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Original Article

Effects of long-term exposure to tenofovir disoproxil fumarate-containing antiretroviral therapy on renal function in HIV-positive Chinese patients

Qing Tan [a,b], Yuan-Hong He [b], Tong-Tong Yang [b], Dong-Mei Yan [b], Yan Wang [b], Xia Zhao [b], Huan-Xia Liu [b], Sheng-Hua He [a,b,**], Zhong-Hui Zhou [a,*]

[a] *Department of Infection, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan Province, China*
[b] *Department of Infection, Public Health Clinical Center of Chengdu, Sichuan Province, China*

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Abstract *Background:* The regimen containing tenofovir disoproxil fumarate (TDF)+lamivudine or emtricitabine + efavirenz remains the recommended first-line antiretroviral therapy (ART) by the WHO. Limited studies, however, have been conducted on the incidence of renal impairment among Chinese patients with long-term exposure to TDF-containing ART regimens.
Methods: We retrospectively analyzed 269 eligible patients who had no comorbidities and received TDF-containing ART from July 2014 to April 2015. TDF-related renal impairment was defined as a decrease of eGFR by >25% from baseline or eGFR <90 ml/min/1.73 m^2. Decreased renal function was defined as a decrease of eGFR by > 10 mL/min/1.73 m^2 from baseline.
Results: 97.0% of study patients were male (median age 29, eGFR 124.0 ml/min/1.73 m^2). After 168-week of ART, renal impairment occurred in 7 patients (2.7%). The incidence of decreased renal function was significantly higher at Week 168 compared with that observed at Week 12 (24.8% vs 3.7%, $p < 0.001$). In generalized estimating equation analysis, patients receiving ART for 144-week (aOR4.1, 95%CI 2.0–8.4) and 168-week (aOR8.4, 95%CI 4.2–16.4) were more likely to develop decreased renal function compared with those receiving ART for 12-week, so were the patients with a weight <58 kg (aOR2.3, 95%CI 1.2–4.3) and 58–66 kg (aOR2.0, 95%CI 1.0–3.8) compared to those with a weight ≥67 kg. At 168-week,

* Corresponding author. Department of Infection, Affiliated Hospital of North Sichuan Medical College, No. 234, Fujiang Road, Shunqing District, Nanchong, Sichuan Province, China. Fax: +28 64369007.
** Corresponding author. Department of Infection, Chengdu Public Health Clinical Medical Center, No. 377, Jingming Road, Jinjiang District, Chengdu, Sichuan Province, China. Fax: +028 64369118.
E-mail addresses: 19981812571@163.com (S.-H. He), zhonghuiz829@sina.com (Z.-H. Zhou).

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41.0% of 100 patients examined had elevated urine β2-microglobulin levels, which were negatively correlated with eGFR ($r = -0.22$, $p = 0.02$).
Conclusions: TDF-related renal impairment remained rare in HIV-positive Chinese patients with a median age of 29 years who had no comorbidities. A lower weight and duration of ART were associated with decreased renal function.

Introduction

By the end of 2017, an estimated 36.9 million patients were living with HIV worldwide, and 21.7 million patients were receiving antiretroviral treatment.[1] While HIV/AIDS-related morbidity and mortality have declined significantly since the initiation of combination antiretroviral therapy (ART),[2,3] life-long ART is required for the people living with HIV. With the prolonged exposure to ART, adverse effects often emerge with involvement of various organs such as the kidney, liver, heart, and bone.[4–6] For example, tenofovir disoproxil fumarate (TDF), a nucleotide reverse-transcriptase inhibitor (NRTI) widely used in the developed and developing countries,[7] is effective in the treatment of HIV and HBV infection and prevention of mother-to-child transmission, and, in combination with emtricitabine, as pre- and post-exposure prophylaxis in populations at high risk for HIV infection.[8] However, prolonged exposure to TDF has been shown to cause declines of estimated glomerular filtration rate (eGFR) and reduction of bone mineral density (BMD), which have raised concerns about the long-term successful management of HIV infection with ART.[9–12]

After oral administration, TDF is converted to the active acyclic nucleotides (tenofovir, TFV), which was filtered by the glomeruli and completely reabsorbed by the proximal renal tubules.[13,14] It is primarily transported from basolateral circulation into proximal renal tubular cells via the organic anion transporter 1 (OAT-1), and then excreted into the tubular lumen by the multidrug resistance transporter 2 (MRP-2) and MRP-4.[15] Increased accumulation of TDF in the renal tubular cells causes mitochondrial dysfunction and proximal tubular injury (proximal tubulopathy).[15–17]

The D: A: D study showed that an older age, low baseline eGFR, hepatitis C virus (HCV) coinfection, concomitant use of ritonavir-boosted protease inhibitors (PI/r), injection drug use,[12] sex, race, low body weight,[18,19] low CD4 count,[10] high plasma HIV RNA load (PVL), and presence of comorbidities (diabetes mellitus and hypertension)[10] were risk factors for TDF-related renal impairment. Moreover, Nishijima et al. have shown that TDF-related renal dysfunction was more pronounced in Japanese patients with a lower weight,[18] and the duration of exposure to TDF was associated with TDF-related nephrotoxicity.[20]

In this study, we aimed to examine the trends of eGFR in HIV-positive Chinese patients who had long-term exposure to a TDF-containing ART regimen and to evaluate the associated factors with TDF-related renal impairment or decline.

Methods

Study design

In this single-center retrospective observational study, we included HIV-positive patients who received care at a public health clinic in Chengdu from July 2014 to April 2015 and were followed up to October 2018. Inclusion criteria were 1) ART-naïve Chinese; 2) aged ≥18 years; and 3) initiation of TDF (300 mg/day) + lamivudine (3 TC, 300 mg/day) + efavirenz (EFV, 600 mg/day). Exclusion criteria were 1) no baseline eGFR; 2) eGFR <60 ml/min/1.73 m^2 (CKD-EPI formula); 3) history of hypertension, diabetes mellitus, heart disease, chronic liver disease, and chronic kidney disease; 4) pregnant and lactating women; 5) loss to follow-up due to adverse events that were judged unlikely caused by TDF; 6) switch of ART because of resistance-associated mutations; and 7) transfer of care to other medical care facilities. The study was approved by the Research Ethics Committee (National Center for STD/AIDS Control and Prevention, China, CDC Institutional Review Board, registration number, X140121322) and all included patients gave written informed consent to their data being used in this study.

Data collection and measurement

HIV-positive patients who received ART visited our clinic every 3–6 months and were followed for up to 168 weeks. We collected clinical characteristics and laboratory data at each follow-up visit (baseline, 12, 24, 48, 96, 144, 168 weeks), including gender, age, HIV transmission route, height, weight, body-mass index (BMI), creatinine, urine protein, urine glucose, PVL, and CD4 and CD8 cell counts. Data of urine β2 microglobulin were only available for 100 patients at week 168. PVL was determined using Abbott Real Time M2000sp Viral Quantitative Tester (Abbott Inc., USA) with a lower detection limit of 40 copies/ml. T-lymphocyte subsets were tested using the FACS Calibur (BD Company, USA). Urine β2 microglobulin was detected with the use of Roche COBAS C 501 automatic biochemical analyzer and home-made reagents.

Definitions

TDF-related renal impairment was defined as a reduction of eGFR by >25% from baseline or an eGFR <90 ml/min/1.73 m^2. TDF-related decreased renal function was defined

as a decrease of eGFR by > 10 ml/min/1.73 m^2 from baseline.[21,22] eGFR was calculated at each follow-up point with the use of the creatinine formula for the Chronic Kidney Disease Epidemiology (CKD-EPI).[23] The normal range of β2 microglobulin was <0.5 mg/L.[24]

Statistical analysis

Statistical analysis was performed by SPSS22.0 software. Kolmogorov-Smirnov and Shapiro-Wilk were performed to test the normality of all quantitative data including eGFR. Measurements of non-normal distribution were expressed as median value and interquartile range (IQR) while eGFR changes were compared before and after ART. Wilcoxon and Mann-Whitney U-rank sum tests were used for intra-group and inter-group comparisons, respectively. Categorical variables were analyzed by the contingency tables involving chi-square test to determine the statistical difference between groups, Pearson chi-square was used for the expected frequency greater than 5. Fishers' exact test was performed for 20% of cells with an expected frequency of less than 5 or less than 1. The associated factors with a decline of eGFR by > 10 ml/min/1.73 m^2 after ART were analyzed by the generalized estimating equation (GEE). These factors were expressed by adjusted odds ratio (aOR) and 95% confidence interval (CI). Correlation between values was tested by Spearman correlation coefficient, and 2-sided test was used for all statistics. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the included patients

From July 2014 to April 2015, 298 outpatients receiving TDF + 3 TC + EFV as the initial ART regimen were followed up to October 1, 2018; 29 were excluded and 269 patients were eligible for inclusion in the analysis (Fig. 1). Table 1 shows the demographics and laboratory data at baseline for the study population. The great majority of the patients were male (97.0%), and 69.1% were men who have sex with men (MSM), followed by heterosexuals (26.0%). Their median age was 29 years (IQR, 25—34), and the median weight and BMI was 62 kg (IQR, 56—68) and 20.9 kg/m^2 (IQR, 19.2—22.9), respectively. The median CD4 cell count was 312 cells/μl (IQR, 234—402), and PVL 36000 copies/ml (IQR, 12600—102000). Baseline median eGFR was 124.0 ml/min/1.73 m^2 (IQR, 115.7—130.4), while the results of urine proteinuria were reported as negative, suspected positive, 1+, 2+, and 3+ in 76.6%, 17.4%, 6.0%, 4.9% and 1.1%, respectively, of the urine specimens tested at baseline; and no case of non-diabetic glycosuria was found (Table 1).

Concomitantly use of nephrotoxic medications for the treatment or prevention of opportunistic infections such as trimethoprim-sulfamethoxazole (TMP-SMX) for *Pneumocystis jirovecii* pneumonia may cause renal impairment.[25] In our study, 17.5% (47/269) patients received trimethoprim-sulfomethoxazole (TMP/SMX) to prevent *P. jirovecii* pneumonia because of lower baseline CD4 count (<200 cells/μl) on the initiation of ART, and most of these patients [76.6% (36/47)] discontinued TMP/SMX during 48 weeks, there were three, two, and three patients who experienced decreased renal function at weeks 12, 24, and 48, respectively. Seven patients (14.9%) continued to received TMP/SMX and their treatment duration ranging from 52 to 116 weeks, and one patient who experienced a decline in renal function during the use of TMP/SMX. The treatment duration of TMP/SMX for these 43 patients was 31.0 weeks (SD, 3.1).Four patients (8.5%) continued to take trimethoprim-sulfomethoxazole to prevent *P. jirovecii* pneumonia throughout the follow-up period, and only one had a decline in renal function at week 168 week. In our study, none of the patients received ganciclovir or foscarent during the follow-up. Therefore, according to the results of our study, the nephrotoxicity induced by TMP/SMX seemed to be minimal.

Overall, 1, 8, 6 and 9 patients had missing eGFR data at week 48, 96, 144, 168, respectively; 2 more patients who switched ART regimen were withdrawn from the study because of persistent proteinuria between week 144 and week 168. The other patients with missing data at the follow-up points and continued the regimen were not withdrawn from the analysis. However, no effect on the changes of eGFR was observed despite the missing data. Virological suppression, defined as PVL <40 copies/ml, was achieved in 98.1% of the patients (253 of 258 patients) at weeks 156—168 of ART.

Trends of eGFR, TDF-related renal impairment and decreased renal function

Renal function indicated by eGFR from baseline through Week 168 of ART is shown in Fig. 2A. The median (IQR) change from baseline in eGFR (Fig. 2B) was 0.8 (−2.8—4.2), 0.7 (−3.6—4.1), −0.9 (−4.3—2.8), −1.5 (−4.7—3.3), −1.8 (−7.1—2.3), and −3.8 (−10.2—0.9) ml/min/1.73 m^2 at Week 12, 24, 48, 96, 144, and 168, respectively ($p < 0.001$), while the respective incidence of renal impairment, defined as a decline of eGFR by >25% was 0, 0, 0, 0.8% (2/261), 0.8% (2/261), and 1.2% (3/258), respectively (p for trend, 0.12), Though renal impairment occurred in 7 (2.7%) patients, only 3 patients (2 with persistent proteinuria during 144—168 weeks and 1 with eGFR<60 ml/min/1.73 m^2 at weeks 168 of ART.) had to change their ART regime during the study due to concerns about nephrotoxicity. The incidence of decreased renal function, defined as a decline of eGFR by > 10 ml/min/1.72 m^2 from baseline was 3.7% (10/269), 2.6% (7/269), 6.3% (17/268), 6.5% (17/261), 14.2% (37/261), and 24.8% (64/258) (p for trend <0.001) (Table 2). Three patients (1.1%) with baseline renal impairment improved with initiation of ART and proteinuria resolved completely after ART in 15 of 16 patients with proteinuria ≥1 + at baseline, while 1 patient was transferred to another treatment site after 8 weeks of ART with no follow-up of proteinuria.

Factors associated with TDF-related renal impairment and decreased renal function

In univariate analysis, there was no statistically significant difference in the incidence of decreased renal function among the different age groups (18—29, 30—39, and 40

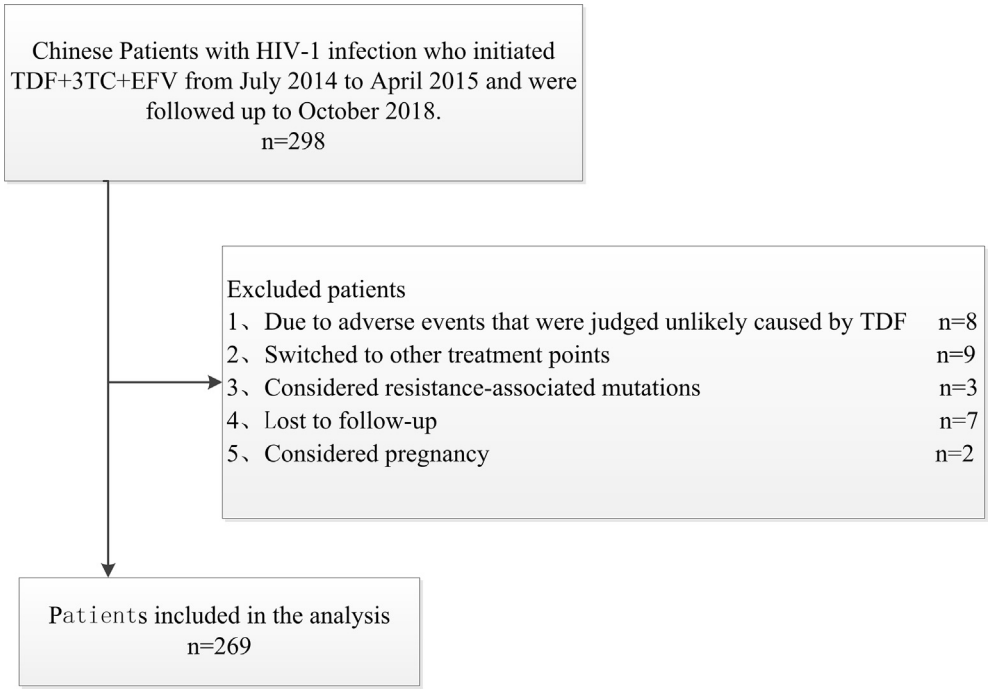

Figure 1. Flow diagram of patient selection.

years) throughout the follow-up course to 168 weeks, nor were there statistically significant associations between decreased renal function and CD4 cell stratum (≤200, 201−349, ≥350 cells/μl), CD4/CD8 ratio or PVL ($<10^4$, $10^4-<10^5$, $\geq 10^5$ copies/ml) (Table 2).

Three weight groups (<58, 58−66, and ≥67 kg) were defined to identify the association between weight and decreased renal function at different follow-up timepoints. After ART initiation from Week 12 through Week 144 weeks, we did not find statistically significant association between weight group and decreased renal function. However, at Week 168 of ART, the incidence of decreased renal function was significantly higher in weight group of <58 kg compared with that in weight group of ≥67 kg (33.8% vs 14.9%, $p = 0.01$) in univariate analysis; in contrast, there was no significant difference in the incidence of decreased renal function between the weight group of <58 kg and weight group of 58−66 kg ($p = 0.21$). In multivariate analysis using GEE by including these comparisons with $p < 0.1$, we found that the patients in the weight group of <58 kg (aOR 2.3, 95% CI 1.2−4.3, $p = 0.01$) and those in the weight group of 58−66 kg (aOR 2.0, 95% CI 1.0−3.8, $p = 0.04$) were more likely to develop decreased renal function after ART compared to those in the weight group of ≥67 kg.

We also examined the association between ART duration and decreased renal function. Compared with the risk among the patients followed at Week 12, the risk of decreased renal function increased significantly among the patients who continued to receive ART at 144 weeks (aOR 4.1, 95% CI 2.0−8.4) and Week 168 (aOR 8.4, 95% CI 4.2−16.4) (Table 3). In contrast, there was no statistically significant association with decreased renal function found for the patients continued to receive ART at Week 24 (aOR 0.7, 95% CI 0.3−1.4), Week 48 (aOR 1.7, 95% CI 0.9−3.5), or Week 96 (aOR 0.9, 95% CI 0.4−2.1).

Results of urine protein, glucose, and β2-microglobulin

The proportion of urine specimens tested positive for protein at baseline was 6.0%, which was 3.7% (10/269), 2.6% (7/269), 1.9% (5/251), 4.4% (11/268), 6.1% (15/245), and 5.1% (13/254) at Weeks 12, 24, 48, 96, 144, and 168, respectively ($p = 0.11$). Only 1 patient (0.35%) experienced non-diabetic glycosuria (1+) at 48 weeks after ART. At Week 168 of ART, β-2 microglobulinuria was determined in 100 patients. There were no statistically significant differences between those with testing for β-2 microglobulinuria and those without in terms of age, sex, CD4 cell count, PVL, body weight, BMI, baseline eGFR, and baseline proteinuria. The prevalence of β-2 microglobulinuria >0.5 mg/L was 41.0% (41/100), which was significantly higher than that of proteinuria and glycosuria (both $p < 0.001$). Abnormal β-2 microglobulinuria was negatively correlated with eGFR (correlation coefficient $r = -0.22$, $p = 0.02$) (Fig. 3). Decreased renal function was observed in 46.3% (19/41) and 35.6% (21/59) of patients with urinary β2 microglobulin abnormalities and those without, respectively ($p = 0.28$).

Changes in eGFR in patients with chronic hepatitis B infection

In total, 22 patients (8.2%) had chronic hepatitis B infection who had no renal impairment at baseline. After ART initiation, the incidence of decreased renal function was 13.6%, 4.6%, 5.0%, 0%, 4.6%, and 9.1% at Weeks 12, 24, 48, 96, 144, and 168, respectively ($p = 0.68$).

Table 1 Baseline demographics and laboratory data.

Characteristics	
Male, n (%)	261 (97.0)
Median age, (IQR), years	29 (25—34)
18—29, n (%)	151 (56.1)
30—39	77 (28.6%)
40—49	32 (11.9%)
≥50	9 (3.4%)
Route of infection, n (%)	
Male homosexual	186 (69.1)
Heterosexual	70 (26.0)
Unspecified	13 (1.1)
Median weight (IQR), kg	62 (56—68)
<58 n (%)	82 (30.5)
58—66	109 (40.5)
≥67	78 (29.0)
Median BMI, (IQR), kg/m^2	20.9 (19.2—22.9)
<18.5, n (%)	39 (14.5)
18.5—24.9	199 (74.0)
25—29.9	29 (10.8)
≥30	2 (0.7)
Median CD4, (IQR), cells/μl	312 (234—402)
<100, n (%)	9 (3.4)
100—200	39 (14.5)
201—349	109 (40.5)
≥350	112 (41.6)
Median CD4/CD8 ratio (IQR)	0.28 (0.21—0.40)
<0.3, n (%)	144 (53.5)
0.3—0.449	75 (27.9)
≥0.45	50 (18.6)
Median PVL, (IQR), copies/ml	36000 (12,600-102,0000)
<10^4, n (%)	57 (21.2)
≥10^4 to <10^5	144 (53.5)
≥10^5	68 (25.3)
Median eGFR, (IQR), ml/min/1.73 m^2	124.0 (115.7—130.4)
Baseline renal impairment, n (%)	3 (1.2)
Urine protein (n = 265)	
Negative, n (%)	203 (76.6)
probable positive	46 (17.4)
positive	16 (6.0)
1+	13 (4.9)
2+	3 (1.1)
3+	0
Non-diabetic glycosuria, n (%)	0 (0)
Hepatitis B virus infection, n (%)	22 (8.2)

Discussion

The worldwide use of TDF (300 mg) as a backbone of combination ART raises the concerns about the long-term safety of TDF.[26] In this study of 269 young HIV-positive Chinese who were treatment-naïve, had no preexisting comorbidities and started a TDF-containing ART regimen (TDF + 3 TC + EFV), we assessed the incidence of renal impairment and decreased renal function during the 168-week follow-up period. We found that the rate of renal impairment, defined as a decline of eGFR by >25% from baseline, remained low (2.7%) and a lower weight and a longer exposure duration to TDF-containing ART were associated with decreased renal function.

Our study results showed that the change in eGFR at Week 48 from baseline was not statistically significant among our patients with a median age of 29 years (IQR, 25—34). This is consistent with the findings of another study among HIV-positive patients in Singapore.[27] However, the finding that eGFR insignificantly increased from baseline to Weeks 12 and 24 of ART in our patients was not consistent with that of a previous study,[28] which demonstrated, during the first 24 weeks of ART, renal impairment occurred with a TDF-containing ART in Africans who started ART at a median CD4 of 151 cells/μl (IQR, 82—223). A study from Japan showed a significant decrease in eGFR (−26.4 mL/min/1.73 m^2/year) during the first 3 months of initiation of the TDF-containing ART. The discrepancy observed between ours and the Japanese study may be because of use of a different formula used in estimating GFR, a high median age (37 years), and inclusion of patients with co-morbidities such as diabetes mellitus and hypertension in the Japanese study.[19] In a four-year retrospective cohort study from Taiwan, the decrease in eGFR was more prominent in TDF-exposed of HIV-positive patients (the average annual decreased eGFR was 2.7 mL/min/1.73 m^2).[29] [Author: also elaborate a bit more; the characteristics of patients included in the study by Huang YS in Taiwan; the author names are incorrect for this cited reference].

Our study showed that 24.8% (64/258) of the patients had a decrease of eGFR by > 10 ml/min/1.73 m^2 after 168 weeks of follow-up, which was consistent with the results of a 144-week study in Korea.[30] Only seven patients experienced renal impairment in our study, suggesting that TDF had minimal effect on renal function in younger HIV-positive patients who had no opportunistic infection or co-morbidities during the three years of exposure. However, our study did demonstrate that a longer duration of exposure to TDF beyond 144 weeks was associated with decreased renal function, highlighting that the effect of long-term exposure to TDF on renal function warrants studies of longer duration of follow-up and regular monitoring of renal function in older Chinese patients with comorbidities are needed during the treatment period.

HIV infection may lead to renal impairment.[31] HIV-related nephropathy and HIV-immune complex nephropathy are the two main types of HIV-related renal disease, for which effective antiretroviral therapy may confer benefits in improving the renal function in HIV-positive patients.[32—34] It is worth noting in our study that proteinuria resolved with ART in 15 of 16 patients, and 3 patients with mildly decreased renal function at baseline showed progressive improvement in renal function after ART initiation, suggesting that these 3 patients might have had HIV-related nephropathy prior to treatment initiation, and glomerular and tubular injury recovered with effective ART.

Patients with a weight <58 kg had a 2.23-fold higher risk of an eGFR decline by > 10 ml/min/1.73 m^2 after ART for 168 weeks than those with a weight of ≥67 kg, which is consistent with the findings by Nishijima and colleagues in their single-center cohort study in Japan, which showed that a lower weight was significantly associated with TDF-related nephrotoxicity and that patients in the weight group of <59 kg were more likely to develop TDF-related

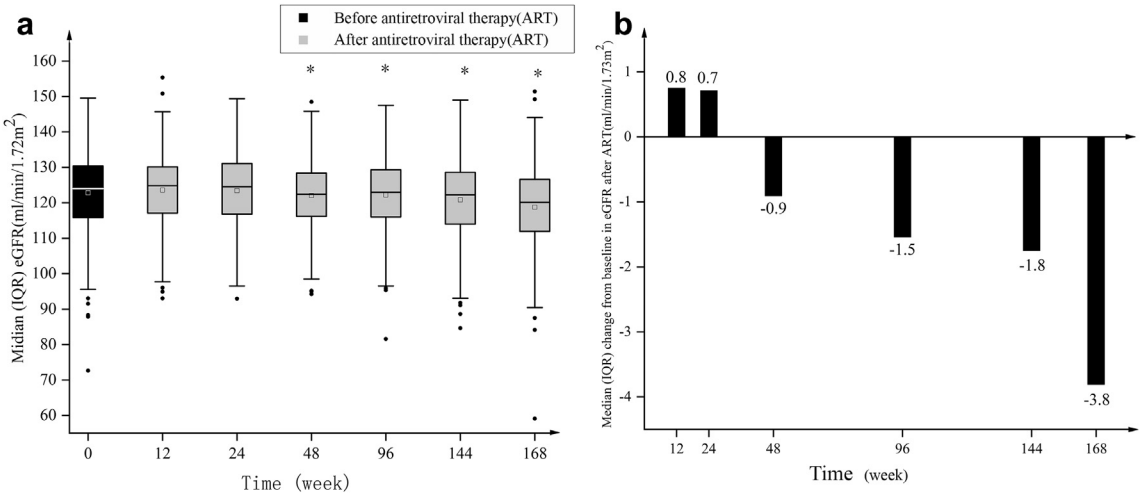

Figure 2. a. Boxplot of eGFR at baseline and along the follow-up timepoints. Baseline eGFR was 124.0 ml/min/1.73 m^2 (IQR, 115.7, 130.4). After 12, 24, 48, 96, 144 and 168 weeks of ART, the median eGFR was 124.8 ml/min/1.73 m^2 (IQR, 117.0, 130.4), 124.5 ml/min/1.73 m^2 (IQR, 116.7, 131.1), 122.4 ml/min/1.73 m^2 (IQR, 116.1, 128.4), 123.0 ml/min/1.73 m^2 (IQR, 115.9, 129.4), 122.2 ml/min/1.73 m^2 (IQR, 113.8, 128.6), and 120.1 ml/min/1.73 m^2 (range, 111.9, 126.6), respectively. *: statistically significant differences of median eGFR compared with baseline after 12, 24, 48, 96, 144 and 168 weeks of ART ($P = 0.08$, 0.26, 0.01, 0.04, <0.001, and <0.001, respectively). **b. Median change (IQR) from baseline in eGFR after ART.**

nephrotoxicity than patients weighing ≥67 kg.[19] It is likely that both Chinese and Japanese are of a smaller body habitus, lower plasma TDF clearance, and higher plasma concentrations of TDF, which might lead to the potentially increased risk for TDF-related renal tubular dysfunction.[35] While older age has been shown to be as an independent risk factor for renal impairment in HIV-positive patients, particularly those aged ≥50 years who were receiving TDF-based ART,[36] only few patients (n = 9) included were in this age group, which precluded us from analyzing the impact of an older age on renal dysfunction.

A multicenter, randomized, unblinded study in Europe and the United States found that HBV or HCV infection could increase the incidence of chronic kidney disease in HIV-positive patients.[37] In contrast, our study and another 104-week retrospective study[18] did not find the association between chronic HBV infection and decreased renal function. Other than the differences in the characteristics of the included patients and ART regimens administered, our study was underpowered to demonstrate the difference in that the case number of patients with chronic HBV infection in our study was only 22 (8.2%).

A recent study by Nishijima et al. showed that, among 116 patients with renal tubular dysfunction,[20] the incidence of β2-microglobulin elevation was just lower than that of high urinary N-acetyl-β-D-glucosaminidase (NAG). In our study, 41 out of 100 patients had abnormal β-microglobulinuria, a significantly higher incidence than that of proteinuria and glycosuria. We found that elevated β2 microglobulinuria was negatively associated with eGFR though only one patient had renal impairment, suggesting that TDF caused a greater incidence of renal tubular injury than clinically detected by the changes of eGFR. However, not all patients had urine β2-microglobulin testing at the start of treatment and in subsequent periodic follow-up in our study and, therefore, it was not possible to confirm whether renal tubular dysfunction could be detected prior to the observed decline in eGFR in patients receiving TDF.

Other than the limitations mentioned above, this study has several limitations. First, the patient number included in this study was small and the duration of follow-up was short. Second, this study included predominantly young, male patients with no opportunistic infection. The results observed may not be generalizable to women, the elderly, and patients with comorbidities, to whom TDF-containing ART are administered. Third, due to the constraints on hospital resources, we were not able to perform testing to identify if there were any episode of microalbuminuria, phosphaturia, hypophosphatemia and hypouricemia in this retrospective study, nor were we able to measure N-acetyl-β-D-glucosaminidase and retinol-binding protein in the urine specimens. Only glycosuria and semi-quantitative analysis of proteinuria were included in this study and less than 50% of the included patients underwent testing for β-2 microglobulinuria. More investigations by early detecting the abnormalities of those biomarkers are needed because the loss of renal function becomes irreversible in a substantial proportion of the HIV-positive patients after long-term exposure even if TDF is discontinued.[38] Fourth, all included ART-naïve patients in this study received TDF + 3 TC + EFV as their initial ART regimen. It has been shown a greater reduction in renal function with the use of PI/r, such as lopinavir/ritonavir, which increased the concentration of TDF in the renal tubular cells,[39] compared with patients receiving TDF plus non-nucleotide reverse-transcriptase inhibitors (nNRTI). Whether those HIV-positive Chinese patients who have to switch from TDF + 3 TC + EFV to TDF + 3 TC + PI/r due to treatment failure or intolerance would be at higher risk for renal dysfunction warrants further studies.

In conclusion, the cumulative incidence of renal impairment in this TDF-containing ART (TDF + 3 TC + EFV)

Table 2 Post-ART Incidence of Change in eGFR, TDF-related renal impairment and decreased renal function.

Variable	Baseline (n = 269)	12 weeks (n = 269)	24 weeks (n = 269)	48 weeks (n = 268)	96 weeks (n = 261)	144 weeks (n = 261)	168 weeks (n = 258)	P value
Median eGFR, (IQR), ml/min/1.73 m^2	124.0 (115.7−130.4)	124.8 (117.0−130.2)	124.5 (116.7−131.2)	122.4 (116.1−128.4)	122.7 (115.1−129.2)	122.2 (113.8−128.6)	120.1 (111.9−126.6)	<0.001
eGFR compared with baseline	p value	0.08	0.26	0.01	0.04	<0.001	<0.001	
Median change from baseline in eGFR after ART, (IQR), ml/min/1.73m^2		0.8 (−2.8−4.2)	0.7 (−3.6−4.1)	−0.9 (−4.3−2.8)	−1.5 (−4.7−3.3)	−1.8 (−7.1−2.3)	−3.8 (−10.2−0.9)	<0.001
Incidence of renal impairment	1.1% (3/269)	0	0	0	0.8% (2/261)	0.8% (2/261)	1.2% (3/258)	0.12
Incidence of decreased renal function		3.7% (10/269)	2.6% (7/269)	6.3% (17/268)	6.5% (17/261)	14.2% (37/261)	24.8% (64/258)	<0.001
Age group, % (n/N)	P value	0.45	0.87	0.06	0.07	0.11	0.63	
18−29 years		4.6% (7/151)	3.3% (5/151)	8.0% (12/151)	8.8% (13/148)	14.9% (22/148)	22.2% (32/144)	<0.001
30−39		1.3% (1/77)	1.3% (1/77)	1.3% (1/77)	1.3% (1/75)	8.2% (6/73)	28.0% (21/75)	<0.001
≥40		4.9% (2/41)	2.4% (1/41)	10.0% (4/40)	7.9% (3/38)	2.3% (9/40)	25.6% (10/39)	<0.001
Weight group, % (n/N)	P value	0.47	>0.99	0.82	0.45	0.79	0.03	
<58 kg		4.9% (4/82)	2.4% (2/82)	6.1% (5/82)	6.3% (5/79)	16.5% (13/79)	33.8% (26/77)	<0.001
58−66		4.6% (5/109)	2.8% (3/109)	5.5% (6/109)	8.6% (9/105)	13.2% (14/106)	25.2% (27/107)	<0.001
≥67		1.3% (1/78)	2.6% (2/78)	7.8% (6/77)	3.9% (3/77)	13.2% (10/76)	14.9% (11/74)	<0.001
$CD4^+$ cell count, cells/μl	P value	0.05	0.69	0.60	0.99	0.56	0.22	
≤200		8.3% (4/48)	4.2% (2/48)	8.3% (4/48)	6.8% (3/44)	14.9% (7/47)	29.8% (14/47)	<0.001
201−349		4.6% (5/109)	1.8% (2/109)	4.6% (5/109)	6.5% (7/107)	12.2% (13/107)	25.5% (27/106)	<0.001
≥350		0.9% (1/112)	2.7% (3/112)	7.2% (8/111)	6.4% (7/110)	17.5% (17/97)	23.2% (22/95)	<0.001
CD4/CD8 ratio	P value	>0.99	0.25	0.67	0.07	0.53	0.31	
<0.3		4.4% (5/144)	1.4% (2/144)	6.3% (9/144)	7.2% (10/139)	16.3% (23/141)	23.6% (33/140)	<0.001
0.3−0.449		4.0% (3/75)	5.3% (4/75)	8.1% (6/74)	9.6% (7/73)	10.8% (8/74)	31.0% (22/71)	<0.001
≥0.45		4.0% (2/50)	2.0% (1/50)	4.0% (2/50)	0 (0/49)	13.0% (6/46)	19.2% (9/47)	<0.001
HIV-RNA, copies/ml	P value	0.57	0.40	0.89	0.95	0.63	0.73	
$<10^4$		3.5% (2/57)	0 (0/57)	5.3% (3/57)	7.3% (4/55)	17.9% (10/56)	22.6% (12/53)	<0.001
$\geq 10^4$ to $<10^5$		4.9% (7/144)	2.8% (4/144)	6.3% (9/143)	6.4% (9/140)	13.8% (19/138)	26.8% (37/138)	<0.001
$\geq 10^5$		1.5% (1/68)	4.4% (3/68)	7.4% (5/68)	6.1% (4/66)	11.9% (8/67)	22.4% (15/67)	<0.001

Patients with testing for urine protein	265	269	269	268	251	245	254	
Negative, % (n)	76.6% (203)	80.3% (216)	85.5% (230)	87.7% (235)	78.9% (198)	74.3% (182)	83.5% (212)	
probable positive	17.4% (46)	16.0% (43)	11.9% (32)	10.5% (28)	16.7% (42)	19.6% (48)	11.0% (28)	
positive	6.0% (16)	3.7% (10)	2.6% (7)	1.9% (5)	4.4% (11)	6.1% (15)	5.1% (13)	0.11
+	4.9% (13)	1.9% (5)	1.9% (5)	1.1% (3)	3.6% (9)	4.5% (11)	4.3% (11)	
2+	1.1% (3)	1.5% (4)	0.7% (2)	0.4% (1)	0	1.6% (4)	0.8% (2)	
3+	0	0.4% (1)	0	0.4% (1)	0.8% (2)	0	0	
Non-diabetic glycosuria	0	0	0	0.4% (1)	0	0	0	
Urinaryβ2 microglobulin >0.5 mg/L	—	—	—	—	—	—	41.0% (41/100)	

Table 3 Factors associated with TDF-related renal decline after ART by the generalized estimating equations (GEE).

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	aOR	95% CI	P value
Age, years						
18–29	1			1		
30–39	0.9	0.5–1.4	0.56	1.1	0.6–1.8	0.79
≥40	1.2	0.6–2.4	0.62	1.4	0.7–2.9	0.36
Weight, kg						
≥67	1			1		
58–66	1.8	0.9–3.3	0.08	2.0	1.0–3.8	0.04
<58	2.1	1.1–4.0	0.02	2.3	1.2–4.3	0.01
CD4, cells/μl						
≥350	1			1		
201–349	1.1	0.7–1.9	0.66	1.1	0.7–1.9	0.60
≤200	1.5	0.8–2.8	0.24	1.5	0.8–2.9	0.26
CD4/CD8 ratio						
≥0.45	1			1		
0.3–0.449	1.5	0.7–2.5	0.22	1.5	0.7–3.0	0.26
<0.3	1.4	0.8–3.0	0.33	1.3	0.6–2.5	0.52
PVL, copies/ml						
$<10^5$	1			1		
$\geq 10^5$	0.8	0.5–1.4	0.44	0.7	0.4–1.3	0.24
ART duration, weeks						
12	1			1		
24	0.6	0.3–1.4	0.32	0.7	0.3–1.4	0.31
48	1.7	0.9–3.5	0.11	1.7	0.9–3.5	0.12
96	0.9	0.4–2.1	0.80	0.9	0.4–2.1	0.79
144	4.1	2.0–8.3	<0.001	4.1	2.0–8.4	<0.001
168	8.2	4.2–16.0	<0.001	8.4	4.2–16.4	<0.001

regimen remained low (2.7%) among ART-naïve HIV-positive patients who were of a young age and had no comorbidities, and a lower weight and longer exposure duration to TDF-

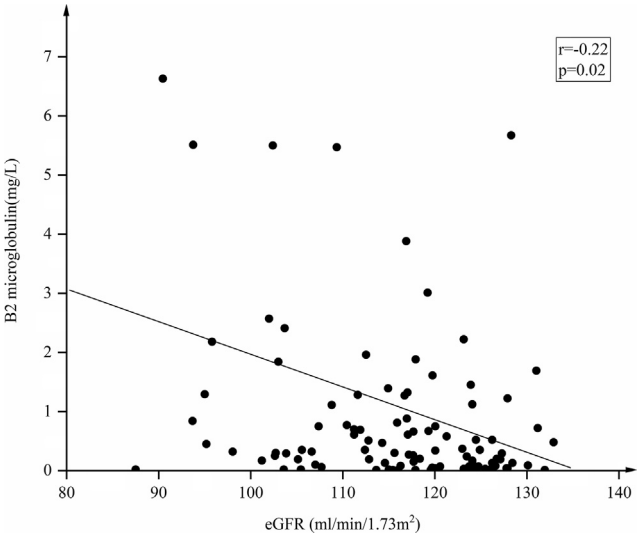

Figure 3. Correlation diagram of eGFR with β2 microglobulinuria.

containing ART were associated with decreased renal function.

Conflict of interest declaration

The authors have declared that no competing interests exist.

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