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The Incidence and Clinical Characteristics of Acute Serum Creatinine Elevation more than 1.5 mg/dL among the Patients Treated with Tenofovir/Emtricitabine-containing HAART Regimens

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Background: The combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has been the first choice nucleoside reverse transcriptase inhibitor (NRTI) according to many reliable antiretroviral treatment (ART) guidelines because of its high efficacy. However, TDF-related renal toxicity reported in Western countries is a challenging issue regarding clinical use. We conducted this study to evaluate the incidence and characteristics of an acute increase in serum creatinine (Cr) level > 1.5 mg/dL among TDF/FTC-based highly active antiretroviral treatment (HAART)-treated patients.

Materials and Methods: We retrospectively reviewed the medical records of 205 HIV-infected patients treated with TDF/FTC-containing regimens between 1 February 2010 and 30 April 2014. Three groups of TDF/FTC + ritonavir-boosted protease inhibitor (PI/r), TDF/FTC + non-nucleoside reverse transcriptase inhibitor (NNRTI), and TDF/FTC + integrase strand transfer inhibitor (INSTI), and three PI/r subgroups of TDF/FTC + lopinavir (LPV)/r, TDF/FTC + atazanavir (ATV)/r, TDF/FTC + darunavir (DRV)/r were evaluated.

Results: A total 136 patients (91 in the TDF/FTC + PI/r group, 20 in the TDF/FTC + NNRTI group and 25 in the TDF/FTC + INSTI group) were included in the statistical analysis. Four cases (4.9%; all in the TDF/FTC + PI/r group) among 136 patients showed an acute increase in serum Cr more than 1.5 mg/dL, so the overall incidence was 2.8 cases per 100 patient-years. One case was a patient treated with TDF/FTC + LPV/r, and the others were treated with TDF/FTC + ATV/r. No case of an acute increase in serum Cr was observed in the TDF/FTC + DRV/r group. The incidence of serum Cr increase more than 1.5 mg/dL in TDF/FTC + PI/r group was 4.0 cases per 100 patient-years.

Conclusion: Although only a small number of patients were evaluated retrospectively from a single center, the TDF/FTC + PI/r regimen may have been related with relatively higher tendency of increment of serum Cr level. These findings reinforce the importance of close follow-ups of HIV-infected patients treated with the TDF/FTC + PI/r regimens.

Key Words: Antiretroviral agents; Tenofovir; Nephrotoxicity; Protease inhibitors; Human immunodeficiency virus

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Introduction

Tenofovir disoproxil fumarate (TDF) is the preferred nucleoside reverse transcriptase inhibitor (NRTI) to initially treat human immunodeficiency virus (HIV)-infected patients except pregnant women. TDF was approved by Food and Drug Administration in 2001 to treat hepatitis B virus (HBV) and HIV infection [1]. Tenofovir and emtricitabine (TDF/FTC) are preferred treatment among the NRTIs according to US Department of Health and Human Services (DHHS) and the US International Antiviral Society guidelines [2, 3].

Despite continuous use of antiretroviral therapeutics and the development of new drugs, kidney disease is a critical problem in HIV-infected patients [4]. Proteinuria, interstitial nephritis, renal tubular damage, and nephrolithiasis have been detected as renal complications of HIV infection [5]. Comorbidities, such as diabetes mellitus, hypertension, hepatitis C virus (HCV) co-infection, and specific antiretroviral drug use, are risk factors for kidney disease, which causes atherosclerosis and increases mortality rates [6, 7]. Nephrotoxicity can appear either during long or short-term use of TDF. TDF-induced nephrotoxicity is reported in about 15% of patients treated with TDF for 2–9 years [8]. Previous studies have reported several risk factors for TDF-induced nephrotoxicity, including high basal serum creatinine (Cr) level, concomitant use of nephrotoxic drugs, low body weight, old age, and low CD4+ T cell count [9]. It is presumed that proximal tubule damage, diabetes insipidus, decreased bone density, and reduced glomerular filtration rate (GFR) could also occur in association with TDF use [10-13]. In addition, combinations of protease inhibitors (PI), such as atazanavir (ATV) or lopinavir (LPV), can an additional decrease in GFR, compared to a combination with a non-nucleoside reverse transcriptase inhibitor (NNRTI), such as efavirenz (EFV) [14, 15].

In this study, we investigated the incidence and clinical characteristics of an acute increase in serum Cr level more than 1.5 mg/dL during TDF/FTC-based highly active antiretroviral treatment (HAART) in HIV-infected patients.

Materials and Methods

1. Study design and subjects

This retrospective study was conducted using the medical records of patients treated with HAART including TDF/FTC at Kyungpook National University Hospital between February 1, 2010 and April 30, 2014 (Fig. 1). Exclusion criteria were too short treatment duration (<6 days), lack of blood chemistry or other blood laboratory data, and the patient's medical records could not be reviewed. The patients were divided into three groups of TDF/FTC + ritonavir-boosted PI (PI/r) (group 1), TDF/FTC + NNRTI (group 2), and TDF/FTC + integrase strand transfer inhibitors (INSTI) (group 3) and three PI/r subgroups of TDF/FTC + LPV/r (subgroup 1), TDF/FTC + ATV/r (subgroup 2), and TDF/FTC + darunavir (DRV)/r (subgroup 3).

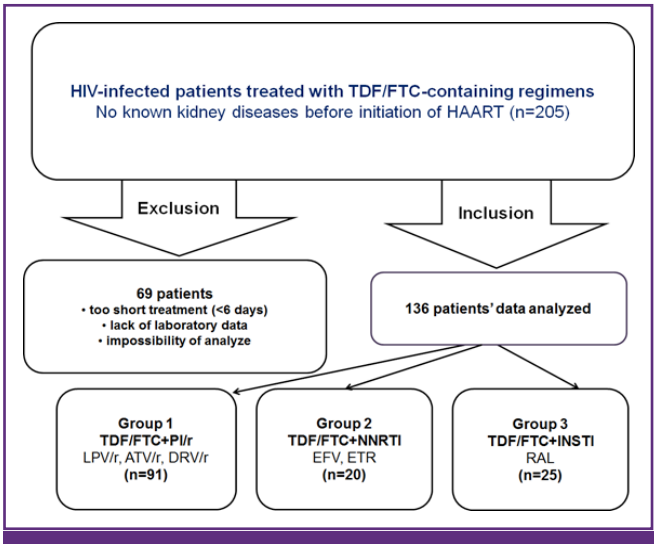

Figure 1. Study design.
HIV, human immunodeficiency virus; TDF/FTC, tenofovir/emtricitabine; HAART, highly active antiretroviral treatment; PI/r, ritonavir-boosted protease inhibitor; LPV, lopinavir; ATV, atazanavir; DRV, darunavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; EFV, efavirenz; ETR, etravirine; INSTI, integrase strand transfer inhibitor; RAL, raltegravir.

The clinical factors investigated included age, sex, period of treatment and follow-up, treatment failure rate, comorbidities, such as syphilis, hepatitis C, hepatitis B, hypertension, diabetes mellitus, thyroid disease, concomitant medications [anti-tuberculosis drugs, ganciclovir (GCV) or valganciclovir (VGCV), analgesics, antipsychotic drugs, trimethoprim/sulfamethoxazole (TMP/SMX)], CD4+ T cell counts, HIV-1 RNA levels, blood urea nitrogen (BUN), and serum creatinine (Cr). Beginning levels and peak levels of serum BUN and serum Cr were measured in each group and compared. The acute increase more than 1.5 mg/dL in serum Cr level was used as an indicator of nephrotoxicity.

2. Statistical analysis

Patients' characteristics were described as mean [SD] for normally distributed continuous variables, median [IQR] for non-normally distributed continuous variables, and percentages for categorical variables. We evaluated differences among

three groups via analysis of variance (ANOVA) or Kruskal-Wallis H test for continuous variables, and chi-square test for categorical variables, as appropriate. Statistical analyses and data sorting were performed using SPSS ver. 22.0 (SPSS Inc., Chicago, IL, USA). A *P*-value of less than 0.05 (two-tailed) was considered statistically significant.

Results

1. Baseline characteristics and concomitant medications of the patients treated with TDF/FTC-based HAART

Among the 205 patients, 69 were excluded. Thus, 136 patients were included in the final analysis. The distribution of patients was 91 in group 1, 20 in group 2, and 25 in group 3 (Fig. 1). Table 1 shows the demographic data of the study groups. No differences in the distributions of comorbidities for syphilis, hepatitis C, hepatitis B, hypertension, diabetes mellitus, and thyroid disease were found among the groups (Table 1). A considerable number of patients were taking other medications besides the antiretroviral drug, including were anti-tuberculosis drugs, GCV or VGCV, analgesics, antipsychotic drugs, and TMP/SMX, but no significant differences were found among the groups (Table 1). All three groups showed significant increases in CD4+ T cell counts. Initial HIV RNA level was significantly lower in group 3 [*P*= 0.006] (Table 1).

2. Changes in renal function and the incidence of nephrotoxicity of the three TDF/FTC-based HAART groups

Changes in serum Cr level were detected during TDF/FTC-

Table 1. Baseline characteristics, concomitant medications, and immunological and virological statuses of patients treated with TDF/FTC-based HAART

	Group 1 TDF/FTC+PI/r (n=91)	Group 2 TDF/FTC+NNRTI (n=20)	Group 3 TDF/FTC+INSTI (n=25)	*P*-value
Age (years) (mean ± SD)	40.6 ± 12.2	36.2 ± 12.2	42.4 ± 10.4	0.208
Male gender, n(%)	79 (86.8)	19 (95.0)	24 (96.0)	0.286
Comorbidities, n(%)				
Syphilis	13 (14.3)	1 (5.0)	5 (20.0)	0.349
Hepatitis C	3 (3.3)	0	0	0.464
Hepatitis B	8 (8.8)	1 (5.0)	1 (4.0)	0.653
Hypertension	3 (3.3)	2 (10.0)	1 (4.0)	0.415
Diabetes mellitus	9 (9.9)	1 (5.0)	3 (12.0)	0.717
Thyroid disease	3 (3.3)	2 (10.0)	0	0.197
Concomitant medications, n(%)				
Anti-tuberculosis drugs	8 (8.8)	5 (25.0)	5 (12.0)	0.125
GCV or VGCV	6 (6.6)	1 (5.0)	2 (8.0)	0.922
Analgesics	21 (23.1)	6 (30.0)	3 (12.0)	0.323
Antipsychotic drugs	7 (7.7)	0	1 (4.0)	0.377
TMP/SMX	28 (30.8)	7 (35.0)	5 (20.0)	0.485
Immunologic and virologic status				
Initial CD4+ T cell count (cells/mm^3, median[IQR])	213 (95, 372)	268 (125, 743)	293 (164, 508)	0.925
Peak CD4+ T cell count (cells/mm^3, median[IQR])	412 (273, 573)	473 (128, 845)	505 (319, 673)	0.426
Increase of CD4+ T cell count (cells/mm^3, median[IQR]) [a]	173 (66, 266)	74 (0, 192)	56(6, 251)	0.073
Initial HIV-1 RNA level (log_{10} copies/mL, median[IQR])	4.264 (0, 4.877)	2.609 (0, 5.111)	0 (0, 4.538)	0.006
HAART duration (days, median [IQR])	458 (216, 607)	318 (164, 562)	500 (343, 672)	0.157
Treatment failure, n(%) [b]	16 (17.6)	4 (20.0)	2 (8.0)	0.454

TDF/FTC, tenofovir/emtricitabine; HAART, highly active antiretroviral treatment; PI/r, ritonavir-boosted protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; SD, standard deviation; GCV, ganciclovir; VGCV, valganciclovir; TMP/SMX, trimethoprim/sulfamethoxazole.
[a]Peak CD4+ T cell count – initial CD4+ T cell count.
[b]Treatment failure was defined by immunological (CD4+ T cell count<200/mm^3) and virological (HIV-1 RNA level > 200 copies/mL) status.

based antiretroviral therapy in group 1 (0.12 [0.06, 0.24] mg/dL), group 2 (0.08 [0.02, 0.13] mg/dL), and group 3 (0.16 [0.07, 0.27] mg/dL) [*P* > *0.05*] (Table 2). Four patients (all in group 1) had serum Cr levels more than 1.5 mg/dL. The overall incidence of serum creatinine increase more than 1.5 mg/dL was 2.8 cases per 100 patient-years, and that of TDF/FTC + PI/r group was 4.0 cases per 100 patient-years.

Table 2. Changes in renal function and incidence of serum Cr level > 1.5 mg/dL of the three TDF/FTC-based HAART groups

	Group 1 TDF/FTC+PI/r (n=91)	Group 2 TDF/FTC+NNRTI (n=20)	Group 3 TDF/FTC+INSTI (n=25)	*P*-value
Serum Cr level > 1.5 mg/dL No. of case (%)	4 (4.4%)	0	0	0.403
Incidence of Serum Cr level > 1.5 mg/dL (cases/100 patient-years)	4.0	0	0	
Initial serum BUN (mg/dL, median [IQR])	13.3 (10.4, 16.3)	10.9 (7.7, 13.5)	12.4 (12.1, 16.8)	0.224
Initial serum Cr (mg/dL, median [IQR])	0.80 (0.70, 0.90)	0.80 (0.65, 0.90)	0.85 (0.70, 0.90)	0.608
Peak serum BUN (mg/dL, median [IQR])	12.8 (10.4, 17.7)	11.3 (9.2, 14.4)	14.1 (11.5, 16.8)	0.210
Peak serum Cr (mg/dL, median [IQR])	0.90 (0.80, 1.03)	0.80 (0.75, 0.95)	0.95 (0.90, 1.13)	0.052
Increase of serum BUN (mg/dL, median [IQR]) [a]	-0.1 (-1.9, 3.4)	0.4 (-1.0, 2.9)	0.1 (-0.7, 1.7)	0.877
Increase of serum Cr (mg/dL, median [IQR]) [b]	0.12 (0.06, 0.24)	0.08 (0.02, 0.13)	0.16 (0.07, 0.27)	0.222

Cr, creatinine; TDF/FTC, tenofovir/emtricitabine; HAART, highly active antiretroviral treatment; PI/r, ritonavir-boosted protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; BUN,blood urea nitrogen.
[a]Peak serum blood urea nitrogen (BUN) – initial serum BUN.
[b]Peak serum creatinine (Cr) – initial serum Cr.

Table 3. Baseline characteristics, concomitant medications, and immunological and virological statuses of the patients treated with TDF/FTC + PI/r

	Subgroup 1 TDF/FTC+LPV/r (n=23)	Subgroup 2 TDF/FTC+ATV/r (n=18)	Subgroup 3 TDF/FTC+DRV/r (n=50)	*P*-value
Age (years) (mean ± SD)	38.2 ± 8.9	46.5 ± 13.5	39.5 ± 12.6	0.063
Male gender, n(%)	22 (95.7)	15 (83.3)	42 (84.0)	0.349
Concomitant diseases, n(%)				
Hepatitis C	2 (8.7)	1 (5.6)	0	0.134
Hepatitis B	1 (4.3)	4 (22.2)	3 (6.0)	0.078
Hypertension	0	1 (5.6)	2 (4.0)	0.563
Diabetes mellitus	1 (4.3)	2 (11.1)	6 (12.0)	0.585
Thyroid disease	1 (4.3)	2 (11.1)	0	0.073
Concomitant medication, n(%)				
Anti-tuberculosis drugs	4 (17.4)	1 (5.6)	3 (6.0)	0.241
GCV or VGCV	3 (13.0)	0	3 (6.0)	0.240
Analgesics	7 (30.4)	4 (22.2)	10 (20.0)	0.614
Antipsychotic drugs	0	3 (16.7)	4 (8.0)	0.138
TMP/SMX	10 (43.5)	2 (11.1)	16 (32.0)	0.080
HAART duration (days, median [IQR])	205 (102, 561)	492 (320, 628)	527 (301, 651)	0.073
Initial CD4+ T cell count (cells/mm^3, median [IQR])	213 (84, 293)	346 (238, 677)	168 (55, 321)	0.016
Initial HIV-1 RNA level (log_{10} copies/mL, median [IQR])	4.383 (0, 4.663)	2.583 (0, 4.507)	4.477 (3.723, 5.089)	0.126

TDF/FTC, tenofovir/emtricitabine; PI/r, ritonavir-boosted protease inhibitor; LPV/r, lopinavir/ritonavir; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; SD, standard deviation; GCV, ganciclovir; VGCV, valganciclovir; TMP/SMX, trimethoprim/sulfamethoxazole.

Table 4. Changes in renal function and the incidence of serum Cr level > 1.5 mg/dL in the three TDF/FTC + PI/r subgroups

	Subgroup 1 TDF/FTC + LPV/r (n=23)	Subgroup 2 TDF/FTC + ATV/r (n=18)	Subgroup 3 TDF/FTC + DRV/r (n=50)	*P*-value
Serum Cr level > 1.5 mg/dL No. of case (%)	1 (4.3)	3 (16.7)	0	0.013
Initial serum BUN (mg/dL, median[IQR])	12.3 (11.2, 15.1)	15.5 (13.2, 20.8)	12.8 (9.7, 17.2)	0.090
Initial serum Cr (mg/dL, median[IQR])	0.90 (0.80, 1.00)	0.90 (0.63, 1.00)	0.80 (0.63, 0.80)	0.023
Peak serum BUN (mg/dL, median[IQR])	11.3 (10.2, 14.7)	14.7 (11.8, 18.6)	12.9 (9.7, 18.5)	0.196
Peak serum Cr (mg/dL, median[IQR])	1.00 (0.90, 1.13)	0.90 (0.83, 1.20)	0.90 (0.80, 1.00)	0.058
Increase of serum BUN (mg/dL, median [IQR]) [a]	-0.2 (-1.5, 1.4)	-0.7 (-7.1, 3.4)	0.1 (-1.9, 4.7)	0.363
Increase of serum Cr (mg/dL, median [IQR]) [b]	0.11 (0.05, 0.22)	0.15 (0, 0.34)	0.12 (0.06, 0.23)	0.848

Cr, creatinine; TDF/FTC, tenofovir/emtricitabine; LPV/r, lopinavir/ritonavir; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; BUN, blood urea nitrogen.
[a]Peak serum blood urea nitrogen (BUN) – initial serum BUN.
[b]Peak serum creatinine (Cr) – initial serum Cr.

3. Baseline characteristics and concomitant medications of patients treated with TDF/FTC + PI/r patients subgroups

The distribution of patients in the TDF + PI/r subgroups was: 23 in subgroup 1, 18 in subgroup 2, and 50 in subgroup 3. The demographic data are shown in Table 3. The distributions of comorbidities among the subgroups were not different. About 70–98% of the study subjects took medications other than an antiretroviral drug, including anti-tuberculosis drugs, GCV or VGCV, analgesics, antipsychotic drugs, and TMP/SMX. No difference was found among the subgroups except initial CD4+ T cell count (Table 3). The number of CD4+ T cells at the beginning of treatment was significantly higher in subgroup 2 (median 346/mm^3, IQR [238, 677]) that that in the other subgroups.

4. Changes in renal function and the incidence of nephrotoxicity in the three TDF/FTC + PI/r subgroups

The changes in serum Cr levels during TDF/FTC + PI/r-based HAART were 0.11 [0.05, 0.22] mg/dL in subgroup 1, 0.15 [0, 0.34] mg/dL in subgroup 2, and 0.12 [0.06, 0.23] mg/dL in subgroup 3 [$P > 0.05$] (Table 4).

All four patients whose serum Cr was > 1.5 mg/dL during treatment were in the TDF/FTC + PI/r group (one in subgroup 1 and three in subgroup 2). Initial serum Cr level was lower in subgroup 3, but there were no statistical differences of peak serum Cr levels and increment of serum Cr levels during HAART among three groups (Table 4). No case in subgroup 3 had an acute increase in serum Cr more than 1.5 mg/dL. The clinical characteristics and clinical course of these four patients was summarized in Table 5. The time interval from start of HAART to occurrence of acute serum Cr increase was from 210 to 662 days. Serum Cr levels of all four patients were recovered to the level less than 1.5 mg/dL after HAART regimen change from TDF/FTC + PI/r to abacavir/lamivudine + INSTI.

Discussion

In this study, changes in serum Cr levels in groups classified according to the drug used with TDF, such as PI/r, NNRTI, and INSTI was evaluated. First, four patients (2.9%) in our study had serum Cr levels that increased more than 1.5 mg/dL during HAART. Other study that treated 10,000 HIV-infected patients with TDF and monitored the increase in serum Cr found that 2.2% of cases showed baseline serum Cr more than 0.5 mg/dL and 0.6% increased more than 2.0 mg/dL [8], which was similar to our results. Second, the four patients whose serum Cr increased more than 1.5 mg/dL were administered both TDF and a PI/r drug. Of them, one was in the LPV/r group and three were in the ATV/r group. This finding shows that the risk of deteriorating kidney function may increases when TDF is applied with PI/r. Goicoechea et al. reported that changes in GFR of 146 patients were observed among three groups – TDF + PI/r, TDF + NNRTI, non-TDF combination regimen [14]. No difference was found among the three groups from weeks 1 to 24. However, the TDF + PI/r group revealed the greatest decreased in GFR on week 48, compared with that of the TDF + NNRTI groups [$P = 0.04$], similar with our study results.

Various studies have reported the relationship between

Table 5. Case summaries of four patients who experienced an acute increase in serum Cr (>1.5 mg/dL) during HAART

Case No.	Sex/age	HAART regimen	Comorbidities	Concomitant medications	Other manifestations	HAART change	Time to occurrence of increase in serum Cr (>1.5mg/dL)	Initial sCr (mg/dL)	Peak sCr (mg/dL)	Last sCr (mg/dL)
1	M/40	TDF/FTC+LPV/r	None	None	-	Yes	286 days	1.09	1.75	0.87
2	M/63	TDF/FTC+ATV/r	HCC, HBV	Entecavir, Diuretics	-	Yes	273 days	1.22	2.14	1.28
3	M/61	TDF/FTC+ATV/r	Hypothyroidism	Anti-depressant, Atorvastatin	Nausea	Yes	210 days	1.18	1.94	1.25
4	F/42	TDF/FTC+ATV/r	Cervical cancer (stage 0, cure)	NSAIDs, TMP/SMX, Atorvastatin	Rhabdomyolysis	Yes	662 days	0.63	3.97	1.49

Cr, creatinine; HAART, highly active antiretroviral treatment; sCr, serum creatinine; TDF/FTC, tenofovir/emtricitabine; LPV/r, ritonavir-boosted lopinavir; ATV, atazanavir; HCC, hepatocellular carcinoma; HBV, hepatitis B virus, NSAID; non-steroidal anti-inflammatory drug; TMP/SMX, trimethoprim/sulfamethoxazole.

TDF use and kidney diseases. In a retrospective study conducted on 1,647 cases of initial antiretroviral treatment, a more acute decrease in GFR was noted in the TDF compared to that in the non-TDF group [16]. In another study, more cases of abnormal proximal tubule functioning and decreased GFR occurred in patients who had been taking TDF for > 24 months [17, 18]. TDF is toxic to mitochondria, which may result proximal tubule damage that prevents resorption of filtered phosphate, potassium, amino acids, and glucose [19]. The risks of proteinuria, a sharp decrease in kidney function, and chronic kidney disease increased annually by 34%, 11%, and 33% respectively, in 10,000 patients infected with HIV and treated with TDF [17]. In another prospective cohort study, patients administered a combination of TDF and LPV/r or ATV/r showed a decrease in GFR compared to those administered TDF and EFV. Of the combined PI groups, the ATV/r group showed the poorest result [15, 20]. Ryom et al. reported a study of 22,603 patients whose pre-treatment estimated glomerular filtration rate (eGFR) was > 90 mL/min. Decreases in eGFR (20 mL/min in 2.1% and 60 mL/min in 0.6% of cases) were observed when the patients were treated with TDF, ATV, LPV/r, abacavir (ABC) and another PI/r [21]. Sustained use of LPV/r could be related with chronic deterioration in kidney function [14, 15, 21, 22].

Increased serum Cr, concomitant medications likely to cause toxicity, underweight, older age, the duration and dose of TDF, and a low CD4+ T cell count were known as major risk factors for nephrotoxicity caused by TDF [9]. However, in our study only two patients were more than 60 year-old, the others were not old. Two patients (case 3 and 4 in Table 5) had taken atorvastatin as concomitant medication, which had been well known as the potential drug developing rhabdomyolysis, resulting acute renal injury. Therefore, concomitant statin medication in boosted PI-based HAART patients might need more precaution by clinicians to prevent occurrence of TDF-related acute renal injury.

Because relatively high incidence of adverse effects including nephrotoxicity has been reported in PI/r regimen containing TDF, the primary regimens for the initial HAART treatment of HIV-infected patients were changed in the newly issued DHHS guidelines published in April 2015: the four regimens with INSTI; dolutegravir (DTG)/ABC/lamivudine, DTG + TDF/FTC, EVG/COBI/TDF/FTC, RAL + TDF/FTC, and one regimen with PI/r; DRV/r + TDF/FTC. ATV/r + TDF/FTC regimen, which was the primary regimen before 2014, was changed to a secondary regimen [23].

Our study has several limitations. It was conducted retro-

spectively, therefore we could not sufficiently assess the clinical indicators showing the development of kidney toxicity, and we had to use serum Cr level only. Serum Cr is produced by skeletal muscles. Most HIV-infected patients have an abnormal muscle mass compared to that of a healthy subject; thus, more caution is required for interpretation [24]. Other previous reports investigating renal function decline prospectively had used an estimated glomerular filtration rate (eGFR) [6, 7, 9, 14, 15, 17, 20, 25], albuminuria [6], proteinuria [24], urine protein/creatinine ratio [8], and the rate of creatinine clearance (CrCl) [24] as the indicator of decrement of renal function. However, because of retrospective nature of our study, we could not evaluate these markers that had been known as more predictive and accurate indicator. Also, the study group was limited to patients from one hospital, and the total number of patients was small, which also affected the results assessment. But, our results may be significant because this is the first Korean report on TDF-induced nephrotoxicity.

In conclusion, this study results showed that TDF containing PI/r regimen might be related with relatively higher rate of acute serum Cr elevation during HAART. Therefore, more caution might be needed when clinicians treat HIV-infected patients with TDF containing PI/r regimen, especially using ATV/r or LPV/r with TDF.

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