled the study criteria were enrolled in the study. The baseline characteristics and laboratory data for PLWH with and without RTD are shown in Table 1. RTD was diagnosed in 13 of the 65 (20%) PLWH. Thirty-three (50.5%) of the PLWH were female. Median (IQR) age and

### Table 1. Characteristics of Patients with and Without Renal Tubular Dysfunction.

| Characteristics | Patients with RTD (n = 13) | Patients without RTD (n = 52) | P value |
|-----------------|-----------------------------|-------------------------------|--------|
| Median (IQR) age, years | 42.7 (37.0-51.1) | 43.9 (40.5-50.8) | 0.422 |
| Female, n (%) | 7 (53.9) | 26 (50.0) | 0.804 |
| Heterosexual risk, n (%) | 13 (100.0) | 41 (78.9) | 0.069 |
| Median (IQR) weight, kg | 48.5 (44.0-60.0) | 55.7 (51.1-63.2) | 0.093 |
| Median (IQR) body mass index, kg/m² | 18.1 (16.9-21.9) | 21.5 (19.6-23.9) | 0.026 |
| Median serum creatinine, mg/dL | 0.9 (0.7-1.1) | 0.8 (0.7-0.9) | 0.994 |
| Median (IQR) CrCl CG, mL/min | 69.5 (50.6-83.0) | 82.5 (74.2-99.8) | 0.029 |
| Median (IQR) CrCl MDRD, mL/min | 89.6 (60.3-98.9) | 97.3 (85.7-109.3) | 0.039 |
| Median (IQR) CD4 cell count, cells/mm³ | 589 (494-703) | 548 (425-726) | 0.461 |
| Hypertension, n (%) | 3 (23.1) | 9 (17.3) | 0.632 |
| Hyperlipidemia, n (%) | 8 (61.5) | 15 (28.9) | 0.027 |
| PI-containing regimens, n (%) | 5 (38.5) | 5 (9.6) | 0.010 |
| Lopinavir/ritonavir | 2 (15.4) | 1 (1.9) |
| Atazanavir/ritonavir | 2 (15.4) | 4 (7.7) |
| Darunavir/ritonavir | 1 (7.7) | 0 (0.0) |
| NNRTI-containing regimens, n (%) | 8 (61.5) | 46 (88.5) | 0.035 |
| Nevirapine | 5 (38.5) | 24 (46.2) |
| Efavirenz | 3 (23.1) | 21 (40.4) |
| Etravirine | 0 (0.0) | 1 (1.9) |
| Median (IQR) duration of receiving TDF, months | 49.5 (35.3-59.0) | 45.7 (27.2-54.0) | 0.381 |
| Median (IQR) duration of ART before switching to TDF, months | 62.3 (41.7-90.2) | 68.3 (44.1-96.6) | 0.683 |

### Table 2. Univariate Analysis of Clinical Factors of Renal Tubular Dysfunction in PLWH Receiving TDF.

| Characteristics | OR (95% CI) | P value |
|-----------------|-------------|--------|
| Age | 0.98 (0.90-1.06) | 0.577 |
| Female gender | 1.17 (0.34-3.95) | 0.804 |
| BMI | 0.76 (0.59-0.97) | 0.027 |
| Duration TDF, per month increment | 1.01 (0.98-1.06) | 0.359 |
| CD4 cell count, per 100 cells/mm³ increment | 1.14 (0.87-1.50) | 0.340 |
| PI-containing regimen | 5.88 (1.38-25.01) | 0.017 |
| Hypertension | 1.43 (0.33-6.28) | 0.633 |
| Hyperlipidemia | 3.95 (1.11-14.03) | 0.034 |

**Abbreviations:** BMI: body mass index, CI: confidence interval, TDF: tenofovir disoproxil fumarate, OR: odds ratio, PI: protease inhibitor.
CD4 cell counts were 43.8 (40.4-50.9) years and 554 (437-716) cells/mm³, respectively. Three PLWH had HIV viral load above the lower limits of detection of the assays. Of the total PLWH in the study, 54 (83.1%), 10 (15.4%), and 1 (1.5%) PLWH receiving non-nucleoside reverse transcriptor, PI, and integrase inhibitor-based regimens, respectively. The median duration of TDF using was 46.9 (31.5-54.1) months. Although serum creatinine was comparable in the two groups, creatinine clearance calculation based on both Cockroft-Gault and Modification of Diet in Renal Disease (MDRD) was lower in PLWH with RTD. PLWH with RTD had lower BMI compared to those without RTD. There were significant numbers of individuals with hyperlipidemia and receiving PI-containing regimens in PLWH with RTD. Renal tubular markers and the contribution of each parameter to RTD in this study are shown in Table 1. Univariate analysis of clinical factors showed a significant association between RTD and BMI, concomitant use of PI-containing regimens, and diagnosed hyperlipidemia (Table 2).

SNPs with significant levels after conservative and their distribution of genotypes and alleles are shown in Table 3. All polymorphisms were in Hardy-Weinberg equilibrium in all samples. The single SNP analysis showed a greater percentage of individuals with RTD among the SNP 4976T→C, rs1059751 of ABCC4. The effect of this SNP was more evident in PLWH with C/C homozygote than heterozygote following the additive genetic model. OR of having RTD in PLWH carrying C/C homozygote was 13.13 times compared to those who harbored T/T homozygote (Table 4). No significant association was found between other SNPs and RTD.

Tables

Table 3. Genotype, Allele Frequencies and Univariate Analysis of SNPs in PLWH Receiving TDF.

| Genotype                  | Patients with RTD (n = 13) | Patients without RTD (n = 52) | OR (95% CI) | P value |
|---------------------------|-----------------------------|------------------------------|-------------|---------|
| ABCC4 (MRP4) T→C, rs1059751 (3’UTR) |                             |                              |             |         |
| T/T                       | 1 (7.69)                    | 21 (40.38)                   | 1           |         |
| T/C                       | 7 (53.85)                   | 23 (44.23)                   | 6.39 (0.72-56.38) | 0.095   |
| C/C                       | 5 (38.46)                   | 8 (15.38)                    | 13.13 (1.32-130.42) | 0.028   |
| T                         | 9 (65.33)                   | 65 (62.50)                   |             |         |
| C                         | 17 (65.38)                  | 39 (37.50)                   | 0.010       |         |
| T→C rs9634642 (intron)    |                             |                              |             |         |
| T/T                       | 6 (46.15)                   | 10 (19.23)                   | 1           |         |
| T/C                       | 4 (30.77)                   | 24 (46.15)                   | 0.28 (0.06-1.20) | 0.086   |
| C/C                       | 3 (23.08)                   | 18 (34.62)                   | 0.28 (0.06-1.36) | 0.114   |
| T                         | 16 (61.54)                  | 44 (42.30)                   |             |         |
| C                         | 10 (38.46)                  | 60 (57.69)                   | 0.079       |         |
| ABCC10 (MRP7) T→C, rs2125739 (exon 12) | | | | |
| T/T                       | 13 (100.00)                 | 39 (75.00)                   | N/A*        | N/A*    |
| T/C                       | 0 (0.00)                    | 13 (25.00)                   | N/A*        | N/A*    |
| C/C                       | 0 (0.00)                    | (0.00)                       |             |         |
| T                         | 26 (100.00)                 | 91 (87.50)                   | 0.057       |         |
| C                         | 0 (0.00)                    | 13 (12.50)                   |             |         |

*Not applicable because of complete discrimination between the two groups of patients with and without renal tubular dysfunction, no odds ratio could be estimated for the SNP rs2125739.

Abbreviations: CI: confidence interval, N/A: not applicable, RTD: renal tubular dysfunction, OR: odds ratio

Table 4. Multivariate Analysis of Significant Clinical and Genetic Risks Factor Associated with RTD in PLWH Receiving TDF.

| Characteristics          | aOR (95% CI) | P value |
|--------------------------|--------------|---------|
| BMI                      | 0.76 (0.59-0.98) | 0.037   |
| PI-containing regimen    | 11.39 (1.59-81.56) | 0.015   |
| Hyperlipidemia           | 8.59 (1.46-50.40) | 0.017   |

Each variable was adjusted for the SNP rs1059751.

Abbreviations: aOR: adjusted odds ratio, CI: confidence interval, BMI: body mass index, PI: protease inhibitor

Multivariate logistic regression model combining both clinical and genetic factors was performed, only clinical factors remained independently associated with RTD in PLWH receiving TDF; concomitant use of PI (aOR 11.39; 95% CI, 1.59-81.56; P = 0.015), hyperlipidemia (aOR 8.59; 95% CI, 1.46-50.40; P = 0.017), and BMI (aOR 0.76; 95% CI, 0.59-0.98; P = 0.037). Youden index showed predictive ability of BMI to predict low versus high risk for RTD at a cut-off of 18.6 kg/m² (a sensitivity, specificity, area under the ROC curve of 58.3%, 80.9%, and 0.70, respectively).

Discussion

We investigated the risk factors of Thai PLWH receiving TDF. RTD in this group of PLWH is not uncommon. We demonstrated low BMI, concomitant use of PI, and hyperlipidemia as associating factors of RTD in Thai PLWH receiving TDF. When clinical and genetic factors were combined in the
multivariate regression model, only clinical factors remained statistical significant.

TFV-associated nephrotoxicity is multifactorial. Clinical and genetic polymorphisms of renal tubular cell transporter proteins have been shown to influence the risk of developing TFV-related RTD.\textsuperscript{3,19,20,26,33} Previous studies also showed low BMI as one of the risk factors for TFV-associated renal dysfunction.\textsuperscript{33,34} Pharmacokinetic studies demonstrated that small body weight is associated with reduced plasma TFV clearance and thus high plasma TFV concentrations, which could result in RTD.\textsuperscript{35,36} Concomitant use of PI has been shown to associate with risk factors for tubular dysfunction and/or nephrotoxicity.\textsuperscript{26,37} The mechanism could be explained by possible inhibition of TDF excretion from the proximal tubule and increasing the intracellular concentration. A previous study demonstrated lower renal clearance of TFV in PLWH on lopinavir-ritonavir combination than in those not taking a protease inhibitor.\textsuperscript{38} Our findings were consistent with earlier studies. We also revealed an association between hyperlipidemia and proximal tubular dysfunction. Dyslipidemia is known to accelerate the progression of chronic kidney disease leading to tubule-interstitial injury. In cell culture, low-density lipoprotein (LDL) was demonstrated to induce stress in human proximal tubular cells by multiple mechanisms.\textsuperscript{39}

Although genetic polymorphism in this study was not associated with RTD by the multivariate model in the study, OR of having C/C genotype at SNP rs1059751 was 13 times compared to T/T genotype. The mechanism by which polymorphism in the \textit{ABCC4} gene influences the risk of RTD could be explained by its encoding protein, MRP4, function. MRP4 is the transporter for TFV excretion at the luminal membrane of the kidney proximal tubule cells. The efflux at the luminal membrane is a rate-limiting step for many antiviral drugs and occasionally results in intracellular accumulation. The SNP 4976T→C, rs105975 locates in the 3′UTR region of the gene. Polymorphism in this region may affect translation efficiency or mRNA stability of the protein and hence could affect tubular excretion of TFV. A previous study in Thai population also showed the association of \textit{ABCC4} 4976T→C variation with \(\beta2\) microglobulinuria.\textsuperscript{40} Other studies demonstrated the association of \textit{ABCC4} 3463A→G and \textit{ABCC4} 4131T→G polymorphisms in association with higher intracellular\textsuperscript{36} and plasma\textsuperscript{41} concentrations of TFV, respectively.

Previous studies have demonstrated genetic polymorphisms in association with RTD. Izzedine et al reported the role of 1249 G→A SNP and CATC haplotype (−24C, 1249A, 3563T, 3972C) of \textit{ABCC2} in RTD.\textsuperscript{19} This study defined renal toxicity based on metabolic acidosis, urine potassium loss, hyperphosphatemia, low uric acid levels, and aminoaciduria within one month after TDF initiation. Rodriguez-Novoa et al demonstrated genotype CC at \textit{ABCC2} position −24 as one of the risk factors of RTD.\textsuperscript{25} Nishijima et al also demonstrated genotype CC at position −24 and additional genotype AA at position 1249 of the \textit{ABCC2} gene associated with RTD in the Japanese population.\textsuperscript{20} Rodriguez-Novoa et al studied the PLWH with a median duration of exposure to TDF of 34 months and the presence of at least 2 criteria of the proximal tubular abnormalities. Nishijima et al collected data in the Japanese population with a median 35-month follow-up time in PLWH with the presence of at least three criteria of the proximal tubular dysfunction. We did not find a significant association of previously identified SNPs with RTD in the present study in Thai PLWH. The previous study on factors associated with TDF discontinuation also showed no significant association of genetic variants in the multivariable analyses.\textsuperscript{42}

The results of these studies, however, are not exactly comparable owing to inconsistency in the criteria for RTD diagnosis. Our cross-sectional study collected PLWH with a median TDF treatment duration of 47 months. The criteria for the diagnosis of RTD in our study were different from those of previous studies. The discrepancy in diagnosis criteria suggested the need for uniformly established criteria for the diagnosis of TDF-associated RTD.

The strength of our study is the genetic factors that were retrieved from GWAS, in which common polymorphisms in genes of the candidate transporter proteins were investigated. This study, however, has some limitations. First, the study was a small cross-sectional study among PLWH receiving TDF in a subset of the previously studied cohort. Second, PLWH with more significant renal toxicity at earlier time points could have been missed, and baseline renal function was not collected. These factors might lead to selection bias. Third, other transporters that were not considered in this study could be involved in the transportation of the drug. Prospective studies with a larger sample size and full genetic analysis are needed.

In conclusion, concomitant use of PI-containing antiretroviral regimen, hyperlipidemia, and low BMI are significantly associated with RTD in Thai PLWH receiving TDF. Closed monitoring of RTD should be warranted in PLWH who have these factors.

Acknowledgements

We thank all participants in the study for their kind cooperation.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval and Informed Consent

The protocol of this study was reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA2012/217). All patients provided written informed consent prior to enrollment in the study.

Funding

This study was supported by research grants from Pharmacogenomics Projects, the collaboration between Ramathibodi Hospital, Mahidol University and Thailand Center of Excellence of Life Sciences (TCELS).
References

1. Sungkanuparp S, Techasathit W, Utaipiboon C, et al. Thai National guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2010. *Asian Biomed.* 2010;4(4):515–528.

2. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Res Treat.* 2011;2011:354908.

3. Cooper RD, Wiebe N, Smith N, et al. Systematic review and meta-analysis: Renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis.* 2010;51(5):496–505.

4. Izzedine H, Hulot JS, Villard E, et al. Association between ABC2 gene haplotypes and tenofovir-induced proximal tubulopathy. *J Infect Dis.* 2006;194(11):1481–1491.

5. Lebrecht D, Venhoff AC, Kirschner J, et al. Mitochondrial tubulointerstitial abnormalities in the absence of impaired glomerular function in HIV-infected patients. *Kidney Int.* 2011;78(11):1177.

6. Peyriere H, Reynes J, Rouanet I, et al. Renal tubular dysfunction associated with tenofovir therapy: Report of 7 cases. *J Acquir Immune Defic Syndr.* 2004;35(3):269–273.

7. Verhelst D, Monge M, Meynard JL, et al. Fanconi syndrome and renal failure induced by tenofovir: A first case report. *Am J Kidney Dis.* 2002;40(6):1331–1333.

8. Tanuma J, Jiamsakul A, Makane A, et al. Renal dysfunction during tenofovir use in a regional cohort of HIV-infected individuals in the Asia-Pacific. *PLoS One.* 2016;11(8):e0161562.

9. Surial B, Mugglin C, Calmy A, et al. Weight and metabolic changes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in people living with HIV: A cohort study. *Ann Intern Med.* 2021;174(6):758–767.

10. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: Is there a true difference in efficacy and safety? *J Virus Erad.* 2018;4(2):72–79.

11. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: A review of the evidence. *Am J Kidney Dis.* 2011;57(5):773–780.

12. Herlitz LC, Mohan S, Stokes MB, et al. Tenofovir nephrotoxicity: Acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. *Kidney Int.* 2010;78(11):1171–1177.

13. Lehrecht D, Vennhoff AC, Kirschner J, et al. Mitochondrial tubulopathy in tenofovir disoproxil fumarate-treated rats. *J Acquir Immune Defic Syndr.* 2009;51(3):258–263.

14. Cihlar T, Ho ES, Lin DC, Mulato AS. Human renal organic anion transporter 1 (hOAT1) and its role in the nephrotoxicity of antiviral nucleotide analogs. *Nucleosides Nucleotides Nucleic Acids.* 2001;20(4–7):641–648.

15. Ray AS, Cihlar T, Robinson KL, et al. Mechanism of active renal tubular efflux of tenofovir. *Antimicrob Agents Chemother.* 2006;50(10):3297–3304.

16. Vormfeldes SV, Schirmer M, Hagos Y, et al. Torsemide renal clearance and genetic variation in luminal and basolateral organic anion transporters. *Br J Clin Pharmacol.* 2006;62(3):323–335.
Aulchenko YS, Ripke S, Isaacs A, van Duijn CM. GenABEL: an R library for genome-wide association analysis. *Bioinformatics*. 2007;23(10):1294–1296.

Nishijima T, Komatsu H, Gatanaga H, et al. Impact of small body weight on tenofovir-associated renal dysfunction in HIV-infected patients: a retrospective cohort study of Japanese patients. *PLoS One*. 2011;6(7):e22661.

Chaisiri K, Bowonwatanuwong C, Kasettratat N, Kiertiburanakul S. Incidence and risk factors for tenofovir-associated renal function decline among Thai HIV-infected patients with low-body weight. *Curr HIV Res*. 2010;8(7):504–509.

Jullien V, Treluyer JM, Rey E, et al. Population pharmacokinetics of tenofovir in human immunodeficiency virus-infected patients taking highly active antiretroviral therapy. *Antimicrob Agents Chemother*. 2005;49(8):3361–3366.

Kiser JJ, Fletcher CV, Flynn PM, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil fumarate and abacavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. 2008;52(2):631–637.

Dauchy FA, Lawson-Ayai S, de La Faille R, et al. Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy. *Kidney Int*. 2011;80(3):302–309.

Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther*. 2008;83(2):265–272.

Piccoli C, Quarato G, D’Aprile A, et al. Native LDL-induced oxidative stress in human proximal tubular cells: multiple players involved. *J Cell Mol Med*. 2011;15(2):375–395.

Likanonsakul S, Suntisuklapporn B, Nitiyanontakij R, et al. A single-nucleotide polymorphism in ABCC4 is associated with tenofovir-related beta2-microglobulinuria in Thai patients with HIV-1 infection. *PLoS One*. 2016;11(1):e0147724.

Rungtivasuwan K, Avihingsanon A, Thammajaruk N, et al. Influence of ABCC2 and ABCC4 polymorphisms on tenofovir plasma concentrations in Thai HIV-infected patients. *Antimicrob Agents Chemother*. 2015;59(6):3240–3245.

Calcagno A, Fiumano M, Zugna D, et al. Tenofovir disoproxil fumarate discontinuation for renal outcomes: any room for treatment personalization? *Pharmacogenomics J*. 2019;19(1):65–71.