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Incidence and risk factors for tenofovir-associated nephrotoxicity among human immunodeficiency virus-infected patients in Korea

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Background/Aims: Little is known about tenofovir disoproxil fumarate (TDF)-induced nephrotoxicity in human immunodeficiency virus (HIV)-infected patients in Korea. The objective of this study was to evaluate the incidence and risk factors of TDF-associated nephrotoxicity among HIV-infected patients in Korea.

Methods: A single-center retrospective cohort study was conducted on HIV-infected patients in Korea. We included patients who had started TDF or abacavir (ABC)-based antiretroviral therapy (ART) between October 2006 and December 2014. Estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease-Epidemiology Collaboration equation. Renal dysfunction was defined as > 25% decrease of baseline eGFR. A propensity matched case-control study was conducted to compare renal dysfunction rates between the two groups. The risk factors of nephrotoxicity were analyzed by Cox regression analysis.

Results: A total of 210 HIV-infected patients were included in the study, of which, 108 were TDF-based ART group and 102 were ABC-based ART group. Renal dysfunction occurred in 16 patients (14.8%) in the TDF group and 11 (10.8%) in the ABC group. Incidence of renal dysfunction of TDF and ABC group was 9.66 per 100 person-years (PYs) and 5.14 per 100 PYs, respectively (p = 0.176). In propensity-score-matched analysis, renal dysfunction rates were TDF 13.3% versus ABC 13.3% (p > 0.999). In multivariable analysis, Centers for Disease Control and Prevention clinical category C was a significant risk factor for renal dysfunction.

Conclusions: Approximately, 13% of HIV-infected patients treated with TDF had renal dysfunction. Advanced stage of HIV infection was a significant risk factor for renal dysfunction.

Keywords: Tenofovir; HIV-infected patients; Nephrotoxicity; Centers for Disease Control and Prevention clinical category C

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INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is one of the most widely used nucleotide reverse transcriptase inhibitors (NRTI) as a part of combination regimens for the treatment and prevention of human immunodeficiency virus (HIV) infection. TDF is available as either single agent or more frequently a component in several fixed dose combinations that is convenient. Although TDF is generally considered safe and well tolerated, its use has been associated with nephrotoxicity and a decrease in bone mineral density [1-3].

TDF can cause proximal renal tubular damage, in part due to potential mitochondrial toxicity, in severe cases leading to acute kidney injury and Fanconi's syndrome [4]. In addition, TDF nephrotoxicity can be manifested as distal tubular injury in the form of nephrogenic diabetes insipidus [1]. Renal wasting of phosphorus by damaged renal tubules can lead to osteomalacia. Previous studies suggest that older age, advanced HIV disease, low body weight, pre-existing renal impairment, and having comorbidities are risk factors of TDF-associated nephrotoxicity [5-9]. Concomitant use of a ritonavir or cobicistat with TDF was also suggested as a risk factor of renal dysfunction [10-12].

There are limited data on the incidence and risk factors for TDF-associated nephrotoxicity among the HIV-infected population in Korea. The objective of this study was to assess the incidence and risk factors of TDF-associated nephrotoxicity in HIV-infected patients in Korea. We also compared the incidence of nephrotoxicity among patients on TDF-based antiretroviral therapy (ART) with those on abacavir (ABC)-based ART.

METHODS

Study population

A retrospective study was conducted from January 2009 and December 2014 at a tertiary care hospital in Busan, South Korea. All HIV-infected patients who had started TDF (300 mg/day) or ABC (600 mg/day) were identified from computerized medical records from October 1, 2006, to December 31, 2014. The patients who were ≥ 20 years and with an estimated glomerular filtration rate (eGFR) of ≥ 60 mL/min/1.73 m² with the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation at baseline were enrolled. Patients who met any of the following criteria were excluded: (1) both TDF- and ABC-based ART during study periods, (2) too short follow-up periods (12 weeks) and too limited data (no follow-up renal function test and viral load) to assess the effect of ART on renal function, (3) initiating ART in other clinics, (4) non-responder (no suppression of HIV viral load in the test performed 1 month after starting ART) or obviously non-compliant, and (5) administered with 300 mg twice daily dose of ABC and Stribild (combined formulate of cobicistat, elvitegravir, emtricitabine and

TDF). ABC- or TDF-based ART were chosen by attending physicians according to their discretion at baseline. The observational periods were measured from the date of ART initiation to the earliest of the following dates: onset date of renal dysfunction, stop date of ABC or TDF if either of two drugs was switched to other drugs, date of the last follow-up if patients were lost to follow-up or transfer out, 120 weeks after ART initiation, or December 31, 2014.

Assessment of renal dysfunction

Renal dysfunction was defined as > 25% decrease of baseline eGFR. The baseline eGFR was calculated using the CKD-EPI equation: eGFR = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female), where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 [13].

Data collection and definitions

To identify the risk factors of renal dysfunction among HIV-infected patients receiving TDF- or ABC-based ART, we retrospectively collected demographic and clinical characteristic data from medical records including age, sex, body weight, body mass index (BMI), other medical conditions (concurrent use of nephrotoxic drugs, co-infection with hepatitis B and hepatitis C, hypertension, diabetes mellitus, and dyslipidemia), HIV viral load and cluster of differentiation 4+ (CD4+) T cell count. AIDS defining illness was defined according to the 1993 AIDS Centers for Disease Control and Prevention (CDC) definition [14].

Hepatitis B virus (HBV) co-infection was defined as a positive HBs antigen test. Hepatitis C virus (HCV) co-infection was defined as a positive HCV antibody test. Diabetes mellitus, hypertension, dyslipidemia, and other underlying diseases were considered as comorbidities if documented in patients' medical records. Co-administration of nephrotoxic drugs were considered if patients had received aciclovir, valaciclovir, ganciclovir, aminoglycosides (gentamicin, amikacin, streptomycin), vancomycin, colistin, trimethoprim/sulfamethoxazole, and non-steroidal anti-inflammatory agents with ART. The concomitant ART used as boosted protease inhibitors (b-PIs) is ritonavir.

Statistical analysis

Categorical variables were compared using Pearson chi-square test or Fisher exact test, whereas non-categorical variables were tested with Student t test or the Mann-Whitney U test. Incidence of nephrotoxicity was compared between TDF-based ART group and ABC-based ART group. We also performed a propensity score matched analyses to balance for differences in baseline characteristics between the two groups. The risk factors of TDF-associated nephrotoxicity were analyzed by multivariate proportional Cox regression analyses. All variables associated with renal dysfunction ($p < 0.25$) in univariate Cox models were assessed in multivariate models using stepwise forward selection. Statistical analyses were conducted using SPSS for Windows version 22.0 (IBM Co., Armonk, NY, USA).

Ethics statement

This retrospective study was approved by the Institutional Review Board of Pusan National University Hospital Clinical Trial Center, and the requirement informed consent was waived (E-2015062).

RESULTS

Clinical characteristics

Among 458 HIV-infected patients who had started TDF or ABC during the study period, 108 patients in the TDF-based ART group and 102 patients in the ABC-based ART group were enrolled after exclusion process. The baseline characteristics, comorbidities, and medications of the patients in both groups are presented in Table 1.

Both groups had a statistically similar predominance of male (TDF vs. ABC, 86.1% vs. 89.2%, $p = 0.495$), a relatively small body status (median weight, 63.48 ± 12.00 kg; median BMI, 22.1 ± 3.57 kg/m²), a high CD4+ T cell count (TDF vs. ABC, 318.19 ± 231.81/μL vs. 312.94 ± 267.33/μL, $p = 0.879$), and high HIV RNA viral load (TDF vs. ABC, 3.95 ± 1.82 $\log_{10}$/mL vs. 3.53 ± 2.25 $\log_{10}$/mL, $p = 0.137$).

HBV co-infection rates (TDF vs. ABC, 16.7% vs. 3.9%, $p = 0.003$) and baseline eGFR (TDF vs. ABC, 107.63 ± 15.50 mL/min/1.73 m² vs. 101.72 ± 14.89 mL/min/1.73 m², $p = 0.005$) was significantly higher in the TDF-based ART group. Dyslipidemia was more frequent in the ABC-based ART group (TDF vs. ABC, 0.9% vs. 7.8%, $p = 0.013$).

In the TDF-based ART group, the b-PIs and integrase inhibitors (INIs) were preferred than the nonboosted protease inhibitors (nb-PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) as concurrent ART (b-PIs 39.8%, INIs 39.8%, NNRTIs 14.8%, nb-PIs 0.9%), whereas in the ABC-based ART group, the b-PIs were the most favorite concurrent ART and the NNRTIs were preferred (b-PIs 54.9%, NNRTIs 28.4%, nb-PIs 9.8%, INIs 6.9%) (Table 1). The rate of concomitant administration of nephrotoxic drugs (TDF vs. ABC, 34.3% vs. 36.3%, $p = 0.760$) was similar between the two groups. Follow-up duration (weeks) was significantly longer in ABC-based ART group (TDF vs. ABC, 79.68 ± 36.39 vs. 109.01 ± 26.96, $p < 0.001$).

Propensity-score-matched case control study

The propensity-score-matched analysis was done to correct for differences in baseline characteristics between the two groups. To estimate the propensity score to receive TDF-based ART, age, body weight, BMI, baseline Scr, baseline eGFR, diabetes mellitus, dyslipidemia, HBV co-infection, CDC category, administration of nephrotoxic drug and follow-up duration were included. Seventy-five patients in TDF-based ART group were matched with 75 patients in ABC-based ART group with the closest propensity scores. Both groups were statistically similar, except follow-up duration (weeks) and the concurrent ART. Despite of the propensity-score-matched analysis, follow-up duration (weeks) was significantly longer in ABC-based ART group (TDF vs. ABC, 82.49 ± 35.41 vs. 105.59 ± 30.62, $p = 0.004$). In the TDF-based ART group, the INIs and b-PIs were preferred as concurrent ART (INIs 40.0%, b-PIs 38.7%, NNRTIs 14.7%), whereas in the ABC-based ART group, the b-PIs were the most favorite concurrent ART and NNRTIs were preferred (b-PIs 54.7%, NNRTIs 30.7%, nb-PIs 8.0%, INIs 6.7%) (Table 2).

The incidence of renal dysfunction

Renal dysfunction occurred in 16 patients (14.8%) in the TDF-based ART group and 11 (10.8%) in the ABC-based ART group, with an estimated incidence of 9.66 and 5.14 per 100 person-years (PYs), respectively. The median time from initiation of ART to occurrence of renal dysfunction was 30.15 weeks (range, 0 to 110) for the TDF-based arm and 50.62 weeks (range, 5 to 120) for ABC arm.

Table 1. Baseline demographics and laboratory data of patients who received TDF- or ABC-based ART (n = 210)

Variable	TDF (n =108)	ABC (n = 102)	p value
Male sex	93 (86.1)	91 (89.2)	0.495
Age, yr	46.15 ± 13.16	44.75 ± 12.94	0.437
Body weight, kg	62.21 ± 12.20	64.83 ± 11.69	0.114
BMI, kg/m²	21.88 ± 3.77	22.33 ± 3.34	0.359
CD4 count, /μL	318.19 ± 231.81	312.94 ± 267.33	0.879
HIV RNA virus, log/mL	3.95 ± 1.82	3.53 ± 2.25	0.137
Hepatitis B	18 (16.7)	4 (3.9)	0.003
Hepatitis C	7 (6.5)	7 (6.9)	0.912
Hypertension	16 (14.8)	15 (14.7)	0.982
Diabetes mellitus	8 (7.4)	12 (11.8)	0.282
Dyslipidemia	1 (0.9)	8 (7.8)	0.013
Nephrotoxic drug	37 (34.3)	37 (36.3)	0.760
CDC clinical category C	24 (22.2)	16 (15.7)	0.228
Serum creatinine, mg/dL	0.78 ± 0.17	0.85 ± 0.18	0.001
Baseline eGFR, mL/min/1.73 m²	107.63 ± 15.50	101.72 ± 14.89	0.005
Follow-up duration, wk	79.68 ± 36.39	109.01 ± 26.96	< 0.001
Marital status, married	48 (45.3)	48 (47.1)	0.797
Mode of transmission			
Heterosexual	45 (42.9)	52 (52.5)	0.167
Homosexual	59 (56.2)	45 (45.5)	0.125
Others	1 (1)	2 (2)	0.527
Concurrent ART			
b-PIs	43 (39.8)	56 (54.9)	0.029
nb-PIs	1 (0.9)	10 (9.8)	0.004
NNRTIs	16 (14.8)	29 (28.4)	0.016
INIs	43 (39.8)	7 (6.9)	< 0.001
Mix[a]	5 (4.6)	0	0.028

Values are presented as number (%) or mean ± SD.

TDF, tenofovir; ABC, abacavir; ART, antiretroviral therapy; BMI, body mass index; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; CDC, Centers for Disease Control and Prevention; eGFR, estimated glomerular filtration rate; b-PI, boosted protease inhibitor; nb-PI, nonboosted protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INI, integrase inhibitor.

[a]Mix, protease inhibitors + others or switch.

The total observation period was 447.2 patient-years (median, 839 days; interquartile range [IQR], 357 to 1,137) for the TDF arm and 901.7 patient-years (median, 1,119 days; IQR, 660.5 to 1,509) for the ABC arm.

Fig. 1 shows the time from ART initiation to 25% decrease in eGFR by the Kaplan-Meier method in the two groups. The estimated incidence of renal dysfunction in TDF- and ABC-based ART groups was 9.66 per 100 PYs and 5.14 PYs, respectively. In surviving analysis, ABC-based ART group showed lower renal dysfunction prevalence, but the difference across groups did not reach statistical significance (p = 0.176) (Fig. 1A). In propensity-score-matched analysis, renal dysfunction occurred in 10 patients (13.3%) in the TDF-based ART group and 10 (13.3%) in the ABC-based ART group, with an estimated incidence of 8.41 and 6.57 per 100 PYs, respectively (p > 0.999) (Table 2). Fig. 1B shows the time from ART initiation to > 25% decrease in eGFR by the Kaplan-Meier

Table 2. Baseline demographics and laboratory data and comparison of implications of ART on renal function of propensity score-matched patients who received TDF- and ABC-based ART (n = 150)

Variable	TDF (n = 75)	ABC (n = 75)	p value
Male sex	63 (86.0)	66 (88.0)	0.664
Age, yr	45.19 ± 14.34	45.32 ± 13.71	0.956
Body weight, kg	63.63 ± 12.94	63.93 ± 11.00	0.880
BMI, kg/m²	22.13 ± 3.92	22.08 ± 3.14	0.936
CD4 count, /μL	317.95 ± 230.75	292.95 ± 242.17	0.518
HIV RNA virus, log/mL	3.96 ± 1.77	3.69 ± 2.26	0.423
Hepatitis B	1 (1.3)	4 (5.3)	0.367
Hepatitis C	5 (6.7)	7 (9.3)	0.765
Hypertension	11 (14.7)	12 (16.0)	> 0.999
Diabetes mellitus	6 (8.0)	8 (10.7)	0.780
Dyslipidemia	1 (1.3)	5 (6.7)	0.209
Nephrotoxic drug	26 (34.7)	27 (36.0)	> 0.999
CDC clinical category C	15 (20.0)	15 (20.0)	> 0.999
Serum creatinine, mg/dL	0.81 ± 0.17	0.83 ± 0.16	0.440
Baseline eGFR, mL/min/1.73 m²	106.41 ± 15.85	103.96 ± 15.02	0.333
Follow-up duration, wk	82.49 ± 35.41	105.59 ± 30.62	0.004
Marital status, married	32 (43.8)	37 (49.3)	0.515
Mode of transmission			
Heterosexual	33 (45.8)	39 (53.4)	0.408
Homosexual	38 (52.8)	32 (43.8)	0.320
Others	1 (1.4)	2 (2.7)	> 0.999
Concurrent ART			
b-PIs	29 (38.7)	41 (54.7)	0.050
nb-PIs	0	6 (8.0)	0.012
NNRTIs	11 (14.7)	23 (30.7)	0.031
INIs	30 (40.0)	5 (6.7)	< 0.001
Mix[a]	5 (6.7)	0 (0.0)	0.058
eGFR of the end of study, mL/min/1.73 m²	98.91 ± 21.52	100.45 ± 16.08	0.613
Renal dysfunction	10 (13.3)	10 (13.3)	> 0.999

Values are presented as number (%) or mean ± SD.

ART, antiretroviral therapy; TDF, tenofovir; ABC, abacavir; BMI, body mass index; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; CDC, Centers for Disease Control and Prevention; eGFR, estimated glomerular filtration rate; b-PI, boosted protease inhibitor; nb-PI, nonboosted protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INI, integrase inhibitor.

[a]Mix, protease inhibitors + others or switch.

analyses in the two groups ($p = 0.723$).

Risk factors for TDF-associated nephrotoxicity after propensity-score matching

In the univariate analysis, nephrotoxic drug (hazard ratio [HR], 3.68; 95% confidence interval [CI], 1.47 to 9.23;

$p = 0.005$), hypertension (HR, 2.76; 95% CI, 1.06 to 7.19; $p = 0.037$), and CDC clinical category C (adjusted HR, 5.83; 95% CI, 2.41 to 14.09; $p < 0.001$) were significantly associated with the renal dysfunction. However, TDF use was not associated with the renal dysfunction ($p = 0.723$) (Table 3).
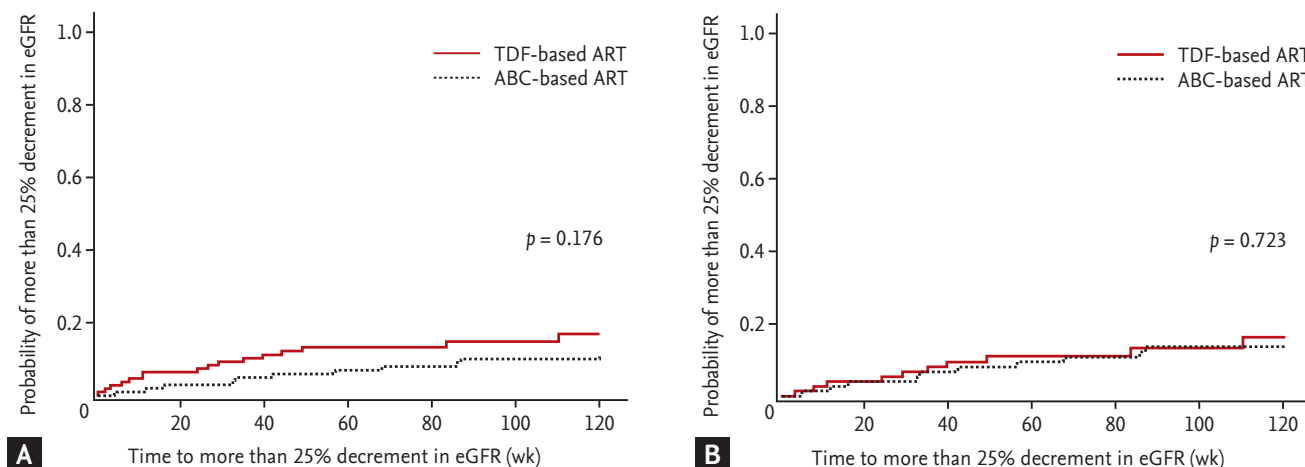
Figure 1. Kaplan-Meier curve showing the time to renal dysfunction in patients with tenofovir (TDF)- or abacavir (ABC)-based antiretroviral therapy (ART). (A) Before propensity score matching. (B) After propensity score matching. eGFR, estimated glomerular filtration rate.

In multivariate analysis, CDC clinical category C (HR, 8.09; 95% CI, 2.46 to 26.57; p = 0.001) was the only significant risk factor for renal dysfunction (Table 3).

DISCUSSION

In this study, the incidence of renal dysfunction, defined as > 25% decrement of eGFR using CKD-EPI from the baseline was 9.66 per 100 PYs in HIV-infected patients who started TDF-based ART. Despite the possibility of some differences in the incidence or prevalence of TDF-associated nephrotoxicity according to the measuring methods of eGFR and definition of TDF-associated nephrotoxicity, the results were broadly in line with those of other studies [6,9,15,16]. A retrospective study conducted in Korea showed that the incidence of acute Scr elevation > 1.5 mg/dL regardless of baseline Scr level among patients treated with TDF-containing regimens was 2.8 per 100 PYs [17].

In our study, TDF- and ABC-based ART groups showed some important differences in baseline characteristics. First, there was a difference in baseline eGFR between two groups possibly because physicians frequently prescribed ABC-based ART than TDF-based ART to patients with lower renal function or several risk factors for renal dysfunction. Second, TDF-based ART was more frequently used in the HIV and HBV co-infected patients than ABC-based ART, since anti-retroviral agent which is effective against both HIV and HBV (for example, tenofovir, lamivudine, emtricitabine) can also prevent the occurrence of clinically significant liver disease by directly inhibiting the replication of HBV [18]. Third, the duration of the use of ABC-based ART was longer than that of ABC-based ART because of the difference of the timing of the introduction of ABC (in 2002) and TDF (in 2012).

The propensity-score-matched analysis was conducted to adjust for group-wise differences in baseline characterics. After propensity-scores were matched, renal dysfunction rate was similar between the two groups (TDF 13.3% vs. ABC 13.3%); and hypertension, co-administration of nephrotoxic drugs and CDC clinical category C were significantly associated with renal dysfunction, but TDF use, older age and ritonavir b-PIs use were not associated in univariate analysis. There was no statistically significant difference in the age distribution between before and after 40 years of age (HR, 2.44; 95% CI, 0.81 to 7.28; p = 0.112) or before and after 60 years of age (HR, 1.54; 95% CI, 0.56 to 4.24; p = 0.404). In multivariate analyses, CDC clinical category C was only significantly associated with the renal dysfunction. Consistent with previous studies, advanced stage was a significant risk factor for TDF-associated nephrotoxicity in our study.

After adjusting for variables, we expected a higher rate of renal dysfunction in TDF-based ART group than ABC-based ART group. However, the difference in rate of renal dysfunction between the two groups was de-

Table 3. Univariate and multivariate analysis for factors associated with nephrotoxicity after propensity-score matching

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Backbone NRTIs				
ABC	1	-	-	-
TDF	1.17 (0.49–2.83)	0.723	-	-
Sex				
Male	1	-	-	-
Female	0.31 (0.04–2.31)	0.252	-	-
Age, yr				
≤ 30	1	-	1	-
31–50	3.04 (0.38–24.30)	0.295	1.55 (0.18–13.31)	0.689
> 50	5.73 (0.74–44.37)	0.095	3.36 (0.39–29.08)	0.272
BMI, kg/m²				
< 18.5	1	-	-	-
18.5–24.9	0.64 (0.21–1.98)	0.441	-	-
≥ 25	0.51 (0.11–2.22)	0.377	-	-
CD4 count, /μL				
> 500	1	-	-	-
201–500	0.74 (0.18–3.10)	0.681	-	-
≤ 200	2.21 (0.62–7.83)	0.219	-	-
HIV RNA virus, log/mL				
Undetectable	1	-	1	-
Log 0–5	2.23 (0.47–10.49)	0.312	2.82 (0.56–14.26)	0.210
> Log 5	3.94 (0.86–17.98)	0.077	1.74 (0.34–8.93)	0.507
Concurrent ART				
b-PIs	1	-	1	-
Others[a]	0.56 (0.23–1.38)	0.207	0.48 (0.18–1.25)	0.131
Hepatitis B vs. none	1.49 (0.20–11.15)	0.697	-	-
Hepatitis C vs. none	1.38 (0.32–5.97)	0.664	-	-
Hypertension vs. none	2.76 (1.06–7.19)	0.037	2.12 (0.52–8.14)	0.293
Diabetes mellitus vs. none	2.87 (0.96–8.57)	0.060	1.81 (0.40–8.20)	0.442
Dyslipidemia vs. none	1.20 (0.16–8.98)	0.858	-	-
Nephrotoxic drug vs. none	3.68 (1.47–9.23)	0.005	1.14 (0.35–3.73)	0.825
CDC, class C vs. A or B	5.83 (2.41–14.09)	< 0.001	8.09 (2.46–26.57)	0.001

HR, hazard ratio; CI, confidence interval; NRTI, nucleotide reverse transcriptase inhibitor; ABC, abacavir; TDF, tenofovir; BMI, body mass index; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; ART, antiretroviral therapy; b-PI, boosted protease inhibitor; CDC, Centers for Disease Control and Prevention.
[a]Others, concurrent ART except the b-PIs.

creased, possibly due to exclusion of a relatively large number of patients in serious condition (category C) in TDF-based ART group than ABC-based ART group by propensity score matching (category C: before matching, TDF 22.2% vs. ABC 15.7%; after matching, TDF 20.0% vs. ABC 20.0%). The mean body weight was slightly lower in the TDF-based ART group before matching and the mean body weight was more similar after matching, without significance (before matching, TDF 62.21 ± 12.20 kg vs. ABC 64.83 ± 11.69 kg, p = 0.114; after matching, TDF

63.63 ± 12.94 kg vs. ABC 63.93 ± 11.00 kg, p = 0.880). Low body weight is a well-known risk factor for renal failure when using TDF [5-7]. Exclusion of low body weight patients in the TDF-based ART group from the matching could have an important effect. Therefore, use of TDF as the NRTIs back bone does not significantly increase the risk of renal dysfunction in cases with good baseline renal function and HIV/AIDS not manifesting as a serious condition.

This study has several limitations. First, this study is a retrospective observational study, so we cannot rule out the presence of unmeasured confounding. Second, there were a differences in the timing of the introduction of the ABC and TDF in Korea. Third, it was difficult to adjust for significant group-wise difference in concurrent ART use; hence, it was difficult to assess nephrotoxicity due to concurrent ART use. Fourth, HIV-infected patients with relatively low eGFR were prescribed more ABC-based ART than TDF-based ART, so there was a difference in baseline eGFR between the two groups. Fifth, because the maximum follow-up duration is 120 weeks, it is necessary to observe a rate of change in nephrotoxicity when long-term follow-up. Sixth, CDC clinical category was a larger confound factor than TDF use because there was a lot of HIV-infected patients with serious clinical condition in our study. Finally, several studies showed useful screening markers for tubular cell damage because of TDF, such as urinary b2M, proteinuria, glycosuria and cystatin C, but we did not evaluate these markers.

In conclusion, HIV-infected patients with TDF use showed a tendency for more frequent occurrence of renal dysfunction than those with ABC use. Advanced stage of HIV infection was an important risk factor for renal dysfunction in HIV-infected patients receiving ART in Korea.

KEY MESSAGE

1. Tenofovir disoproxil fumarate use was not associated with nephrotoxicity in human immunodeficiency virus-infected Korean patients if baseline renal function was normal.
2. The Centers for Disease Control and Prevention category C was identified as an independent risk factor associated with nephrotoxicity.

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