Renal function in Japanese HIV-1-positive patients who switch to tenofovir alafenamide fumarate after long-term tenofovir disoproxil fumarate

Kensuke Abe  (abeken98@gmail.com )
Tohoku University  https://orcid.org/0000-0003-3832-605X

Taku Obara
Tohoku University Hospital

Satomi Kamio
National Hospital Organization Sendai Medical Center

Asahi Kondo
National Hospital Organization Sendai Medical Center

Junji Imamura
National Hospital Organization Sendai Medical Center

Tatsuya Goto
National Hospital Organization Sendai Medical Center

Toshihiro Ito
National Hospital Organization Sendai Medical Center

Hiroshi Sato
JR Sendai Hospital

Nobuyuki Takahashi
Tohoku University

Research

Keywords: Tenofovir alafenamide fumarate, Tenofovir disoproxil fumarate, Renal function, eGFR, HIV

DOI: https://doi.org/10.21203/rs.3.rs-265066/v1

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

BACKGROUND Tenofovir disoproxil fumarate (TDF) has a strong antiviral effect, but TDF is known to cause renal dysfunction. Therefore, we are investigating preventing renal dysfunction by replacing TDF with tenofovir alafenamide fumarate (TAF), which is known to be relatively safe to the kidneys. However, the changes in renal function under long-term use of TAF are not known. In this study, we evaluated renal function in Japanese HIV-1-positive patients switching to TAF after long-term treatment with TDF.

METHODS A single-center observational study was conducted in Japanese HIV-1-positive patients. TDF was switched to TAF after at least 48 weeks of treatment so we could evaluate the long-term use of TDF. The primary endpoint was the estimated glomerular filtration rate (eGFR) at 144 weeks of TAF administration. In addition, we predicted the factors that would lead to changes in eGFR after long-term use of TAF.

RESULTS Of the 125 HIV-1-positive patients who were prescribed TAF at our hospital during the study period, 70 fulfilled the study criteria. The eGFR at the time of switching from TDF to TAF was 81.4 ± 21.1 mL/min/1.73 m². eGFR improved significantly after 12 weeks of taking TAF but significantly decreased at 96 and 144 weeks. At 144 weeks of taking TAF, the factors significantly correlated with the difference in eGFR from baseline were the difference in eGFR at 48 weeks of taking TAF and age at the start of TAF.

CONCLUSIONS In this study, Japanese HIV-1-positive patients who had been taking TDF for a long period of time showed a decrease in eGFR after switching to long-term use of TAF. Japanese HIV-1-positive patients are expected to take TAF for a long time. Depending on age, laboratory values related to renal function need to be monitored carefully.

Background

Tenofovir disoproxil fumarate (TDF), an anti-human immunodeficiency virus (HIV) and hepatitis B virus drug, has a strong antiviral effect. It is one of the recommended nucleoside reverse transcriptase inhibitors (NRTIs) along with lamivudine in major guidelines such as those of the World Health Organization [1], Department of Health & Human Services [2] and European AIDS Clinical Society [3]. However, it is known that renal dysfunction is caused by the use of TDF [4]. In particular, Japanese HIV-1-infected patients with low body weight need to be carefully followed up [5]. Renal dysfunction due to TDF has been reported to be reversible, depending on the duration of treatment [6].

In addition, tubulointerstitial nephropathy, such as tubular necrosis, mitochondrial swelling, tubular atrophy, and interstitial fibrosis, may be observed [7]. The mechanism by which tubulointerstitial nephropathy develops is that tenofovir (TFV), the active ingredient of TDF, is taken up from the blood into tubular cells via organic anion transporter type 1 in the proximal tubule of the kidney, and then multidrug resistance protein type 4 excretes TFV in urine [8, 9]. During this process, TFV is enriched intracellularly, where it causes tubular cell damage [10].
Tenofovir alafenamide fumarate (TAF), which was approved and launched in 2016 in Japan, is said to have less effect on tubular cells than TDF [11]. TAF is highly stable in plasma, is metabolized to TFV after translocation into HIV target cells, and exerts an anti-HIV effect [12]. It shows strong antiviral effects at doses less than one-tenth those of TDF [13]. Therefore, it is expected that TAF may reduce the tubular injury and bone density decrease seen with TDF [11, 14]. The Japanese anti-HIV treatment guideline [15] has recommended TAF instead of TDF as one of the first-line treatments for NRTI since 2017.

We are investigating preventing renal dysfunction by switching TDF to TAF. There are reports that switching from TDF to TAF affects body weight and lipid metabolism [16]. In Japanese, increased body mass index (BMI) is associated with a decreased estimated glomerular filtration rate (eGFR) and chronic kidney disease [17], [18]. Therefore, even under the long-term administration of TAF, we need to pay close attention to some laboratory values. In this study, we evaluated the progression of renal function in Japanese HIV-1-positive patients 144 weeks after switching from long-term TDF to TAF. Furthermore, we investigated the status of weight and lipid metabolism in Japanese HIV-1-positive patients after switching from TDF to TAF.

**Methods**

**Study Design and Patients**

We performed a single-center observational study of Japanese HIV-1-positive patients using the medical records at the National Hospital Organization Sendai Medical Center in Sendai, a regional city in northern Japan.

In our hospital as of December 2019, 170 HIV-1-positive patients were on antiretroviral therapy. In this study, the subjects were Japanese HIV-1-positive patients who had changed from TDF 300 mg per day to TAF 25 mg or TAF 10 mg (the latter in the case of a regimen containing cobicistat or ritonavir) per day at our hospital before March 2020. Only patients who had taken TDF for more than 48 weeks were included in the study so we could assess the long-term use of TDF.

The study included Japanese HIV-1-positive patients who were switched from TDF to TAF based on clinical findings that, according to the physician’s judgment, showed their renal function to be compromised by TDF, as well as Japanese HIV-1-positive patients who had no apparent renal impairment but were switched from TDF to TAF to prevent deterioration of renal function from continued TDF use. The third agent class drugs were selected to be given with TDF or TAF, such as nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs).

In Japan, TDF came to market in April 2004. TAF came to market as part of Genvoya® combination tablets in June 2016 and Descovy® combination tablets HT (including TAF 25 mg) and LT (including TAF 10 mg) in December 2016.
This study was approved by the Clinical Research Department and the Human Research Ethics Committee of National Hospital Organization Sendai Medical Center and is registered under No. 31–93 and C31-86.

**Measurements**

Laboratory values were studied at the start of taking TDF and when the patients were switched to TAF after taking TDF for more than 48 weeks. In addition, after the change from TDF to TAF, laboratory tests were performed at 12, 24, and 48 weeks. After that, the tests were done every 48 weeks up to 144 weeks. The laboratory tests measured the viral load of HIV-1 ribonucleic acid (HIV-1 RNA) and cluster of differentiation 4+ T cell (CD4) counts to determine the status of HIV infection suppression. In addition, eGFR, urine protein (UP), and blood urea nitrogen (BUN) were examined as indices of renal function, and urinary β2-microglobulin (Uβ2MG) was used as an index of renal tubular disorder. BMI was used as a measure of body weight. Triglycerides (TG), the most tested lipid parameter in our clinic, was a measure of lipid metabolism. This is because many patients had missing total cholesterol values. BMI was calculated from the height and the recorded body weight, and its classification was based on World Health Organization Western Pacific Region: BMI (kg/m$^2$) = [body weight] × [height]$^{-2}$ [19]. eGFR was calculated using the Japanese equation based on standardized serum creatinine, age, and sex developed by the Japanese Society of Nephrology, which we believe is more suitable for the Japanese population, rather than the estimated glomerular filtration rate calculated using the Cockcroft-Gault equation (eGFR$_{CG}$): eGFR (mL/min/1.73 m$^2$) = 194 × [serum creatinine]$^{-1.094}$ × [age]$^{-0.287}$ × [0.739 if female] [20].

The primary endpoint was the eGFR at 144 weeks after the change from TDF to TAF. The change in eGFR after the introduction of TAF and the factors affecting the change were also investigated.

**Statistical analysis**

For changes in eGFR, the primary endpoint, statistical analysis was performed using the paired t-test. For Uβ2MG, among other renal function indicators, statistical analysis was performed using the Wilcoxon signed rank test and Wilcoxon rank sum test. The paired t-test was also used for BMI and TG to assess weight trends and lipid metabolism. To identify the factors affecting eGFR, multiple logistic regression analysis was performed. All statistical analyses were performed with JMP®, version 14.2 (SAS Institute, Cary, North Carolina, USA).

**Results**

**Study population**

Of the 125 HIV-1-positive patients who were prescribed TAF at our hospital during the study period, which ran until March 31, 2020, 70 patients fulfilled the inclusion criteria and constituted the study patients. The first set of excluded subjects were 5 patients who had taken TDF for less than 48 weeks before TAF, 13 patients who changed from abacavir, a non-Japanese person and 18 patients who took TAF without having taken TDF. Thus, the study started with 88 patients, but 11 patients were transferred to other
hospitals during the course of the study, and 5 patients discontinued their visits. In addition, 2 patients did not receive TAF for the full 144 weeks.

The characteristics of the 70 patients in the study are shown in Table 1. The median age at the time of conversion from TDF to TAF was 44 years (range = 20 – 76 years), 92.9% of the patients being male. Many of them had good viral control, with a median CD4 count of 480 cells/µL (range = 94 – 1,182 cells/µL). The percentage of patients taking some third agent class drugs is shown in Table 1. Before and after the switch from TDF to TAF, the patients continued to take the third agent class drugs without any change. The median duration of treatment with TDF was 274 weeks (range = 50 – 896 weeks). The median serum creatinine at the time of the switch from TDF to TAF was 0.84 mg/dL (range = 0.36 – 1.28 mg/dL), and the median eGFR was 80.89 mL/min/1.73 m² (range = 42.73 – 148.00 mL/min/1.73 m²). The median Uβ2MG level was 267, but one patient had an abnormally high level of up to 87,400 µg/L. Four patients (5.7%) were switched to TAF after the physician determined that they had TDF-related tubular damage based on their serum creatinine and Uβ2MG levels. They were all male. The other patients were switched from TDF to TAF prophylactically to avoid future renal damage. The median body weight was 70.1 kg (range = 31.7 – 97.6 kg), the median TG was 145 mg/dL (range = 39 – 580 mg/dL), and patients receiving medication for hypertension, diabetes mellitus, and lipid metabolic disorders are shown in Table 1.

**Change in renal function**

The mean eGFR ± standard error (SE) was 104.42 ± 24.60 mL/min/1.73 m² at the time of starting antiretroviral therapy, including the start of TDF (TDF0), as shown in Fig. 1-A. At the time of the change from TDF to TAF (TAF0) after more than 48 weeks of TDF medication, the mean eGFR ± SE was 81.42 ± 21.10 mL/min/1.73 m². Figure 1-A shows a significant decrease in eGFR from TDF0 to TAF0, which was significantly improved with TAF12. TAF96 and TAF144 showed a significant decrease compared to TAF0.

The trends of eGFR in the 3 groups based on GFR classification [21] are shown in Fig. 1-B. The first group, G1, was defined as an eGFR greater than or equal to 90.00 mL/min/1.73 m² at the start of TAF. The second group, G2, had an eGFR greater than or equal to 60.00 mL/min/1.73 m² and less than 90.00 mL/min/1.73 m². The third group, G3a and G3b, had an eGFR less than 60.00 mL/min/1.73 m². Incidentally, there were no G4 or G5 patients in the present study. The eGFR in the G1 group decreased continuously after the switch from TDF to TAF. In particular, 24 weeks after switching to TAF, the eGFR decreased significantly. Next, in the G2 group, eGFR increased significantly at 12 weeks after switching from TDF to TAF. Thereafter, eGFR remained stable, without a significant difference, until 96 weeks, but at 144 weeks, eGFR decreased significantly. Finally, in the G3a and G3b groups, eGFR was also significantly elevated at 12 weeks after the switch from TDF to TAF. It remained significantly elevated at 24 and 48 weeks compared with TAF0. However, no significant difference occurred at 96 and 144 weeks.

As shown in Fig. 2-A, Uβ2MG significantly decreased at TAF12 compared with TAF0 and continued to significantly decrease until TAF144. The trends of UβMG in the 3 groups based on the GFR classification [21] are shown in Fig. 2-B. As in Fig. 1-B, the groups were G1, G2, G3a and G3b. The UβMG of the G3a and
G3b groups at the time of switching from TDF to TAF was significantly higher than that of the G1 and G2 groups. After the switch from TDF to TAF, Uβ2MG in groups G3a and G3b decreased significantly at TAF12, and the significant decrease continued thereafter until TAF144. In groups G1 and G2, Uβ2MG, which was originally low at the time of switching from TDF to TAF, further decreased significantly at TAF48.

Changes in BMI and TG
The changes in BMI are shown in Fig. 3-A. The mean BMI increased significantly from $22.2 \pm 0.4$ kg/m$^2$ to $23.8 \pm 0.4$ kg/m$^2$ from TDF0 to TAF0. BMI continued to increase after the start of TAF treatment and increased even more significantly to $24.5 \pm 0.4$ kg/m$^2$ at TAF48. There was a significant increase in BMI at TAF 96 and TAF 144, but the mean BMI at TAF 144 was $24.8 \pm 0.4$ kg/m$^2$, which was within the normal range for Japanese individuals. Changes in TG are shown in Fig. 3-B. During the period of taking TDF, the mean TG decreased from $190 \pm 17$ mg/dL to $170 \pm 13$ mg/dL after the start of TDF and up to TAF0. However, at week 48 after the switch from TDF to TAF, there was a significant increase in TG to $220 \pm 25$ mg/dL, whereas at TAF96 and TAF144, TG values decreased to the extent that they were not significantly different from those at TDF0.

Factors associated with changes in eGFR from TAF0 to TAF144
Table 2 shows the predicted results of factors that affect the change in eGFR up to 144 weeks after switching from TDF to TAF. Variables to be tested for association with the change in eGFR after switching from TDF to TAF were set as age at the start of TAF, sex, the third agent class drug, TDF duration, the difference in eGFR from TAF0 to TAF48 ($\Delta$ eGFR), body weight, BMI, and TG. At 144 weeks after switching from taking TDF to TAF, the factors significantly correlated with the difference in eGFR from TAF0 to TAF144 were $\Delta$ eGFR and age at the start of TAF.

Discussion
In Japanese HIV-1-positive patients, a long time after switching from TDF to TAF, Uβ2MG significantly improved, but eGFR showed a significant decrease at 144 weeks. BMI increased moderately within the normal range. TG reached its highest value at 48 weeks but did not show a significant difference from the TDF0 or TAF0 value at 144 weeks.

Patients in this study had a significant decrease in eGFR from the time they started taking TDF to the time they switched to TAF. In order to improve or prevent the decline in eGFR, all patients who were taking TDF were switched to TAF. At 12 weeks after switching, eGFR significantly increased from the time of switching and then gradually decreased, and eGFR at 96 and 144 weeks was significantly lower than that at the start of TAF. Therefore, even though TAF is considered to be better for renal function than TDF, the eGFR of Japanese HIV-1-positive patients was significantly decreased after switching from long-term TDF to long-term TAF.

In order to confirm the trend of eGFR in detail, the patients were divided into 3 groups, according to a published eGFR classification [21], based on their eGFR value at the time of switching to TAF. In the G1
group, with high eGFR, eGFR continued to decrease after switching from TDF to TAF and had significantly decreased by 24 weeks. In the G2 group, with moderate eGFR, there was a temporary recovery of eGFR. In the G3a and G3b groups, with low eGFR, eGFR started increasing significantly 12 weeks after switching to TAF, and there was no significant decline from baseline by 144 weeks. Yoshino et al. reported the recovery of 3 groups of Japanese HIV-positive patients who had decreased eGFR due to taking TDF and discontinued TDF. Among them, the median value of eGFR at the time of the switch was higher in the group that showed a worsening of eGFR even after discontinuation of TDF than in the recovery group and the mild recovery group [6]. These findings are consistent with our present progress report. Furthermore, according to Pozniak et al., when eGFR$_{CG}$ was divided into < 50 mL/min and $\geq$ 50 mL/min groups and progression was observed at 24 and 48 weeks, eGFR$_{CG}$ increased from baseline in the < 50 mL/min group at both 24 and 48 weeks but decreased in the $\geq$ 50 mL/min group. The eGFR$_{CG}$ was elevated from baseline in the < 50 mL/min group at 24 and 48 weeks but decreased in the $\geq$ 50 mL/min group [22]. TDF is known to cause tubular damage, and Uβ2MG is recommended as a test marker for tubular damage [23]. In our study, as shown in Fig. 2-A, there was a significant decrease 12 weeks after switching from TDF to TAF, and the decrease continued thereafter, suggesting that tubular damage was improved. In addition, we investigated the course of Uβ2MG by GFR class, as shown in Fig. 2-B. We found that Uβ2MG was higher only in the G3a and G3b groups, in which it was significantly higher than that in the G1 and G2 groups. After switching from TDF to TAF, Uβ2MG continued to decrease significantly in the G3a and G3b groups.

In summary, we believe that switching from TDF to TAF is effective in preventing the decline in eGFR and tubular damage in the low-eGFR group (eGFR less than 60 mL/min/1.73 m$^2$). However, in the group with an eGFR of 60 mL/min/1.73 m$^2$ or higher, the eGFR was significantly reduced by continuing to take TAF for a long period of time, though the extent of the decrease was not clear from the data in this study. We think it will be important to confirm the situation at 192 weeks and 240 weeks in the future.

In recent years, there have been many reports of weight gain and abnormal lipid metabolism associated with taking TAF [24, 25, 26]. In a report by Kuo PH et al. in Taiwanese HIV-positive individuals, another Asian ethnicity, significant weight gain and an increase in TG were observed at 48 weeks after switching from non-integrase inhibitor-based antiretroviral therapy to coformulated elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [27]. Therefore, in this study, we fixed the third agent class drugs and confirmed the changes in BMI and TG after switching from TDF to TAF. BMI showed a significant increase 12 weeks after switching from TDF to TAF but was within the normal range for Japanese people. TG was highest at TAF48 but declined thereafter and was not significantly different from baseline at TAF96 or TAF144. We believe that the reason for these findings is that information on weight gain and abnormalities in lipid metabolism caused by several anti-HIV drugs has been given to patients, and guidance on diet has been implemented during patient visits. Therefore, we consider that it is possible to prevent weight gain and abnormalities in lipid metabolism through an appropriate diet, even if the patient is taking TAF, but this is difficult to track and control in real-world settings.
To predict the factors associated with the change in eGFR after taking TAF, we performed a multiple regression analysis using the variables shown in Table 2, with the difference in eGFR from TAF0 to TAF144 as the objective variable. We predicted the factors associated with the objective variable based on the values of each item at 48 weeks, which we considered the best time to evaluate the effects of TAF because the changes in eGFR between GFR classes [21] differed at this time, as shown in Fig. 1-B. Turner D et al. reported that they did not find any factors associated with changes in eGFR from before to after switching from TDF to TAF [28]. However, in our long-term follow-up after switching from TDF to TAF, age (p = 0.039) and ΔeGFR (p < 0.0001) were significantly associated with the objective variable. On the other hand, Kawamoto R et al. [17] and Nomura I et al. [18] reported that increased BMI is associated with decreased eGFR in Japanese patients. However, we did not find any association in this study. The reason for this is that although BMI increased significantly from TAF0 to TAF144 in our patients, it remained within the normal range for Japanese people. The eGFR decrease was suppressed by switching to TAF, and eGFR ≥ 50 mL/min/1.73 m² was maintained. It should be noted that the results of this study differ from the results of previous studies but may be related, as long-term use of TAF may increase BMI and decrease eGFR.

This study was conducted at a single institution with a small sample size of only Japanese subjects, which are the main limitations of the study. However, this study design is a result of strict regulations and the elimination of missing survey items. We are the first to present the actual eGFR values of Japanese HIV-1-positive patients taking TDF for longer than 48 weeks and then continuing to take TAF for 144 weeks. We also detailed the course of eGFR trends up to 144 weeks after switching from TDF to TAF and predicted the factors affecting the difference from baseline after 144 weeks of taking TAF. This study also provides new details on other renal functions, such as the status of tubular damage as indicated by Uβ2MG, after the transition from baseline to 144 weeks of taking TAF. Furthermore, since there are few reports on BMI and TG after long-term use of TAF in Japanese individuals, these factors were also investigated.

Switching from TDF to TAF may temporarily improve renal function, but long-term use of TAF may lead to a decline in renal function, so continuous monitoring of renal function from all aspects is necessary.

**Conclusions**

In this study, Japanese HIV-1-positive patients who had been taking TDF for a long period of time showed a decrease in eGFR after switching to long-term use of TAF. The status of the transition differs depending on the eGFR at the time of the switch. Since Japanese HIV-1-positive patients are expected to continue taking TAF for a long period of time, renal function and body weight should be closely monitored.

**List Of Abbreviations**

TDF: Tenofovir disoproxil fumarate
HIV: Human Immunodeficiency Virus
NRTI: Nucleoside reverse transcriptase inhibitors
TFV: Tenofovir
TAF: Tenofovir alafenamide fumarate
BMI: Body mass index
eGFR: estimated glomerular filtration rate
NNRTI: Non-nucleoside reverse transcriptase inhibitors
PI: Protease inhibitors
INSTI: Integrase strand transfer inhibitor
HIV-1 RNA: viral load of HIV-1 ribonucleic acid
CD4: Cluster of differentiation 4
UP: Urine protein
BUN: Blood urea nitrogen
UB2MG: Urinary β2-microglobulin
TG: Triglyceride
eGFR_{CG}: estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
SE: Standard error
TDF0: the time of starting antiretroviral therapy including TDF
TAF0: the time of change from TDF to TAF
TAF12, -24, -48, -96 and -144: 12 weeks, 24 weeks, 48 weeks, 96 weeks and 144 weeks after starting TAF
G1, G2, G3a, G3b, G4 and G5: GFR classification
ΔeGFR: the difference in eGFR from TAF0 to TAF48

Declarations

Ethics approval and consent to participate
This study was approved by the Clinical Research Department and the Human Research Ethics Committee of National Hospital Organization Sendai Medical Center and is registered under No. 31-93 and C31-86.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

We received funding from the National Hospital Organization Sendai Medical Center for the purchase of statistical analysis software and publication costs.

Authors' contributions

KA accumulated, analyzed and interpreted the patient data and was a major contributor to writing the manuscript. TO reconfirmed the statistical analysis and the overall structure of the manuscript. HS and NT reviewed the entire manuscript and provided guidance on the content. All authors read and approved the final manuscript.

Acknowledgments

We would like to express our gratitude to the late Dr. Isao Sato and his staff, who founded the Department of Internal Medicine No. 5 at Sendai Medical Center; the staff of the Pharmacy Department at Sendai Medical Center; and the staff of our laboratory at the Graduate School of Pharmaceutical Sciences, Tohoku University, especially Dr. Emiko Sato and Akiyo Sekimoto, for their support in conducting this study.

References

1. World Health Organization. *Interim guidelines on HIV/AIDS.*
   https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf (revised on January, 2021).

2. S. Department of Health & Human Services. *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.* 2019.
3. European AIDS Clinical Society. GUIDELINES Version 10.0. 2019. https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf (revised on January, 2021).

4. Casado JL, del Rey JM, Bañón S, et al. Changes in Kidney Function and in the Rate of Tubular Dysfunction After Tenofovir Withdrawal or Continuation in HIV-Infected Patients. 2016; 72: 416-422.

5. Nishijima T, Kawasaki Y, Tanaka N, et al. Long-term exposure to tenofovir continuously decrease renal function in HIV-1-infected patients with low body weight: results from 10 years of follow-up. AIDS 2014; 28: 1903-1910.

6. Yoshino M, Yagura H, Kushida H, et al. Assessing recovery of renal function after tenofovir disoproxil fumarate discontinuation. J Infect Chemother. 2011; 18: 169-174.

7. Herlitz LC, Mohan S, Stokes MB, et al. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. Kidney Int. 2010; 78: 1171-1177.

8. Ray AS, Cihlar T, Robinson KL, et al. Mechanism of active renal tubular efflux of tenofovir. Antimicrob Agents Chemother. 2006; 50: 3297-3304.

9. Kohler JJ, Hosseini SH, Green E, et al. Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters. Lab Invest. 2011; 91: 852-858.

10. Hall AM, Hendry BM, Nitsch D, et al. Tenofovir-Associated Kidney Toxicity in HIV-Infected Patients: A Review of the Evidence. Am J Kidney Dis. 2011; 57: 773-780.

11. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 2015; 385: 2606-2615.

12. Babusis D, Phan TK, Lee WA, et al. Mechanism for Effective Lymphoid Cell and Tissue Loading Following Oral Administration of Nucleotide Prodrug GS-7340. Pharmaceutics 2013; 10: 459-466.

13. Ruane PJ, DeJesus E, Berger D, et al. Antiviral Activity, Safety, and Pharmacokinetics/Pharmacodynamics of Tenofovir Alafenamide as 10-Day Monotherapy in HIV-1–Positive Adults. 2013; 63: 449-455.

14. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. Lancet HIV 2016; 3: e158-e165.

15. The Japanese Ministry of Health, Labour and Welfare. The guidelines for the treatment of HIV infection. https://www.haart-support.jp/pdf/guideline2020.pdf (revised on January, 2021).

16. Schafer JJ, Sassa KN, O’Connor JR, et al. Changes in Body Mass Index and Atherosclerotic Disease Risk Score After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide. Open Forum Infect Dis. 2019; 6: ofz414. https://doi.org/10.1093/ofid/ofz414 (revised on January, 2021).
17. Kawamoto R, Kohara K, Tabara Y, et al. An association between body mass index and estimated glomerular filtration rate. *Hypertens Res.* 2008; 31: 1559-1564.

18. Nomura I, Kato J, and Kitamura K. Association between body mass index and chronic kidney disease: A population-based, cross-sectional study of a Japanese community. *Vasc Health Risk Manag.* 2009; 5: 315-320.

19. World Health Organization Western Pacific Region. *The Asia-Pacific perspective: Redefining obesity and its treatment.* https://apps.who.int/iris/handle/10665/206936 (revised on January, 2021).

20. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis.* 2009; 53: 982-992.

21. National Kidney Foundation. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Inter. Suppl.* 2013; 3: 5-14.

22. Pozniak A, Arribas JR, Gathe J, et al. Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Patients With Renal Impairment: 48-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study. *JAIDS.* 2016; 71: 530-

23. Nishijima T, Kurosawa T, Tanaka N, et al. Urinary β2 microglobulin can predict tenofovir disoproxil fumarate-related renal dysfunction in HIV-1-infected patients who initiate tenofovir disoproxil fumarate-containing antiretroviral therapy. *AIDS* 2016; 30: 1563-1571.

24. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. *N Engl J Med.* 2019; 381: 803-815.

25. Orkin C, Eron JJ, Rockstroh J, et al. Week 96 results of a phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. *AIDS* 2020; 34: 707-718.

26. Taramasso L, Berruti M, Briano F, et al. The switch from tenofovir disoproxil fumarate to tenofovir alafenamide determines weight gain in patients on rilpivirine-based regimen. *AIDS* 2020; 34: 877-881.

27. Kuo PH, Sun HY, Chuang YC, et al. Weight gain and dyslipidemia among virally suppressed HIV-positive patients switching to co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. *Int J Infect Dis.* 2020; 92: 71-77.

28. Turner D, Drak D, O’Connor CC, et al. Renal function change after switching tenofovir disoproxil fumarate for tenofovir alafenamide in the HIV-positive patients of a metropolitan sexual health service. *AIDS Res Ther.* 2019; 16: 40.

### Tables

**Table 1. Characteristics of patients**
TAF: Tenofovir alafenamide fumarate; TDF: Tenofovir disoproxil fumarate; HIV: Human Immunodeficiency Virus; RNA: Ribonucleic acid; CD4: Cluster of differentiation 4+ T cell; INSTI: Integrase strand transfer inhibitor; PI: Protease inhibitor; eGFR: estimated glomerular filtration rate; GFR: Glomerular filtration rate; Uβ2MG: Urinary β2-microglobulin; UP: Urine protein; BUN: Blood urea nitrogen; BMI: Body mass index; TG: Triglycerides.

* No patients were categorized into G4 or G5.
† No patient took these drugs together.

Table 2. Results of multiple regression analysis to predict factors affecting the difference in eGFR from TAF0 to TAF144.
| Variable                          | Parameter Estimate | Standard Error | p-value(Prob>|t|) |
|----------------------------------|--------------------|----------------|----------------|
| age at the start of TAF          | -0.238856          | 0.113185       | 0.0390        |
| sex, female                      | -4.814999          | 2.571985       | 0.0662        |
| third agent class drug, DTG      | -0.556685          | 1.249017       | 0.6574        |
| TDF duration                     | -0.004262          | 0.006232       | 0.4967        |
| Δ eGFR*                          | 0.7390215          | 0.094558       | <0.001        |
| body weight †                    | -0.360379          | 0.242478       | 0.1425        |
| BMI †                            | 0.3128311          | 0.798046       | 0.6965        |
| TG †                             | 0.0073838          | 0.005236       | 0.1638        |

adjusted R²: 0.54881

TAF: Tenofovir alafenamide fumarate; DTG: Dolutegravir; TDF: Tenofovir disoproxil fumarate; eGFR: estimated glomerular filtration rate; BMI: Body mass index; TG: Triglyceride.

* The difference in eGFR from TAF0 to TAF48.

† Variable at TAF48.

Statistically significant p values are written in italics.