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ORIGINAL ARTICLE

Kidney dysfunction associated with tenofovir exposure in human immunodeficiency virus-1-infected Taiwanese patients

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Abstract *Background/Purpose:* Tenofovir disoproxil fumarate (TDF) is associated with kidney tubular dysfunction, for which the risk may vary among patients of different ethnicities. Data are limited, however, on the association between renal function changes and TDF exposure in human immunodeficiency virus (HIV)-infected Taiwanese patients.

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nucleotide reverse-transcriptase inhibitor;
proximal renal tubulopathy;
tenofovir

Methods: Medical records of HIV-infected Taiwanese patients seeking HIV care at a university hospital from 2011 to 2014 were reviewed. The change of estimated glomerular filtration rate (eGFR) was compared between patients not receiving combination antiretroviral therapy (cART) and those starting cART with or without TDF. The determinants of annual eGFR changes and factors associated with greater annual eGFR decline in TDF-exposed patients were explored.
Results: A total of 775 patients were included: 140 were cART-naïve, 393 received TDF-containing cART, and 242 received cART without TDF. Compared with cART-naïve patients, the annual eGFR decline was greater in TDF-exposed patients (0.57 ± 8.6 mL/min/1.73 m^2 and 2.7 ± 8.9 mL/min/1.73 m^2, $p = 0.012$). The annual eGFR decline between patients receiving cART with or without TDF was similar (2.7 ± 8.9 mL/min/1.73 m^2 and 1.8 ± 8.3 mL/min/1.73 m^2, $p = 0.567$). Diabetes was associated with worsening eGFR decline in all studied patients. TDF exposure correlated with an additional annual eGFR decline of 2.73 mL/min/1.73 m^2 (95% confidence interval 0.139—5.326, $p = 0.039$) in patients with CD4 count < 350 cells/μL. Among TDF-exposed patients, the factors associated with annual eGFR decline of > 3 mL/min/1.73 m^2 were higher baseline eGFR and lower CD4 counts.
Conclusion: Among HIV-infected Taiwanese patients, cART exposure correlated with the decline of renal function. However, TDF-exposed patients are more likely to have prominent eGFR decline, especially those with higher baseline eGFR, advanced HIV disease, and diabetes.

Introduction

Tenofovir disoproxil fumarate (TDF) is a widely used nucleotide reverse-transcriptase inhibitor, and is an important component of combination antiretroviral therapy (cART) for patients with human immunodeficiency virus (HIV) infection.[1,2] With the introduction of cART, survival of HIV-infected patients has significantly improved. However, aging, multiple comorbidities, complex medications, and prolonged cART may increase the risk of kidney injury. In recent years, kidney dysfunction has become a clinically relevant and important issue.[3—5]

Since its introduction for clinical use, TDF has been found to be associated with an increased risk of kidney tubular dysfunction including Fanconi syndrome, diabetes insipidus, or osteomalacia.[6,7] Decline in renal function was also reported in patients with exposure to TDF, experiencing either acute or chronic kidney injury, or merely a decrease of estimated glomerular filtration rate (eGFR) when compared with baseline values.[8]

The magnitude and clinical impact of TDF on renal function are still being debated. Variable degrees of eGFR loss have been reported, ranging from < 5 mL/min/1.73 m^2 to $>$ 10 mL/min/1.73 m^2 annually.[8—10] In a 10-year longitudinal prospective follow-up study, there was only a mild decline of eGFR that was attributable to TDF.[11] By contrast, a study on a cohort of Japanese patients showed that the loss of eGFR increased continuously for up to 5 years.[12] Moreover, increased frequency of proteinuria has been observed in patients receiving TDF-containing cART.[13,14] Because proteinuria may often precede GFR loss, measurements of biomarkers, such as urine β-2-microglobulin, have been proposed for early detection of renal tubular dysfunction.[15]

Previous studies have shown different incidences and profiles of adverse effects of cART in Asian populations compared with those reported in Western countries.[16,17] The predictive factors of TDF-related kidney injury have been recognized, which vary among patients of different ethnicities. For Asian people, a lower weight[18,19] and certain genetic variability[20] may contribute to the development of kidney injury. A few studies have reported on the change in renal function in TDF-exposed Asians,[19,21—24] however, most of the studies had short observation periods. This study aimed to assess the eGFR changes and to identify the risk factors for decline of renal function associated with TDF exposure in HIV-1-infected Taiwanese patients.

Methods

Patient population

This retrospective cohort study was conducted between January 2011 and December 2014 at a university hospital that is the largest designated hospital for HIV care in Taiwan. Because TDF was not introduced into clinical use in Taiwan until 2011, the study population included all HIV-infected patients who regularly sought HIV care at the hospital since 2011. Three groups of patients were defined according to their treatment status: those not receiving cART, those receiving TDF-containing cART, and those receiving cART not containing TDF.

Patients were included if they were aged ≥ 20 years with at least two serum creatinine measurements with an interval of 90 days or more. The exclusion criteria included receipt of ART < 90 days, intermittent or unknown duration of ART exposure, and end-stage renal disease on dialysis. ART was initiated and prescribed according to the national treatment guidelines for HIV infection proposed by the Taiwan Centers for Disease Control.[25] The decision to

switch or stop cART was at the discretion of the HIV-treating physicians. The study was approved by the Research Ethics Committee of National Taiwan University Hospital (registration number NTUH-201301041RIND). The data were analyzed anonymously, and written or oral informed consent was waived.

Data collection and evaluation of renal function

We used a standardized case record form to collect the information on the demographics, sexual preference, weight and height, comorbidity, treatment history of cART, plasma HIV RNA load, CD4 lymphocyte count, concomitant medications, and serum creatinine at the start of the study from the medical records of the patients. Chronic kidney disease was defined as an eGFR $<$ 60 mL/min/1.73 m^2. Dyslipidemia was defined by regular use of lipid-lowering agents, or a total cholesterol of $\geq$ 240 mg/dL, or a triglycerides level of $\geq$ 200 mg/dL. Serum creatinine measurements were performed every 6–12 months until the study ended. All patients underwent annual proteinuria screening. If the patients discontinued TDF due to renal dysfunction, serum creatinine levels and urinalysis results were monitored and followed up until the end of study (December 31, 2014).

We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, incorporating serum creatinine, age, sex, and race as four parameters to estimate GFR. The CKD-EPI equation was shown to be more accurate than the Modification of Diet in Renal Disease (MDRD) equation in the subgroup with GFR $>$ 60 mL/min/1.73 m^2.[26] Such populations include patients without kidney disease and young patients, which are very much similar to our study population. Guidelines published by the Kidney Disease Improving Global Outcomes organization, managed by the National Kidney Foundation of the United States, recommends the CKD-EPI equation for patients with higher GFR.[27] Proteinuria, detected using spot urine sample, was defined as $>$ 1+ (i.e., urine protein level $\geq$ 30 mg/dL).

Our primary outcome of interest was the change of GFR for each group of patients. The secondary objective was to identify the risk factors associated with GFR decline in patients with TDF exposure.

Statistical analysis

Patients' demographics and basic characteristics were evaluated by descriptive statistics. Data were presented as mean (standard deviation) or count (percent). Categorical variables were compared using chi-square test or Fisher exact test. Continuous variables were compared using the Kruskal–Wallis one-way analysis of variance or Mann–Whitney *U* test. For data from two related samples, variables were compared using paired *t* test. A two-tailed *p* value $<$ 0.05 was considered statistically significant. Factors associated with annual eGFR change in all patients were identified using multivariate linear regression model. Factors associated with annual eGFR decline by $>$ 3 mL/min/1.73 m^2 in patients exposed to TDF were explored using the multivariate logistic regression model. Variables were entered into the model with a backward stepwise linear or logistic regression approach with p value $<$ 0.1 as a requirement for acceptance. Data were analyzed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of patients

During the 4-year study period, a total of 775 HIV-infected patients with available serial serum creatinine data over a 90-day interval were included for analysis: 140 were not receiving cART, 393 had exposure to TDF-containing cART (TDF-exposed group), and 242 received cART not containing TDF (non-TDF-exposed group). The baseline characteristics of the patients are shown in Table 1. Overall, most patients were middle-aged homosexual men. The average weight of patients was 66.6 kg. One fourth of the patients in the TDF-exposed group had chronic hepatitis B virus infection. More patients in the non-TDF-exposed group had diabetes mellitus, hypertension, dyslipidemia, and longer duration of cART exposure with 80% of the regimens containing protease inhibitor(s). The mean follow-up duration of the patients was 672 days (standard deviation 292 days).

Renal function change of HIV patients exposed or unexposed to tenofovir

The trends of changes in eGFR in each group of patients are demonstrated chronologically by the timing of serum creatinine tests in Figure 1. In the 4-year study period, patients not starting cART had stable eGFR at around 110 mL/min/1.73 m^2. By contrast, patients receiving cART had significant decline of eGFR: a decline from 105.6 mL/min/1.73 m^2 to 97.6 mL/min/1.73 m^2 in the TDF-exposed group, and from 99.4 mL/min/1.73 m^2 to 92.7 mL/min/1.73 m^2 in the non-TDF-exposed group (Figure 1).

In Table 2, we compared the changes between the first and the last eGFR among the three groups. Both groups of patients receiving cART with or without TDF had significantly lower eGFR in the last measurements, compared with their respective first eGFR measurements (105.6 $\pm$ 16.4 mL/min/1.73 m^2 and 100.5 $\pm$ 17.1 mL/min/1.73 m^2; 99.4 $\pm$ 17.6 mL/min/1.73 m^2 and 96.4 $\pm$ 18.1 mL/min/1.73 m^2, respectively; both $p < 0.001$), however, patients not receiving cART had similar levels (110.1 $\pm$ 14.4 mL/min/1.73 m^2 and 109.8 $\pm$ 13.4 mL/min/1.73 m^2; $p = 0.387$). Compared with patients not receiving cART, the annual decline of eGFR was greater in the TDF-exposed group (0.57 $\pm$ 8.6 mL/min/1.73 m^2 and 2.7 $\pm$ 8.9 mL/min/1.73 m^2; $p = 0.012$). However, the annual declines of eGFR between the TDF-exposed group and the non-TDF-exposed group were not statistically significantly different (2.7 $\pm$ 8.9 mL/min/1.73 m^2 and 1.8 $\pm$ 8.3 mL/min/1.73 m^2; $p = 0.567$). The annual percentage of decline in eGFR was 0.1 $\pm$ 8.1% for the patients not receiving cART, which was significantly lower than that for the TDF-exposed group (2.3 $\pm$ 8.6%, $p = 0.032$) or the non-TDF-exposed group (1.3 $\pm$ 10.3%, $p = 0.035$). A urine specimen tested positive for proteinuria (protein level $\geq$ 30 mg/dL) in 23.2% of the patients not receiving cART, 13.9% of the patients in the TDF-exposed group, and 14.0% of the patients in the non-TDF-exposed group. The

Table 1 Baseline characteristics of the HIV-infected patients with different treatment status.

	Not on cART (n = 140)	cART experienced, TDF exposed (n = 393)	cART experienced, non-TDF exposed (n = 242)	P
Age (y)	31.5 ± 7.3	38.2 ± 10.0	43.4 ± 12.3	<0.001
Male sex	131 (93.6)	379 (96.4)	230 (95.0)	0.345
MSM	115 (82.1)	330 (84.0)	172 (71.1)	<0.001
Injecting drug user	15 (10.7)	6 (1.5)	5 (2.1)	<0.001
Weight (kg)	67.8 ± 14.1	65.9 ± 10.7	67.0 ± 11.4	0.63
BMI (kg/m^2)	23.0 ± 4.1	22.6 ± 3.4	23.4 ± 3.4	0.038
Comorbidity				
HBsAg positive	12 (8.6)	100 (25.4)	30 (12.4)	<0.001
Anti-HCV positive	28 (20)	37 (9.4)	10 (4.1)	<0.001
Hypertension	6 (4.3)	37 (9.4)	40 (16.5)	<0.001
Diabetes mellitus	5 (3.6)	15 (3.8)	21 (8.7)	0.018
CKD [a]	0 (0)	2 (0.5)	11 (4.5)	<0.001
Malignancy	1 (0.7)	28 (7.1)	15 (6.2)	0.554
Heart failure	0 (0)	2 (0.5)	2 (0.8)	0.017
Years since HIV diagnosis	5.5 ± 2.5	7.0 ± 4.8	9.9 ± 4.9	<0.001
Duration of ART (y)	0 ± 0	5.9 ± 4.6	9.1 ± 4.9	<0.001
CD4 count (cells/μL)	541 ± 173	374 ± 291	547 ± 258	<0.001
Plasma HIV RNA load ($\log_{10}$ copies/mL)	3.96 ± 0.8	3.3 ± 1.9	1.70 ± 0.9	<0.001
Exposed to PI	0 (0)	140 (35.6)	197 (81.4)	<0.001
ACEI or ARB use	3 (2.1)	14 (3.6)	17 (7.0)	0.042
Dyslipidemia	2 (1.4)	18 (4.6)	49 (20.2)	<0.001
Follow-up duration (d)	549 ± 267	797 ± 316	541 ± 137	<0.001

[a] Defined as eGFR < 60 mL/min/1.73 m^2.

Results are presented as n (%) or mean ± standard deviation.

ACEI = angiotensin II-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; cART = combination antiretroviral therapy; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MSM = men who have sex with men; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate.

prevalence of proteinuria was significantly higher in the patients not receiving cART than the TDF-exposed and non-TDF-exposed groups (23.2% vs. 13.9%, $p = 0.032$; 23.2% vs. 14.0%, $p = 0.035$, respectively), but it was similar between the TDF-exposed and the non-TDF-exposed groups (13.9% vs. 14.0%, $p = 0.524$).

The factors influencing annual change of eGFR in HIV-infected patients were explored by multivariate linear regression (Table 3). The analysis indicated that presence of diabetes mellitus and dyslipidemia would lead to greater eGFR decrement annually at a rate of 5.01 mL/min/1.73 m^2 [95% confidence interval (CI), 1.539−7.128, $p = 0.002$] and 2.46 mL/min/1.73 m^2 (95% CI, 0.838−6.177, $p = 0.010$), respectively. On the contrary, chronic kidney disease (defined as eGFR < 60 mL/min/1.73 m^2) and every additional CD4 cell count increase would lessen the annual decrement of eGFR. TDF exposure had no significant influence on annual eGFR change.

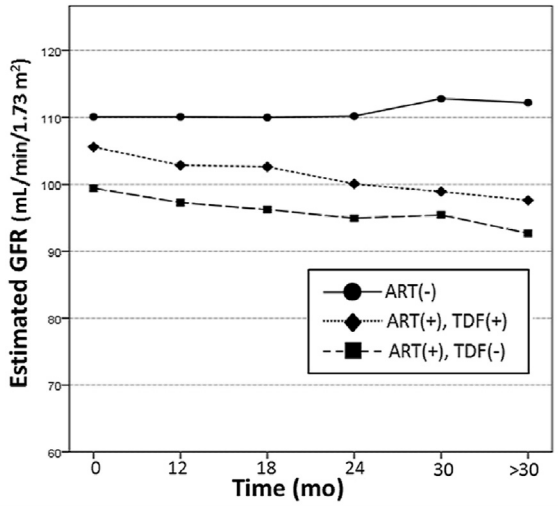
In the subgroup analysis, we investigated the influence of TDF exposure on the annual eGFR change in patients with different CD4 levels using linear regression. In 277 patients with CD4 count < 350 cells/μL, those exposed to TDF had an additional 2.73-mL/min/1.73 m^2 eGFR decrement annually (95% CI 0.139−5.326; $p = 0.039$). Diabetes mellitus continued to have a significant impact on eGFR decline in this analysis (Table 3, Analysis 2).

Factors associated with renal function decline in patients with TDF exposure

Analysis of the risk factors associated with annual eGFR loss >3 mL/min/1.73 m^2 in 393 TDF-exposed patients is shown in Table 4. In univariate analysis, factors associated with annual eGFR loss >3 mL/min/1.73 m^2 were increased plasma HIV RNA load and higher baseline eGFR. Patients with higher CD4 counts and longer TDF exposure appeared to have a lower rate of annual eGFR loss >3 mL/min/1.73 m^2. In multivariate logistic regression, higher baseline eGFR levels were associated with an increased risk of annual eGFR loss > 3 mL/min/1.73 m^2 [for every 10 mL/min/1.73 m^2 increase, odds ratio (OR) 1.292; 95% CI 1.123−1.486; $p < 0.001$], and higher CD4 counts were protective against HIV RNA (for every 1 cell/μL increase, OR 0.999; 95% CI 0.998−1.000; $p = 0.008$).

Outcomes of patients with TDF-related renal failure

During the study period, 11 of 393 (2.8%) patients discontinued TDF. Six patients switched to other cART regimens due to emergence of antiretroviral resistance, and five (1.3%) patients withdrew TDF due to increased serum



Months	0	12	18	24	30	>30
ART(-), *N*	140	77	66	53	21	12
ART(+),TDF(+), *N*	393	257	284	298	289	238
ART(+),TDF(-), *N*	242	220	217	95	12	4

Figure 1. Trends of changes in estimated glomerular filtration rate (eGFR) in HIV-infected patients with three different status of combination antiretroviral therapy (cART). The three groups were as follows: patients not receiving cART [ART (−)], patients receiving TDF-containing cART [ART (+), TDF (+)], and patients receiving cART not containing TDF [ART (+), TDF (−)]. The maximal follow-up duration was 48 months. TDF = tenofovir disoproxil fumarate.

creatinine levels. The details of these five patients are shown in Table 5. Their average eGFR at baseline was 74 mL/min/1.73 m^2. At TDF discontinuation, the average loss of eGFR was 32 mL/min/1.73 m^2, and the average increase of serum creatinine levels was 0.67 mg/dL. Three patients had pre-existing hypertension or diabetes mellitus. The other two patients had no chronic illness, but their body mass indices were < 20 kg/m^2. The serum creatinine level of four patients recovered partially after TDF discontinuation (median follow-up duration 161 days). The only one patient with worsening renal function despite discontinuation of TDF was the oldest, with poorly controlled diabetes mellitus.

Discussion

In this Taiwanese cohort, the average annual decline of eGFR in TDF-exposed patients was 2.7 mL/min/1.73 m^2. In multivariate analysis, TDF exposure was correlated with an additional annual eGFR decrement of 2.73 mL/min/1.73 m^2 in patients with CD4 count < 350 cells/μL. For patients receiving TDF, the factors associated with annual eGFR decrement > 3 mL/min/1.73 m^2 were lower CD4 counts and higher baseline eGFR in multivariate analysis. The prevalence of proteinuria was higher in patients not receiving cART, but similar between patients receiving TDF- or non-TDF-containing cART. During the 4-year study period, five (1.3%) patients withdrew TDF due to deteriorating renal function.

The first study in HIV-infected Asians to evaluate change of creatinine clearance after TDF initiation was performed in Thai patients.[21] Using the Cockcroft—Gault formula and MDRD formula, the authors concluded that creatinine clearance remained stable after a median of 21 weeks of TDF exposure. Later studies in HIV-infected Japanese,[12,18,23] Chinese,[22] and Vietnamese[28] patients all suggested a harmful effect of TDF on renal function, yet expressed the result in different ways, such as TDF exposure shown to increase the risk of eGFR < 60 mL/min/1.73 m^2, eGFR > 10 mL/min/1.73 m^2 or a 25% decline of eGFR from baseline, or presence of urine markers for proximal renal tubulopathy. Overall, these studies suggested a higher risk for TDF-related renal dysfunction among Asians than the patients in Western countries.

Few studies in Asian people calculated the eGFR changes over time. Cao et al[22] reported an 8.8-mL/min/1.73 m^2 decline in eGFR at Week 48 in patients receiving both TDF and protease inhibitors.[22] Kinai and Hanabusa[23] reported a 17-mL/min/1.73 m^2 loss of eGFR at Week 96 in TDF-treated patients. The degrees of eGFR decline in these two studies are much greater compared with our observation. This could be due to the difference in observation duration. Several reports have found that eGFR of TDF-treated patients tends to decline rapidly within the first few months of TDF exposure, and then stabilizes.[22,29,30] It has been suggested that changes in eGFR may be due to inhibition of creatinine secretion of the proximal tubule due to TDF exposure rather than due to actual damages to glomerular functions.[31] When patients are followed up for longer periods, the average annual decline in eGFR would be smaller. Another factor leading to discrepancies in eGFR levels among the different studies is the equation used to estimate GFR. In HIV-infected patients with eGFR > 120 mL/min/1.73 m^2, MDRD may give higher mean eGFR estimates than CKD-EPI.[32]

Advanced HIV disease, characterized by a low CD4 count and high plasma HIV RNA load, had been recognized as a predictor of TDF-related renal function decline.[10] Current guidelines suggest initiating cART in HIV-infected individuals with a CD4 count < 500 cells/μL, and as the priority, for patients who have a CD4 count < 350 cells/μL.[1] In our study, TDF exposure was associated with a 2.73-mL/min/1.73 m^2 eGFR decline annually in patients with CD4 count < 350 cells/μL. Our results suggest that more frequent monitoring of renal function is needed in patients with advanced HIV disease preparing for initiation of TDF-based regimens. Among the factors that would increase the risk of renal dysfunction in TDF-exposed patients, a lower body weight is frequently mentioned in Asian populations.[18,28,33] The hypothesis is that a lower weight would lead to a higher TDF plasma concentration, which increases the risk of nephrotoxicity. A recent study measuring TDF plasma concentration revealed that overexposure to TDF was associated with a time-dependent decrease in eGFR.[34] In multivariate analysis, we did not find a statistically significant association between a lower weight and kidney dysfunction. However, two of the five patients with no comorbidity who discontinued TDF due to worsening renal function in our study did have a low body mass index.

Our analyses showed TDF-exposed patients with higher eGFR at baseline tend to have more prominent eGFR loss.

Table 2 Renal function change and incidence of proteinuria of HIV-infected patients with different treatment status.

	Not on cART (n = 140)	cART experienced, TDF exposed (n = 393)	cART experienced, TDF unexposed (n = 242)	Three groups p	Not on cART vs. TDF exposed	Not on cART vs. TDF unexposed	cART experienced, TDF vs. non-TDF
					p		
First serum Cr (mg/dL)	0.89 ± 0.14	0.89 ± 0.18	0.91 ± 0.18				
Last serum Cr (mg/dL)	0.88 ± 0.13	0.93 ± 0.19	0.94 ± 0.22				
First eGFR [a] (mL/min/1.73 m^2)	110.1 ± 14.4	105.6 ± 16.4	99.4 ± 17.6				
Last eGFR (mL/min/1.73 m^2)	109.8 ± 13.4	100.5 ± 17.1	96.4 ± 18.1				
Annual eGFR change (mL/min/1.73 m^2)	−0.57 ± 8.6	−2.7 ± 8.9	−1.8 ± 8.3	0.057	0.012	0.12	0.567
Annual eGFR change (%)	−0.1 ± 8.1	−2.3 ± 8.6	−1.3 ± 10.3	0.059	0.032	0.035	0.524
Proteinuria (≥ 30 mg/dL)	23.2% (16/69)	13.9% (47/338)	14.0% (32/235)	0.115	0.052	0.055	0.922

[a] eGFR was calculated by CKD-EPI equation.
Results are n (%), or mean ± standard deviation.
cART = combination antiretroviral therapy; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; Cr = creatinine; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; TDF = tenofovir disoproxil fumarate.

Similar findings have also been reported previously.[18,35,36] Horberg et al[35] demonstrated that TDF-exposed patients with a baseline eGFR > 80 mL/min/1.73 m^2 had a more pronounced eGFR loss than those with baseline eGFR between 50 mL/min/1.73 m^2 and 79 mL/min/1.73 m^2. A later study from Japan found that high eGFR levels at baseline was a risk factor for a decline in eGFR by > 25%.[18] CKD patients were expected to have faster decline of renal function after initiating a nephrotoxic drug treatment. The exact reason for these conflicting data is unclear. One possible explanation is that by using the MDRD or CKD-EPI formula, patients with high eGFR had greater eGFR change than those with low eGFR in response to a same level of serum creatinine elevation. To avoid this phenomenon, methods that evaluate renal function directly, such as ^{51}Cr-EDTA clearance, might be more accurate.

Proteinuria was observed in a higher percentage of patients not receiving cART compared with the patients

Table 3 Determinants of annual change of eGFR in HIV-infected patients using multivariate linear regression.

Variable	Univariate analysis		Multivariate analysis	
	Regression coefficient (95% CI)	p	Regression coefficient (95% CI)	p
Analysis 1: All patients [a] (N = 775)				
Male sex	−3.574 (−6.493 to −0.600)	0.018		
Diabetes mellitus	−3.969 (−6.698 to −1.241)	0.004	−5.011 (−7.768 to −2.254)	<0.001
Chronic kidney disease	7.747 (2.997−12.497)	0.001	10.149 (5.403−14.895)	<0.001
Dyslipidemia	−1.986 (−4.138 to 0.165)	0.070	−2.455 (−4.610 to −0.301)	0.026
CD4 count (cells/μL)	0.004 (0.002−0.007)	<0.001	0.005 (0.003−0.007)	<0.001
Tenofovir exposure	−1.376 (−2.600 to −0.151)	0.028		
ACEI or ARB use	−2.616 (−5.608 to 0.377)	0.087		
Analysis 2: Patients with CD4 < 350 (cells/μL)[b] (N = 277)				
Diabetes mellitus	−13.862 (−20.757 to −6.967)	<0.001	−14.507 (−21.389 to −7.625)	<0.001
Tenofovir exposure	−2.246 (−4.905 to 0.412)	0.097	−2.733 (−5.326 to −0.139)	0.039

[a] In analysis 1, univariate linear regression showed no significant contribution (p > 0.1) of age, injective drug user, body weight, HBsAg-positivity, Anti-HCV-positivity, hypertension, congestive heart failure, duration of cART, plasma HIV RNA load, exposure to protease inhibitor, and follow-up duration on eGFR (not listed in the table).
[b] In analysis 2, univariate linear regression showed no significant contribution (p > 0.1) of age, injective drug user, body weight, HBsAg-positivity, Anti-HCV-positivity, chronic kidney disease, hypertension, congestive heart failure, dyslipidemia, ACEI or ARB use, duration of ART, plasma HIV RNA load, exposure to protease inhibitor, and follow-up duration on eGFR (not listed in the table).
ACEI = angiotensin II-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; cART = combination antiretroviral therapy; CI = confidence interval; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

Table 4 Determinants of annual decline of eGFR by ≥ 3 mL/min/1.73 m^2 in HIV-infected patients treated with tenofovir.

	Annual decline of eGFR		Univariate analysis		Multivariate analysis	
	≥ 3 mL/min/1.73 m^2 (n = 146)	< 3 mL/min/1.73 m^2 (n = 247)	OR (95% CI)	p	OR (95% CI)	p
Age (Y) [a]	38.8 ± 11.1	37.8 ± 9.3	1.009 (0.989–1.030)	0.363		
Male sex	143 (97.9)	236 (95.5)	2.222 (0.61–8.099)	0.226		
Weight < 50 kg	11 (7.5)	13 (5.5)	1.423 (0.62–3.268)	0.406		
HBsAg-positive	32 (21.9)	68 (27.5)	0.739 (0.457–1.196)	0.218		
Anti-HCV-positive	11 (7.5)	26 (10.5)	0.693 (0.332–1.447)	0.328		
Hypertension	17 (11.6)	20 (8.1)	1.496 (0.756–2.957)	0.247		
Diabetes mellitus	8 (5.5)	7 (2.8)	1.988 (0.706–5.600)	0.194		
Malignancy	11 (7.5)	17 (6.9)	1.102 (0.502–2.423)	0.808		
Congestive heart failure	1 (0.7)	1 (0.4)	1.697 (0.105–27.33)	0.709		
Dyslipidemia	5 (3.4)	13(5.3)	0.638 (0.223–1.828)	0.403		
CD4 count (cells/μL) [a]	308 ± 294	412 ± 282	0.999 (0.998–0.999)	0.004	0.999 (0.998–1.000)	0.008
HIV PVL (log_{10} copies/mL) [a]	3.6 ± 1.9	3.1 ± 1.8	1.156 (1.035–1.291)	0.010		
Exposure to PI	54 (37.0)	86 (34.8)	1.099 (0.718–1.682)	0.665		
ACEI or ARB use	6 (4.1)	8 (3.2)	1.280 (0.435–3.766)	0.653		
Tenofovir exposure (d) [a]	736 ± 178	833 ± 332	0.999 (0.998–1.000)	0.003	1.000 (0.999–1.000)	0.186
Baseline eGFR (mL/min/1.73 m^2) [a]	110.2 ± 16.4	102.9 ± 15.9	1.342 (1.168–1.542)	<0.001	1.292 (1.123–1.486)	<0.001

[a] For continuous variable in logistic regression, the odds ratios are shown for each 1-year increase in age, for each 1-cell/μL increase of CD4 count, for each 1 log_{10} copy/mL increase of PVL, for each 1-day increase of TDF exposure, and for each 10-mL/min/1.73 m^2 increase of baseline eGFR.

ACEI = angiotensin II-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CI = confidence interval; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; HIV = human immunodeficiency virus; OR = odds ratio; PI = protease inhibitor; PVL = plasma HIV RNA load; TDF = tenofovir disoproxil fumarate.

receiving cART in our study. This is not unexpected because with the introduction of cART, there has been a decreasing incidence of HIV-associated nephropathy. A previous study also showed that cART initiation was associated with improvement in proteinuria.[37] Being a simple laboratory test, urine dipstick test is recommended for screening proteinuria in TDF-treated patients.[38] One study that included 10,841 HIV-infected patients reported that 1 additional year of TDF exposure was associated with 34% increased risk of proteinuria.[39] Limited by the small sample size of our study, we did not find a statistically significant difference in the prevalence of proteinuria between the TDF-exposed and non-TDF-exposed groups.

Five (1.3%) patients withdrew TDF due to increased serum creatinine levels during the study period. The average increase in serum creatinine levels was 0.67 mg/dL at TDF discontinuation. In a cohort study of 10,343 HIV-infected patients receiving TDF-containing cART, 2.2% of patients had an increase in serum creatinine levels of ≥ 0.5 mg/dL, and 0.5% experienced a serious renal adverse event of any type.[40] A more recent study in Thailand reported that 41 of 1204 (3.4%) TDF-treated patients had an increase in serum creatinine level of ≥ 0.5 mg/dL from baseline.[41] Published guidelines suggest obtaining measurements of serum creatinine levels consistently for TDF-treated patients.[38] However, there is no consensus on the optimal timing to discontinue TDF in patients whose kidney function declines progressively, and the best marker for TDF-related kidney injury has yet to be defined. After discontinuation of TDF, four of the five patients in this study had their eGFR partially recovered, which is in line with the previous studies showing that the loss of renal function may not be fully reversible with TDF withdrawal.[42]

There are several limitations of our study and our results should be interpreted with caution. First, this is a retrospective study. Patients included in our study might not have a uniform schedule of blood sampling, and their adherence to cART might be incomplete. Second, although we provided a relatively longer observation period than previous studies in Asia,[21,22] the duration of TDF exposure was no more than 4 years. Because the pattern of eGFR decline may not be linear, the changes of renal function in the short-term observation period may not predict the long-term clinical effect. Third, we did not examine other parameters representing renal tubular dysfunction, such as glycosuria, urine phosphate, or urinary β2-microglobulin. Likewise, we assessed proteinuria only qualitatively. Measurement of microalbuminuria or urine protein-to-creatinine ratio would more precisely reflect the urine protein loss. Finally, HIV-infected women and patients with a low eGFR comprised only a small proportion of our study populations. Whether our findings can be generalized to these patients warrants further investigations.

In conclusion, cART exposure correlated with the decline of renal function among HIV-infected Taiwanese patients. However, TDF-exposed patients are more likely to have

Table 5 Details of the patients who discontinued tenofovir due to worsening renal dysfunction.

Patient No.	Age/Sex	Weight (kg)/BMI (kg/m^2)	Comorbidity	Concomitant ART	CD4 (cells/μL)	TDF duration (d)	Baseline		Maximal		Protein in urinalysis (mg/dL)	After TDF withdrawal	
							Cr (mg/dL)	eGFR (mL/min/1.73 m^2)	Cr	eGFR		Cr	eGFR
1	40/M	55/18.2	Nil	3TC/LPVr	242	663	0.9	106	1.6	53	30 (1+)	1.3	67
2	43/M	67/22.3	HTN	3TC/EFV	497	869	1.5	53	1.9	42	Negative	1.5	55
3	50/M	73/26.1	HTN, DM	3TC/NVP	15	530	1.2	70	1.8	42	100 (2+)	1.7	45
4	54/M	60/19.2	Nil	3TC/RAL	13	311	1.1	76	1.9	39	30 (1+)	1.8	41
5	75/M	62/24.2	HTN, DM	3TC/LPVr	410	738	1.1	65	1.9	33	50 (1+)	2.2	28

3TC = lamivudine; ART = antiretroviral therapy; BMI = body mass index; Cr = creatinine; DM = diabetes mellitus; EFV = efavirenz; eGFR = estimated glomerular filtration rate; HTN = hypertension; LPVr = lopinavir/ritonavir; M = male; NVP = nevirapine; RAL = raltegravir; TDF = tenofovir disoproxil fumarate.

prominent eGFR decline, especially those with advanced HIV disease (lower CD4 and high HIV RNA), diabetes mellitus, and higher baseline eGFR levels. Our results highlight the importance of renal function monitoring when starting TDF in patients initiating cART. As the survival rates of HIV-infected patients are approaching that of the general population in the cART era, the impact of prolonged TDF exposure on renal function should be carefully monitored.

Conflicts of interest

C.-C. H. has received research support from Janssen and speaker honoraria from AbbVie, Bristol-Myers Squibb, Gilead Sciences, and ViiV, and served on advisory boards for Gilead Sciences and AbbVie. All other authors have no conflicts of interest to declare.

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References

1. World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva, Switzerland: World Health Organization; 2013.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf [Last accessed June 24, 2015].
3. Wu PY, Chen MY, Hsieh SM, Sun HY, Tsai MS, Lee KY, et al. Comorbidities among the HIV-infected patients aged 40 years or older in Taiwan. *PLoS One* 2014;**9**:e104945.
4. Hsieh MH, Lu PL, Kuo MC, Lin WR, Lin CY, Lai CC, et al. Prevalence of and associated factors with chronic kidney disease in human immunodeficiency virus-infected patients in Taiwan. *J Microbiol Immunol Infect* 2015;**48**:256—62.
5. Kalyesubula R, Perazella MA. Nephrotoxicity of HAART. *AIDS Res Treat* 2011;**2011**, Article id 562790.
6. Haverkort ME, van der Spek BW, Lips P, Slieker WA, ter Heine R, Huitema AD, et al. Tenofovir-induced Fanconi syndrome and osteomalacia in two HIV-infected patients: role of intracellular tenofovir diphosphate levels and review of the literature. *Scand J Infect Dis* 2011;**43**:821—6.
7. Rollot F, Nazal EM, Chauvelot-Moachon L, Kélaïdi C, Daniel N, Saba M, et al. Tenofovir-related Fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired immunodeficiency syndrome: the role of lopinavir-ritonavir-didanosine. *Clin Infect Dis* 2003;**37**:e174—6.
8. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? *J Am Soc Nephrol* 2013;**24**:1519—27.
9. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir

disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010;**51**:496—505.
10. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, Sanchez-Niño MD, Izquierdo MC, Poveda J, et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Res Treat* 2011;**2011**, Article id 354908.
11. Laprise C, Baril JG, Dufresne S, Trottier H. Association between tenofovir exposure and reduced kidney function in a cohort of HIV-positive patients: results from 10 years of follow-up. *Clin Infect Dis* 2013;**56**:567—75.
12. Nishijima T, Kawasaki Y, Tanaka N, Mizushima D, Aoki T, Watanabe K, et al. Long-term exposure to tenofovir continuously decrease renal function in HIV-1-infected patients with low body weight: results from 10 years of follow-up. *AIDS* 2014;**28**:1903—10.
13. 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**:773—80.
14. Kelly MD, Gibson A, Bartlett H, Rowling D, Patten J. Tenofovir-associated proteinuria. *AIDS* 2013;**27**:479—81.
15. Nishijima T, Shimbo T, Komatsu H, Takano M, Tanuma J, Tsukada K, et al. Urinary beta-2 microglobulin and alpha-1 microglobulin are useful screening markers for tenofovir-induced kidney tubulopathy in patients with HIV-1 infection: a diagnostic accuracy study. *J Infect Chemother* 2013;**19**:850—7.
16. Sun HY, Hung CC, Lin PH, Chang SF, Yang CY, Chang SY, et al. Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. *J Antimicrob Chemother* 2007;**60**:599—604.
17. Lin KY, Cheng CY, Yang CJ, Tsai MS, Hsieh SM, Sun HY, et al. Skin rash related to once-daily boosted darunavir-containing antiretroviral therapy in HIV-infected Taiwanese: incidence and associated factor. *J Infect Chemother* 2014;**20**:465—70.
18. Nishijima T, Komatsu H, Gatanaga H, Aoki T, Watanabe K, Kinai E, 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**:e22661.
19. Mizushima D, Tanuma J, Kanaya F, Nishijima T, Gatanaga H, Lam NT, et al. WHO antiretroviral therapy guidelines 2010 and impact of tenofovir on chronic kidney disease in Vietnamese HIV-infected patients. *PLoS One* 2013;**8**:e79885.
20. Nishijima T, Komatsu H, Higasa K, Takano M, Tsuchiya K, Hayashida T, et al. Single nucleotide polymorphisms in ABCC2 associate with tenofovir-induced kidney tubular dysfunction in Japanese patients with HIV-1 infection: a pharmacogenetic study. *Clin Infect Dis* 2012;**55**:1558—67.
21. Gayet-Ageron A, Ananworanich J, Jupimai T, Chetchotisakd P, Prasithsirikul W, Ubolyam S, et al. No change in calculated creatinine clearance after tenofovir initiation among Thai patients. *J Antimicrob Chemother* 2007;**59**:1034—7.
22. Cao Y, Han Y, Xie J, Cui Q, Zhang L, Li Y, et al. Impact of a tenofovir disoproxil fumarate plus ritonavir-boosted protease inhibitor-based regimen on renal function in HIV-infected individuals: a prospective, multicenter study. *BMC Infect Dis* 2013;**13**:301.
23. Kinai E, Hanabusa H. Progressive renal tubular dysfunction associated with long-term use of tenofovir DF. *AIDS Res Hum Retroviruses* 2009;**25**:387—94.
24. Nishijima T, Gatanaga H, Shimbo T, Komatsu H, Endo T, Horiba M, et al. Switching tenofovir/emtricitabine plus lopinavir/r to raltegravir plus Darunavir/r in patients with suppressed viral load did not result in improvement of renal function but could sustain viral suppression: a randomized multicenter trial. *PLoS One* 2013;**8**:e73639.
25. Centers for Disease Control, ROC, Taiwan. Guidelines for diagnosis and treatment of HIV/AIDS. Available from: http://www.cdc.gov.tw/uploads/files/201310/1e64c227-32fc-49ab-8bfc-9484ec50c4f3.pdf [Last accessed June 24, 2015].
26. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med* 2012;**156**:785—95.
27. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1—150.
28. Mizushima D, Tanuma J, Dung NT, Dung NH, Trung NV, Lam NT, et al. Low body weight and tenofovir use are risk factors for renal dysfunction in Vietnamese HIV-infected patients. A prospective 18-month observation study. *J Infect Chemother* 2014;**20**:784—8.
29. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis* 2005;**40**:1194—8.
30. Goicoechea M, Liu S, Best B, Sun S, Jain S, Kemper C, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis* 2008;**197**:102—8.
31. Hall AM. Update on tenofovir toxicity in the kidney. *Pediatr Nephrol* 2013;**28**:1011—23.
32. Ibrahim F, Hamzah L, Jones R, Nitsch D, Sabin C, Post FA, et al. Comparison of CKD-EPI and MDRD to estimate baseline renal function in HIV-positive patients. *Nephrol Dial Transplant* 2012;**27**:2291—7.
33. 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**:504—9.
34. Lê MP, Landman R, Koulla-Shiro S, Charpentier C, Sow PS, Diallo MB, et al. Tenofovir plasma concentrations related to estimated glomerular filtration rate changes in first-line regimens in African HIV-infected patients: ANRS 12115 DAYANA substudy. *J Antimicrob Chemother* 2015;**70**:1517—21.
35. Horberg M, Tang B, Towner W, Silverberg M, Bersoff-Matcha S, Hurley L, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients. *J Acquir Immune Defic Syndr* 2010;**53**:62—9.
36. Antoniou T, Raboud J, Chirhin S, Yoong D, Govan V, Gough K, et al. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. *HIV Med* 2005;**6**:284—90.
37. Wyatt CM, Kitch D, Gupta SK, Tierney C, Daar ES, Sax PE, et al. Changes in proteinuria and albuminuria with initiation of antiretroviral therapy: data from a randomized trial comparing tenofovir disoproxil fumarate/emtricitabine versus abacavir/lamivudine. *J Acquir Immune Defic Syndr* 2014;**67**:36—44.
38. Gupta SK, Eustace JA, Winston JA, Boydstun II , Ahuja TS, Rodriguez RA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005;**40**:1559—85.
39. Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS* 2012;**26**:867—75.
40. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS* 2007;**21**:1273—81.
41. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Gvetadze RJ, et al. Renal function of participants in the Bangkok tenofovir study—Thailand, 2005—2012. *Clin Infect Dis* 2014;**59**:716—24.
42. Jose S, Hamzah L, Campbell LJ, Hill T, Fisher M, Leen C, et al. Incomplete reversibility of estimated glomerular filtration rate decline following tenofovir disoproxil fumarate exposure. *J Infect Dis* 2014;**210**:363—73.