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Change in Renal Function among HIV-Infected Koreans Receiving Tenofovir Disoproxil Fumarate-Backbone Antiretroviral Therapy: A 3-Year Follow-Up Study

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Purpose: Tenofovir disoproxil fumarate (TDF) is commonly prescribed as a fixed-dose, co-formulated antiretroviral drug for HIV-1 infection. The major concern of long-term TDF use is renal dysfunction. However, little is known about the long-term patterns of changes in renal function in HIV-infected Koreans receiving TDF.

Materials and Methods: We prospectively followed 50 HIV-infected Koreans, performing laboratory tests every 3 months during the first year and every 6 months for the next 2 years. Urine N-acetyl-β-D-glucosaminidase (NAG) and plasma cystatin-C were measured using samples collected in the first year. Data on renal function were retrospectively collected on HIV-infected patients receiving first-line TDF (n=40) and in antiretroviral therapy (ART)-naïve patients (n=24) for 3 years. Renal function was evaluated as estimated glomerular filtration rate (eGFR) from serum creatinine [Modification of Diet in Renal Disease (MDRD)] and cystatin-C.

Results: The eGFR (cystatin-C) showed significant changes from 0 to 48 wks (p=0.002), with the lowest levels at 24 wks (84.3±18.8 mL/min vs. 90.3±22.5 mL/min, p=0.021 by post hoc test). Urine NAG levels did not differ at 0, 12, 24, and 48 wks, although eGFR (MDRD) significantly decreased from 0 (98.7±18.9 mL/min/1.73 m^2) to 144 wks (89.0±14.7 mL/min/1.73 m^2) (p=0.010). The first-line TDF group had significantly lower eGFR (MDRD) than the ART-naïve group at 144 wks (89.7 mL/min/1.73 m^2 vs. 98.4 mL/min/1.73 m^2, p=0.036). Thirteen (26%) participants experienced a decrease in renal impairment of 10 mL/min/1.73 m^2 in eGFR (MDRD) at 144 wks.

Conclusion: These data suggest that clinically meaningful renal injury can develop in HIV-infected Koreans receiving long-term TDF.

Key Words: HIV, anti-retroviral therapy, tenofovir, renal toxicity, eGFR, cystatin-C

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a widely prescribed nucleoside analogue reverse transcriptase inhibitor (NRTI) for first-line or second-line antiretroviral therapy (ART) for HIV-1 infection, even in resource-limited settings.[1-4] Generally, TDF is used in fixed-dose drug combinations as an NRTI backbone with emtricitabine, emtricitabine/efavirenz, emtricitabine/ripivirine, or emtricitabine/elvitegravir/cobicistat as a once-a-day single-tablet regimen. This development has improved conditions of HIV-infected individuals by reducing the burden of numerous pills. TDF is relatively well tolerated, compared to other antiretroviral drugs,[5] although it has several distinguishing adverse effects, such as renal toxicity and decreased bone mineral density.[1,6,7]

Renal damage presenting with clinical features ranging from subclinical dysfunction to Fanconi syndrome is a major con-

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cern of long-term use of TDF.[6,8,9] TDF accumulates in the cytoplasm of proximal renal tubular epithelial cells, inhibiting mitochondrial DNA polymerase and causing dysfunction of the oxidative respiratory chain and energy deprivation.[6,10,11] This acquired renal tubular mitochondriopathy eventually drives epithelial cells to apoptosis, resulting in proximal tubular damage and renal injury.[10-12]

The long-term adverse outcomes of antiretroviral drugs or their indirect effects are becoming major factors in the deteriorating quality of life of HIV-infected individuals in a highly active ART era. Therefore, distinguishing clinical or laboratory predictors of proximal renal tubular dysfunction (PRTD) with regular monitoring of renal function in HIV-infected individuals receiving TDF is important for prevention.

PRTD occurrence rates vary, ranging from 6.3 to 22%, depending on the definitions of PRTD, study populations, study design, and observational duration.[13-17] Previous studies have reported that older age, lower body weight, cumulative exposure to TDF, and genetic polymorphisms in the adenosine triphosphate-binding cassette gene (*ABCC2*) encoding multidrug-resistant proteins implicated in TDF efflux are risk factors of PRTD in HIV-infected individuals receiving TDF-based ART.[13-16] Several reports from Japan have shown the importance of low body weight and body mass index (BMI) for developing TDF-associated renal dysfunction defined as a ≥25% decline in estimated glomerular filtration rate (eGFR).[18-20] However, in studies conducted in Europe and North America, body weight or BMI was not related to the development of TDF-induced renal insufficiency, as evaluated with decreased eGFR.[1,15,17,21,22]

This discrepancy according to study population might be caused by ethnic differences associated with single-nucleotide polymorphisms in genes encoding efflux transporter proteins.[22] It is important to determine the global implications of whether lower-BMI HIV-infected individuals who receive long-term TDF-based ART are at high risk for development of chronic renal disease. If this is indeed true, TDF use will increase, suggesting the need for strict, regular monitoring of renal function, which might be hindered in resource-limited settings or patients with malnutrition. This study evaluated changes in renal function and development of PRTD in HIV-infected Koreans receiving TDF-based ART who have similar body compositions and genetics to Japanese and Asian populations, compared to Caucasians.

MATERIALS AND METHODS

Study design and participants

We conducted this prospective, longitudinal study over 3 years starting in January 2013 in at tertiary care, university-affiliated Severance Hospital in Seoul, Republic of Korea. HIV-infected Koreans who met the following criteria were eligible: 1) ≥18 years old and 2) beginning TDF-based ART as first-line therapy or antiretroviral drug change to decrease pill burden. We excluded patients with 1) any acute or chronic opportunistic infections or malignancies treated at enrollment, 2) any concurrent medications other than antiretroviral drugs during the previous 3 consecutive months before study inclusion, 3) at least one ≤60 mL/min/1.73 m^2 eGFR using Modification of Diet in Renal Disease (MDRD) study equations and serum creatinine (SCr) measurement ≥1.2 mg/dL between HIV infection and study inclusion, 4) past or current history of diabetes mellitus or hypertension, 5) co-infected with hepatitis B virus or hepatitis C virus, and 6) at least one irregular visit with ≥6 months interval after diagnosis of HIV infection. All participants continuously received TDF-based ART and regularly visited the hospital every 3 months for measurements of renal function using blood and urine tests during the 3-year follow-up period. A total of 70 HIV-infected Koreans were included, and 50 participants finished the study after 20 were lost to follow-up, transferred to another hospital, or switched from TDF to other NRTIs.

A retrospective study in the same hospital was conducted separately by review of electronic medical records to minimize the effects of previous use of other antiretroviral drugs on renal function. The study compared the renal effects of TDF with a control group of ART-naïve HIV-infected Koreans. We included 40 HIV-infected individuals who received first-line TDF-based ART for ≥3 years who did not participate in the prospective study and 24 naïve individuals never exposed to ART over ≥3 years. All patients were at least 18 years of age, regularly visited Severance Hospital every 3 months after HIV diagnosis, and received urine and blood tests, including for HIV viral load (VL), CD4+ T lymphocyte counts, and SCr every 3 or 6 months. We applied the exclusion criteria of the prospective study to the retrospective study.

This study was approved by the local Ethics Committee of the Institutional Review Board. All participants in the prospective study provided written informed consent. Consent was waived for the retrospective study.

Sample and data collection and Measurements of NAG and cystatin-C

For the prospective study, plasma and urine were stored immediately at -80°C after collection every 3 months during the first year for measurements of plasma cystatin-C and urine N-acetyl-β-D-glucosaminidase (NAG). We measured phosphate, uric acid, creatinine, and β2-microglobulin (β2-MG) by random urine tests using an automated urine chemistry analyzer AU5800 (Beckman Coulter, Fullerton, CA, USA) and LIAISON system (DiaSorin, Saluggia, Italy) every 3 months during the first year after enrollment. Blood from each participant was analyzed for complete blood cell count using a Hematology Analyzer, Advia 2120 (Siemens Healthcare Diagnostics, Deerfield, IL, USA), CD4+ T lymphocyte counts using a flow cytometer (Beckman Coulter, Fullerton, CA, USA), HIV VL using a COBAS AMPLICOR HIV-1 MONITOR, version 2.42 (Roche Diagnostics, Roche, Ba-

sel, Switzerland), and SCr, serum uric acid, and serum inorganic phosphate (IP) using an automatic chemistry spectrophotometric analyzer, Hitachi 7600 (Hitachi, Ltd., Tokyo, Japan) every 3 months during the first year and every 6 months during the last 2 years.

Urine NAG was measured by kinetic rate assay using *N*-Assay L NAG NITTOBO® [6-methyl-2-phylidil-N-acetyl-1-thio-β-D-glucosaminide (MPT-NAG)] substrate (Nittobo Medical Co., Ltd., Tokyo, Japan) within 1 month of urine collection.[13] NAG converts MPT-NAG into MPT after dissociation within the urine sample. NAG concentration was calculated by measuring the rate (ΔE/min) of absorbance increase for MPT at 340 nm. Optical densities as absorbance were measured in an automatic chemistry spectrophotometric analyzer (HITACHI 7600, Hitachi High-Technologies Corp., Tokyo, Japan). Plasma cystatin-C was measured by particle-enhanced turbidimetric immunoassay using a HITACHI 7600 analyzer (Hitachi High-Technologies Corp.).[23]

BMI was calculated by measuring weight and height at the time of enrollment. We collected detailed clinical information about drugs and duration of ART. In the retrospective study, the age, sex and SCr levels were gathered from electric medical records.

Definitions

PRTD was defined as meeting at least two of the following criteria: 1) normoglycemic glycosuria (random urine glucose ≥1+ with fasting plasma glucose <126 mg/dL), 2) serum uric acid <3.5 mg/dL with fractional excretion of uric acid (FE_{UA}) >15%, 3) urine β2-MG/urine creatinine >0.3 mg/L, 4) fractional excretion of phosphate (FE_{IP}) <82%, and 5) metabolic acidosis (blood pH ≤7.34 and serum bicarbonate ≤22 mmol/L).[13-16] Hypophosphatemia was defined as serum phosphate <2.9 mg/dL.

The cut-off value for obesity in Korea was defined as 25 kg/m^2 BMI according to Asia-Pacific BMI criteria established by the World Health Organization Western Pacific Region and the Korean Centers for Disease Control and Prevention.[24,25]

We defined undetectable HIV VL as <20 copies/mL in a plasma quantitative real-time reverse transcription-polymerase chain reaction test.

Calculation of renal function and tubular abnormalities tests

To evaluate renal function, we used three values of eGFR: the MDRD study equations, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and eGFR from cystatin-C. The detailed equations are as follows: 1) eGFR (MDRD)= $175\times(SCr)^{-1.154}\times(age)^{-0.203}\times(0.742 \text{ if female})$,[26] 2) eGFR (CKD-EPI)= $141\times\text{minimum}(SCr/\kappa \text{ or } 1)^{\alpha}\times\text{maximum}(SCr/\kappa \text{ or } 1)^{-1.209}\times0.993^{age}\times(1.018 \text{ if female})$, (κ=0.9 if male, 0.7 if female and α=-0.411 if male, -0.329 if female),[23] and 3) eGFR (cystatin-C) (Larsson formula)= $77.239\times\text{cystatin C}^{-1.2623}$.[23,27]

FE_{IP} and FE_{UA} were calculated with the following equations: 1) FE_{IP}=(urine phosphate×SCr)/(urine creatinine×plasma phosphate)×100 and 2) FE_{UA}=(urine uric acid×SCr)/(urine creatinine×plasma uric acid)×100.[28]

Statistical analysis

Continuous variables were compared using a linear mixed model, and categorical data were compared using general estimating equations. Post hoc tests were performed on continuous data by paired t-test using Bonferroni correction and on categorical data using chi-square analysis and the McNemar test. We used the nonparametric Mann Whitney U test to compare continuous variables between groups. All *p*-values were two-tailed, and values ≤0.05 were considered statistically significant. All statistical analyses were performed using SPSS v.23 (IBM Corp., Armonk, NY, USA) and GraphPad Prism V6 (GraphPad Software, Inc., La Jolla, CA, USA) software.

RESULTS

The clinical features of participants

All participants in both the prospective and retrospective stud-

Table 1. Clinical Characteristics of Total Participants Enrolled in Prospective Cohort

Characteristics	n=50
Age, yr	44.5±10.8
Gender, male (%)	49 (98)
BMI, kg/m^2	23.7±2.7
Time interval between HIV infection and enrollment, month	84 (52–106)
CD4+T lymphocyte, /mm^3	
0 wk	594.5±233.5
12 wk	598.0±212.1
24 wk	619.5±233.9
48 wk	650.1±222.8
Plasma HIV viral load, <20 copies/mL (%)	
0 wk	43 (86)
12 wk	45 (90)
24 wk	46 (92)
48 wk	49 (98)
ART	
Total ART duration before enrollment, month	58 (37–85)
TDF use as ART starting regimen (%)	3 (6)
Drug combined with TDF at study period (%)	
NNRTIs	22 (44)
PI/r	4 (8)
Unbooted PIs	1 (2)
Integrase inhibitor	22 (44)
PI/r+integrase inhibitor	1 (2)

BMI, body mass index; ART, antiretroviral therapy; TDF, tenofovir; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; PI, protease inhibitor.
Data are mean±SD or median (IQR) or number (percent).

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ies received TDF-based ART with TDF as a co-formulation of TDF/FTC. Baseline clinical characteristics of the participants in the prospective study are summarized in Table 1. The BMI range was 18.5 to 30.3 kg/m^2, with 14 (28%) obese patients with BMI ≥25 kg/m^2. The median weight was 66 kg (range, 51–93 kg). In the retrospective study, the median age was 41 [interquartile range (IQR) 34–49] years, and the total naïve duration of naïve individuals was 58 (IQR 42–69) months. The median BMI was 23.8 kg/m^2, and the percentage of obese individuals was 29.2% in ART-naïve individuals; these were 22.5 kg/m^2 and 27.5% in patients receiving first-line TDF-based ART, respectively.

Change of renal function and parameters for proximal tubular dysfunction during 1 year in prospective study

All eGFR values measured as cystatin-C, CKD-EPI, and MDRD showed significant changes from 0 to 48 wks (p=0.016 for cystatin, 0.026 for CKD-EPI, and 0.002 for MDRD). The eGFR decreased to the lowest level at 12 wks by CKD-EPI and MDRD and at 24 wks by cystatin-C. However, eGFR determined using all measures increased at 48 wks to a level similar to that at 0 wk. SCr levels at 12 wks were significantly higher than at 48 wks (0.92±0.19 mg/dL vs. 0.87±0.14 mg/dL, p=0.034 in post hoc test) (Table 2).

FE_{IP} values continuously increased from 9.75±4.64 at 0 wks to 12.03±4.63% at 48 wks, a significant change (p=0.020). $Log_{10}{}^{U\beta2\text{-}MG/Ucr}$ also continuously increased from -2.93±0.33 at 0 wks to -2.66±0.67 at 48 wks, a significant change (p=0.013). PTRD incidence increased from 4% at 0 wks to 12% at 48 wks, which was not a significant change (p=0.274). Urine NAG level did not differ according to the four different tests (p=0.969) (Table 2).

A decrease ≥10 mL/min and spontaneous recovery of eGFR by cystatin-C were seen for 17 (34%) participants over the 48 wks. The lowest eGFR by cystatin-C was at 12 wks in 7 (41.2%) participants and 24 wks in 10 (17%) (Fig. 1A). A largest continuous decrease in eGFR by cystatin-C was 23.35 mL/min, from 93.44 mL/min at 0 wks to 70.09 mL/min at wks 48 (Fig. 1B).

Chaining patterns of renal function: 3-years follow-up data

In the prospective study, we collected eGFR values calculated from SCr levels measured as MDRD and CKD-EPI over 3 years to evaluate long-term changes in patterns of renal function. The eGFR values for CKD-EPI and MDRD showed a similar tendency to decrease at 12 wks, compared to 0 wks, then increase until 48 wks. At 48 wks, eGFR values by CKD-EPI and MDRD decreased until 144 wks. SCr levels decreased from 12 to 48 wks, and then significantly increased until 144 wks. All three parameters demonstrated significant changes between 0 and 144 wks (eGFR by CKD-EPI, p<0.001; eGFR by MDRD, p<0.001; SCr, p=0.001) (Fig. 2).

Comparison of renal functions in first-line TDF-based ART and treatment-naïve individuals

We compared changes in renal functions between patients receiving first-line TDF-based ART without changing antiretroviral drugs (n=40) and patients not receiving ART (n=24) over 3 years to evaluate the effects of TDF on renal functions with exclusion of previous antiretroviral drugs. The eGFR measured by CKD-EPI in the TDF group declined between 96 and 120 wks and was significantly lower than that of the naïve group at 144 wks. The TDF group had significantly lower eGFR by MDRD at 12 wks and 144 wks, compared to the naïve group. SCr levels were not significantly different between the two groups except at 48 wks (Fig. 3).

Table 2. Comparisons of Laboratory Tests Evaluating Renal Function and PRTD for 1 Year in Prospective Cohort (n=50)

Parameters	0 wk	12 wk	24 wk	48 wk	*p* value
eGFR					
Cystatin-C, mL/min	90.32±22.53*	89.24±23.77	84.29±18.81*	89.03±18.26	0.016
CKD-EPI, mL/min/1.73 m^2	103.04±15.03	98.77±15.47	99.38±16.29	101.50±14.18	0.026
MDRD, mL/min/1.73 m^2	98.74±18.85*	92.30±17.23*†	94.56±16.51	97.25±17.99†	0.002
Serum creatinine, mg/dL	0.87±0.16	0.92±0.19*	0.90±0.14	0.87±0.14*	0.012
Nondiabetic glycosuria (%)	1 (2)	1 (2)	1 (2)	2 (4)	0.094
FE_{IP}	9.75±4.64*	10.68±3.25	11.25±5.74	12.03±4.63*	0.020
FE_{UA}	8.25±2.66	7.97±2.87	8.01±3.42	8.81±3.13	0.251
Serum IP, mg/dL	3.32±0.48	3.26±0.53	3.42±0.53	3.37±0.50	0.321
Hypophosphatemia (%)	11 (22)	12 (24)	12 (24)	9 (18)	0.844
Urine β2-MG, μg/mL	0.21±0.20	0.26±0.35	0.45±1.09	0.79±1.74	0.107
$Log_{10}{}^{U\beta2\text{-}MG/Ucr}$	-2.93±0.33*	-2.88±0.41†	-2.82±0.63	-2.66±0.67*†	0.013
PRTD (%)	2 (4)	4 (8)	4 (8)	6 (12)	0.274
Urine NAG, U/L	6.91±6.34	7.03±5.94	6.44±5.89	5.80±3.57	0.969

eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; FE, fractional excretion; IP, inorganic phosphate; UA, uric acid; β2-MG, β2-microglobulin; PRTD, proximal renal tubular dysfunction; NAG, N-acetyl-β-D-glucosaminidase. Data are mean±SD or n (%).
*† p<0.05 by Post-hoc test using paired t-test with Bonferroni correction.

DISCUSSION

In our study, parameters indicating renal function were SCr level, eGFR from SCr as MDRD and CKD-EPI, and eGFR from plasma cystatin-C. These parameters showed identical patterns of change over the study period. All of the data indicated that deteriorating renal function at 12 to 24 wks was ameliorated at 48 wks. However, after that, all parameters worsened continuously until 144 wks, although eGFR by cystatin-C was not evaluated. The overall trend over 3 years of follow-up showed significant deterioration of renal function. We also found, using retrospective data, that eGFR by SCr at 144 wks was significantly higher in HIV-infected individuals receiving TDF as first-line ART than in ART-naïve individuals. These results suggest that use of TDF could impair renal function in HIV-infected Koreans after a short time.

Clinical significant renal impairment was defined as a 10 mL/min/1.73 m^2 decrease in eGFR by MDRD or CKD-EPI at 144 wks relative to the level at prospective enrollment.[20,29] Based on this measure, 13 (26%) participants had clinically significant renal impairment at 144 wks after TDF use. When we considered a higher cut-off of 25% from baseline,[18] three (6%) participants had clinical significant renal impairment at 144 wks. According to CKD stage, 18 (36%) patients in the prospective study

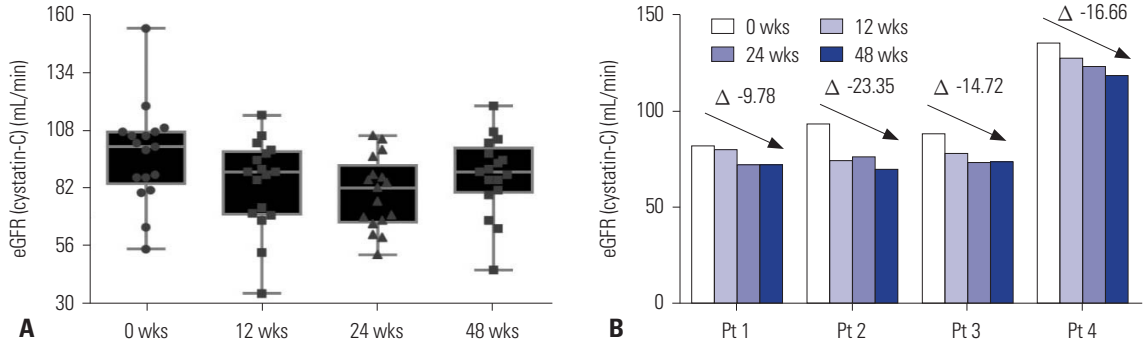

Fig. 1. Characteristics of 50 HIV-infected individuals in a prospective cohort whose eGFR measured by plasma cystatin-C declined between 0, 12, 24, and 48 wks. (A) 17 individuals who had the decline of ≥10 mL/min and spontaneous recovered. All data are expressed as symbols. Lines within boxes are mean values, and upper and lower horizontal lines of boxes are upper and lower values of SD, respectively. Error bars and vertical lines are ranges of total value showing maximum and minimum levels. (B) Four participants with continuously declining eGFR. Δ=subtraction of eGFR at 48 wks from eGFR at 0 wk. eGFR, estimated glomerular filtration rate.

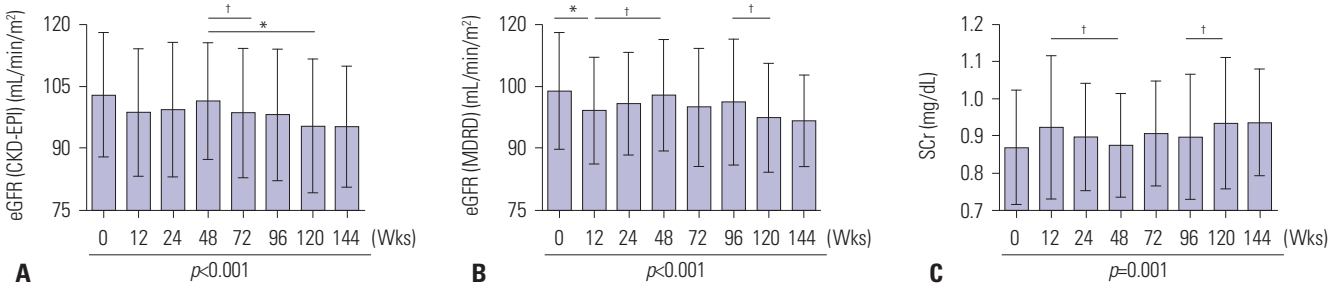

Fig. 2. Changing patterns of eGFR by CKD-EPI (A) or MDRD (B), and SCr (C). Changing patterns of eGFR by CKD-EPI or MDRD and Scr over 3 years in a prospective cohort (n=50). Upper lines of histograms are mean values, and error bars indicate upper and lower values of SD. *p*-values by linear mixed model are at the bottom. **p*<0.01, †*p*<0.05 by Post-hoc test using paired t-test with Bonferroni correction. eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

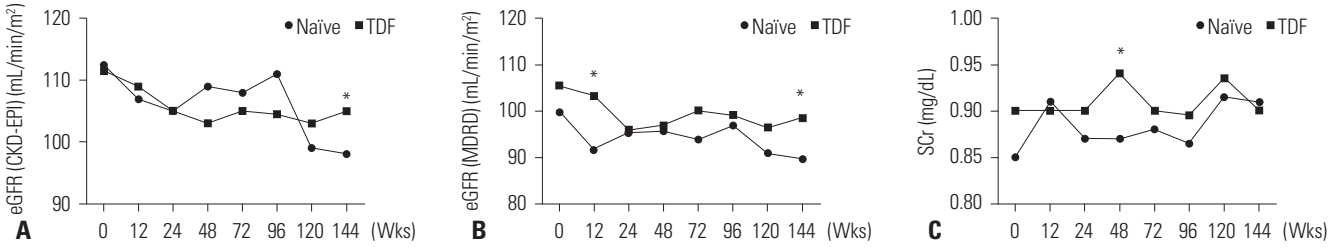

Fig. 3. Changes in eGFR by CKD-EPI (A) or MDRD (B), and SCr (C). Change in eGFR by CKD-EPI or MDRD and SCr level in first-line tenofovir-backbone ART and ART-naïve groups in a retrospective cohort. Symbols in each line indicate median value. **p*<0.05 by Mann-Whitney U test. eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine; ART, antiretroviral therapy; TDF, tenofovir disoproxil fumarate.

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had mild CKD (stage 2).[30] A considerable number of patients had clinically meaningful, mild CKD, with no patients with moderate or severe CKD or kidney failure (≥stage 3) CKD in this 3-year follow-up study. Our CKD incidence of 2.2–12.4% was not low, compared with previous studies in Asian countries, despite a lack of consistency in definition and inclusion population.[13,31-34]

An issue related to TDF-induced renal toxicity is whether low body weight or BMI might be predictive of toxicity development.[1,15,18-20,22,35] We did not find any relationship with BMI or body weight in further analyses using prospective or retrospective data (data not shown). Our results could indicate that the influence of low weight or BMI, mainly reported in Japan, might not be a problem limited to Asian countries. An important global concern is whether HIV-infected individuals with lower body weight are at especially high risk of development of TDF-induced renal injury. We do not have long-term data for ≥10 years about this issue. A large, multicenter cohort study and meta-analysis are needed to clarify if all HIV-infected individuals, even when living in a resource-limited setting, can receive long-term TDF-based co-formulated ART without significant renal damage.

This Korean study has several distinctions and strengths. First, we prospectively observed changing patterns in renal function using different estimation methods over 3 years. We strictly measured laboratory markers for PRTD in urine and blood at predefined, fixed times of every 3 months for 1 year. Second, we applied GFR values estimated through measurement of plasma cystatin-C to evaluate the effect of TDF use on short-term renal function in HIV-infected individuals. Currently, eGFR by cystatin-C is considered the most precise biomarker of creatinine clearance evaluating renal function and the most sensitive method that can predict early mild renal impairment.[23,36] Another advantage of eGFR by cystatin-C is that this measurement is not affected by anthropometric variables of age or sex or by muscle weight, which could differ based on race or lifestyle, such as diet, or diseases, such as chronic exhausting infectious diseases, including HIV infection.[23,36,37] Also, eGFR by cystatin-C is a useful biomarker, especially in proximal tubular injury, because plasma cystatin-C is initially filtered at the glomerulus and reabsorbed by epithelial cells of the proximal tubule, with only small amounts excreted into urine.[38,39] These characteristics indicate that eGFR by cystatin-C may be a more appropriate biomarker for evaluating PRTD and early renal dysfunction in HIV-infected individuals receiving TDF-backbone ART than eGFR calculated from SCr, such as by MDRD or CKD-EPI. However, we must consider that plasma cystatin-C level might be affected by chronic inflammation from the HIV infection or high HIV VL.[40] The evaluation of renal function by eGFR by cystatin-C in our study might have been minimally affected by inflammation, because almost all participants had undetectable HIV VL during the first year. Our unconventional evaluation of eGFR by cystatin-C for short-term changes in renal function with TDF showed a significant decrease in renal function at 24 wks, compared to baseline. However, eGFR by cystatin-C recovered at 48 wks to baseline levels, although this result was insignificant in post hoc tests. In addition, some participants showed a continuous decline until 48 wks. Therefore, further study measuring eGFR by cystatin-C over several years is warranted to establish if eGFR by cystatin-C continuously decreases after 48 wks, similar to eGFR from SCr.

Several new biomarkers for predicting acute renal injury are being evaluated for different clinical conditions. Emerging biomarkers specific for proximal tubular injury are neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, retinol-binding protein, interleukin-1β, and liver fatty acid-binding protein.[8,41,42] The major pathological finding that TDF-induced renal injury is acquired in proximal tubular mitochondriopathy may introduce a new dimension to studies evaluating these biomarkers in HIV-infected individuals receiving TDF. Early detection of PRTD will be important as use of TDF increases as a fixed-dose, co-formulated drug.

Our data showed that renal function evaluated by different tests and equations eventually showed a significant decline at 3 years from the start of TDF use in both a prospective and a retrospective observation. Therefore, clinicians need to carefully consider the development of renal impairment and regularly monitor parameters of renal function, especially in HIV-infected individuals receiving TDF-backbone ART for more than one year. With patients taking once-a-day ART with a co-formulated pill containing mostly TDF, physicians must identify early predictive biomarkers or clinical factors to make a prognosis of the development of long-term renal dysfunction. They must consider changing TDF for HIV-infected individuals showing an early decline of renal function within 1 year of TDF use.

This study had several limitations. First, it was a single-center study with a relatively small number of patients. The predictive risk factors of PRTD and mild CKD could not be analyzed for confounding variables, because few patients fulfilled the criteria for these conditions. The measurement of cystatin-C was performed in only 1 year of the 3-year follow-up. Nevertheless, our findings might have clinical usefulness as a long-term observation of HIV-infected Koreans receiving TDF-based ART for changing patterns in renal functions using several parameters.

In conclusion, we observed that around one-quarter of HIV-infected Koreans receiving TDF-backbone ART over 3 years had clinically meaningful, mild renal injury without a relationship to body weight or BMI. Therefore, physicians should perform regular renal function tests during long-term treatment with TDF and should consider TDF discontinuance if eGFR decline develops.

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