DOI: 10.1111/hiv.13061
HIV Medicine (2021), **22**, 457–466

ORIGINAL RESEARCH

Outcomes associated with treatment change from tenofovir disoproxil fumarate to tenofovir alafenamide in HIV-1-infected patients: a real-world study in Japan

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Objectives

To investigate the impact of switching from tenofovir disoproxil fumarate (TDF)- to tenofovir alafenamide (TAF)-containing regimens on bone, kidney, serum lipids and body weight among Asian patients.

Methods

A prospective, multicentre, observational cohort study was conducted at three centres for HIV infection in Japan during 2017–2019. HIV-infected adults previously treated with TDF-containing regimens and scheduled to switch to TAF-containing regimens were included. Bone mineral density (BMD), renal markers, lipids and weight were measured consecutively from 12 months before to 12 months after the switch.

Results

Among 118 patients evaluated, the mean percentage change to spine BMD during 1 year of TAF treatment was higher than that during 1 year of TDF treatment (mean difference = 1.9%; 95% confidence interval (CI): 0.8–3.1). Urine protein and β_2-microglobulin levels decreased significantly after the switch, while low-density lipoprotein cholesterol and triglycerides increased. During the TDF and TAF periods, the mean weight gains were 0.2 and 1.9 kg, respectively (mean difference = 1.6 kg; 95% CI: 0.9–2.3). Subgroup analysis revealed a significant difference between the mean body weight change associated with an integrase inhibitor (INSTI) (+2.8 kg) and that associated with a non-INSTI (+1.2 kg) third agent treatment only during the TAF period.

Conclusions

Among predominantly Japanese HIV-infected patients, BMD and renal tubular markers improved, while lipid profiles worsened significantly after the switch. Weight gain during the TAF period was larger than that during the TDF period. Concurrent use of INSTI with TAF may act synergistically to gain body weight.

Keywords: bone mineral density, HIV, integrase inhibitors, renal tubular dysfunction, serum lipid profile, tenofovir, weight gain

Accepted 14 December 2020

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Introduction

Tenofovir disoproxil fumarate (TDF) is a long-standing cornerstone of antiretroviral therapy (ART) for HIV infection and remains one of the first-line agents recommended by international guidelines [1]. However, renal toxicity, including Fanconi syndrome, and bone toxicity [i.e. decreased bone mineral density (BMD)] are known side-effects of TDF and a major concern in the life-long treatment of patients with HIV infection [2].

Tenofovir alafenamide (TAF), another prodrug of tenofovir, is metabolized differently in the human body; compared with TDF, it maintains higher tenofovir intracellular levels despite lower tenofovir plasma levels [3]. Because of this pharmacokinetic feature, the safety profile of TAF is expected to be superior to that of TDF. TAF, in combination with different antiretroviral agents, has been associated with satisfactory efficacy and lower risk of renal and bone toxicities compared with TDF in treatment-naïve and treatment-experienced HIV-infected patients in randomized controlled trials [4–8] and cohort studies [9,10]. Consequently, TAF has been included among the first-line backbone agents recommended by international guidelines [1].

However, patients included in these large trials were predominantly of Caucasian and African-American origin. Patients of Asian origin accounted for approximately 5–6% of the study population [11]. Considering such under-representation, data regarding the effectiveness of switching from TDF to TAF on reducing renal and bone toxicities in Asian patients with HIV infections remain scarce [12]. Further studies are needed to adequately inform HIV treatment in Asian populations.

Weight gain following initiation of ART has recently gained attention. Weight gain associated with ART has been shown to increase the risk of diabetes and cardiovascular diseases [13]. A pooled analysis of randomized comparative clinical trials has found the ART regimens' composition to affect weight gain [14]. Specifically, patients following TAF-containing regimens gained *c.* 3 kg in 1 year; TAF was associated with the largest weight gain compared with TDF, abacavir and zidovudine among nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). Similarly, a few studies have reported on weight gain after switching from TDF- to TAF-containing regimens [15,16]; however, data representative of Asian populations are limited.

In Japan, the TAF-containing fixed-dose combination tablets of TAF/emtricitabine/elvitegravir/cobicistat and TAF/emtricitabine were approved in 2016 and 2017, respectively. Since then, medical practice steadily switched from TDF- to TAF-containing regimens in eligible patients. This study evaluated the impact of switching from TDF- to TAF-containing regimens on BMD, renal tubular biomarkers and body weight in Japanese patients with HIV-1 infection.

Methods

Study design and participants

This prospective, multicentre, observational cohort study was conducted at three HIV referral centres in Japan (Jichi Medical University Saitama Medical Center, Tokyo Metropolitan Health and Medical Treatment Corporation Okubo Hospital and Tokyo Metropolitan Tama Medical Centre) between September 2017 and December 2019. Those included were HIV-1-infected patients (aged $\geq$ 20 years) who were previously treated with TDF for at least 12 months and scheduled to switch to TAF and who had at least one set of renal markers and BMD test results available for the period of 12 months before the switch. This study was a single-arm, self-controlled design, and pragmatic assessment of patients scheduled to switch from TDF to TAF.

The switch day was defined as month 0. The data on BMD, renal markers and body weight were collected from 12 months before (month −12) to 12 months after (month 12) the switch. Consecutive measurements of BMD, laboratory tests [HIV-RNA level, CD4 count, levels of creatinine, cystatin C, phosphate, low-density lipoprotein cholesterol (LDL-C), and triglyceride in serum, and concentrations of creatinine, phosphate, protein and β_2-microglobulin in spot urine) and body weight were performed every 6 months (months −12, −6, 0, 6 and 12). BMD was measured by energy X-ray absorptiometry scans at the lumbar spine (L1–4) and femoral neck levels. Osteopenia was defined as a T-score between −1 and −2.5 and osteoporosis as a T-score $\leq$ −2.5. We also extracted information on comorbidities, including hypertension, diabetes mellitus, chronic hepatitis B virus and hepatitis C virus infections, and co-medication, including bisphosphonates, vitamin D, calcium supplements, systemic steroids, statins and fibrates.

The 1-year period from month −12 to month 0 was defined as the TDF period; similarly, the 1-year period from month 0 to month 12 was defined as the TAF period. All patients provided written informed consent before enrolment. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating facility (approval numbers A17-045, 2017-11 and 29-80).

Outcomes

The primary outcomes of interest were the changes in BMD, renal markers [serum creatinine and estimated glomerular filtration rate (eGFR), calculated with the Japanese version of the Modification of Diet in Renal Disease (MDRD) equation (17), serum cystatin C, tubular reabsorption of phosphate (TRP), urine protein to creatinine ratio, and urine β_2-microglobulin to creatinine ratio], and serum lipid profiles (LDL-C and triglycerides) between TDF period (changes between month −12 and month 0) and TAF period (changes between month 0 and month 12). Percentage TRP (%TRP) was calculated as [1 − (serum creatinine × urine phosphate)/(serum phosphate × urine creatinine)]×100 (%). We also compared the change in body weight between the two periods and its association with the third antiretroviral agent used. The third antiretroviral agents were classified as: (1) integrase inhibitors (INSTIs), (2) nonnucleoside reverse transcriptase inhibitors (NNRTIs), and (3) protease inhibitors (PIs).

Statistical analyses

Continuous variables were presented as means and standard deviations (SDs), except for variables with skewed distribution, which were presented as medians and interquartile ranges (IQRs). Continuous variables were compared using a paired *t*-test or Wilcoxon signed-rank test as appropriate. Categorical variables were compared using McNemar's χ^2 test.

Subgroup analysis of third agent impact on weight gain compared patients who received INSTIs with those who received NNRTIs or PIs. We excluded patients from subgroup analysis if they received both INSTIs and NNRTIs/PIs or if their third agent was changed during the study period. We used a two-sample *t*-test for this analysis. All *P*-values were two-tailed; $P < 0.05$ was indicative of a statistically significant finding. All statistical analyses were performed using R v.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 126 HIV-infected adults treated with TDF-containing regimens were enrolled. Eight patients were excluded due to one of the following reasons: patient data were incomplete (six patients) or TDF treatment was continued without switching to TAF (two patients). Thus, 118 patients were included in the final analysis.

During the TAF period, five patients were lost to follow-up (four changed hospitals, one died in an unrelated accident). All 118 patients were treated with emtricitabine as the second NRTI, and 114 patients remained on the same third agent during the TDF and TAF periods. Four patients had their third drug changed during the TDF and TAF periods: one patient was changed from darunavir/ritonavir to elvitegravir/cobicistat, one from fosamprenavir/ritonavir to dolutegravir, one from lopinavir/ritonavir to dolutegravir, and one from lopinavir/ritonavir to elvitegravir/cobicistat. Statins were prescribed to seven patients, while a patient was prescribed fibrates, and another one patient was prescribed bisphosphonate throughout the study period.

Of 118 patients, 111 (94%) were men, 112 (95%) were Japanese, and 49 (42%) were current smokers. Patient characteristics at the time of switching from TDF- to TAF-containing regimen (month 0) were as follows (Table 1): median (IQR) age = 44 (37–52) years, median (IQR) treatment duration of TDF-containing regimens was 63 (43–91) months, median (IQR) nadir CD4 T-cell count was 152 (58–223) cells/μL, median (IQR) CD4 T-cell count was 516 (401–660) cells/μL, and the proportion of patients whose serum HIV-RNA load was suppressed below 50 copies/mL was 97% (115/118). The third agents prescribed were INSTIs in 60 (51%) patients (46 dolutegragvir, nine raltegravir, and five elvitegravir/cobicistat), ritonavir-boosted PIs in 37 (31%) patients (27 darunavir, five fosamprenavir, three lopinavir, and two atazanavir), and NNRTIs in 24 (20%) patients (23 efavirenz and one rilpivirine).

Trends in the outcomes of interest (HIV status, BMD, renal markers, serum lipid profiles and body weight) over the 2-year period are shown in Table 2. The proportions of patients who had osteopenia and osteoporosis measured at the lumbar spine were, respectively, 27.1% and 8.4% at month −12, 25.2% and 7.8% at month 0, and 23.0% and 6.2% at month 12. A relatively larger proportion of patients had osteopenia and osteoporosis at the hip (femoral neck): 45.8% and 3.7% at month −12, 48.7% and 7.8% at month 0, and 45.1% and 8.0% at month 12, respectively (Fig. 1). After switching from TDF to TAF, BMD of the spine significantly increased; the mean (± SD) percentage change during the TAF period (month 0 to month 12) was 2.2 ± 4.2%, which was significantly higher than that during the TDF period (month −12 to month 0), which was 0.3 ± 3.5% [mean difference = 1.9%, 95% confidence interval (CI): 0.8–3.1%, $P = 0.002$]. Similarly, there was a trend towards an increase in percentage change of the hip BMD from −0.8 ± 5.2% during the TDF period to 1.5 ± 7.7% during the TAF period (mean difference = 2.1%, 95% CI: −0.2–4.5%, $P = 0.077$) that did not meet the criteria for statistical significance.

Table 1 Patient characteristics at the time of switching (month 0) from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF)

	Month 0 (*n* = 118)
Men [*n* (%)]	111 (94%)
Age, median (IQR), years	44 (37–52)
Origin	
Japanese [*n* (%)]	112 (95%)
Japanese descendant [*n* (%)]	2 (2%)
Asian other than Japanese	4 (3%)
Cigarette smoker	
Current [*n* (%)]	49 (42%)
Former [*n* (%)]	20 (17%)
Pack-year [median (IQR)]	18 (11–25)
Comorbidities	
Hypertension [*n* (%)]	9 (8%)
Diabetes mellitus [*n* (%)]	8 (7%)
Chronic hepatitis B virus infection [*n* (%)]	10 (8%)
Chronic hepatitis C virus infection [*n* (%)]	3 (3%)
Nadir $CD4^+$ T-cell count (cells/μL) [median (IQR)]	152 (58–223)
Duration of TDF treatment (months) [median (IQR)]	63 (43–91)
Third antiretroviral agent[†]	
Protease inhibitors [*n* (%)]	37 (31)
Darunavir-ritonavir (*n*)	27
Fosamprenavir-ritonavir (*n*)	5
Lopinavir-ritonavir (*n*)	3
Atazanavir-ritonavir (*n*)	2
Integrase inhibitors [*n* (%)]	60 (51)
Dolutegravir (*n*)	46
Raltegravir (*n*)	9
Elvitegravir-cobicistat (*n*)	5
Nonnucleoside reverse transcriptase inhibitors [*n* (%)]	24 (20)
Efavirenz (*n*)	23
Rilpivirine (*n*)	1

IQR, interquartile range.
[†]Among 118 patients, two received raltegravir and darunavir-ritonavir, and one received dolutegravir and darunavir-ritonavir as third agents.

The proportion of patients whose eGFR was 60 mL/min/1.73 m^2 or higher was 89.8% (106/118), 87.2% (102/117) and 89.4% (101/113) at months −12, 0 and 12, respectively. Figure 2 shows changes to renal markers during the TDF (month −12 to month 0) and TAF periods (month 0 to month 12). There was no effect of the regimen change on eGFR and %TRP. Levels of protein and β_2-microglobulin in urine significantly decreased after switching from TDF to TAF. The median (IQR) percentage change in the urine protein to creatinine ratio during the TDF period was significantly higher than that during the TAF period: 23.4% (−19.1–190.0%) *vs.* −18.5% (−70.9–13.8%) ($P < 0.001$). Similarly, the percentage change in the urine β_2-microglobulin to creatinine ratio during the TDF period was significantly higher than that during the TAF period: 7.3 (−26.7–88.5%) *vs.* −63.8 (−75.7 to −25.9%) ($P < 0.001$).

The median changes of LDL-C and triglyceride levels were 5 and −4 mg/dL during the TDF period, and 16 and 28 mg/dL during the TAF period, respectively ($P = 0.007$ and $P < 0.001$, respectively) (Fig. 3a,b). The mean (SD) body weight and body mass index were, respectively, 65.3 ± 11.0 kg and 23.0 ± 3.5 kg/m^2 at month −12; 65.5 ± 11.0 kg and 23.1 ± 3.5 kg/m^2 at month 0; and 67.4 ± 11.7 kg and 23.8 ± 3.8 kg/m^2 at month 12 (Table 2). The mean body weight differences (weight gain) increased significantly from 0.2 ± 2.4 kg during the TDF period to 1.9 ± 2.6 kg during the TAF period (mean difference = 1.6 kg, 95% CI: 0.9–2.3 kg, $P < 0.001$). Similarly, the mean percentage change in body mass index was significantly greater during the TAF period (2.9 ± 3.9%) than during the TDF period (0.4 ± 3.5%), with a mean difference of 2.4% (95% CI: 1.4–3.5%, $P < 0.001$) (Fig. 3c,d).

Body weight differences observed during the TDF and TAF periods, stratified by the third agent used [INSTI *vs.* non-INSTI (PI or NNRTI)], are shown in Fig. 4. A total of 104 patients who had continued to receive the same third agents during the study period were included in subgroup analysis; 51 patients received INSTIs and 53 patients received non-INSTIs (23 NNRTIs and 30 PIs). There was no significant difference in mean (SD) body weight change between the INSTI (0.2 ± 2.6 kg) and non-INSTI cohorts (0.1 ± 2.3 kg) during the TDF period (mean difference = 0.1 kg, 95% CI: −1.1–0.8 kg, $P = 0.762$). Conversely, there was a significant difference in mean (SD) body weight change between the INSTI (2.8 ± 2.8 kg) and non-INSTI cohorts (1.2 ± 2.1 kg) during the TAF period (mean difference = 1.6 kg, 95% CI: 0.6–2.6 kg, $P = 0.001$).

Discussion

In this pragmatic study of virally suppressed patients with HIV infection in Japan, we observed statistically significant improvements in spinal BMD and renal tubular biomarkers alongside a significant weight gain at 1 year after switching from a TDF- to a TAF-containing regimen without changing other components. Notably, weight gain was more prominent among patients treated with TAF combined with INSTI than those treated with TAF combined with PI or NNRTI.

In our study, 7.8% (25.2%) and 7.8% (48.7%) of patients, with a median age of 44 years, had osteoporosis (osteopenia) defined by the T-score of the lumbar spine and femoral neck, respectively, at the time of switching. In a previous meta-analysis of 11 worldwide studies, 15% and 52% of 884 HIV-infected patients (age range: 31–57 years) had osteoporosis and osteopenia, respectively, at any site, including the lumbar spine, femoral neck and

Table 2 Trends in HIV and immune status, renal markers, bone mineral density and body weight before and after switching from tenofovir disoproxil fumarate (TDF)- to tenofovir alafenamide (TAF)-containing antiretroviral regimens among 118 HIV-infected adults

	Month −12 (n = 118)	Month −6 (n = 118)	Month 0 (n = 118)	Month 6 (n = 115)	Month 12 (n = 113)
HIV and immune status					
CD4 T-cell count (cells/μL) [median (IQR)]	526 (388–644)	533 (393–678)	516 (401–660)	550 (423–682)	563 (432–691)
HIV-1 RNA < 50 copies/mL [n (%)]	116 (98%)	108 (92%)	115 (97%)	111 (97%)	108 (96%)
Bone densitometry					
Lumbar spine BMD (g/cm^2)	1.04 ± 0.16	1.02 ± 0.16	1.04 ± 0.17	1.05 ± 0.18	1.05 ± 0.17
Percentage change from month 0 (%)	−0.3 ± 3.5	0.3 ± 3.2	–	0.8 ± 10.4	2.2 ± 4.3
Lumbar spine T-score	−0.6 ± 1.3	−0.8 ± 1.3	−0.5 ± 1.3	−0.4 ± 1.3	−0.4 ± 1.3
Hip BMD (g/cm^2)	0.80 ± 0.15	0.80 ± 0.15	0.80 ± 0.16	0.80 ± 0.17	0.81 ± 0.15
Percentage change from month 0 (%)	0.8 ± 5.2	0.7 ± 3.6	–	0.4 ± 12	1.5 ± 7.7
Hip T-score	−1.0 ± 0.9	−1.0 ± 0.9	−1.2 ± 0.9	−1.1 ± 1.0	−1.1 ± 1.0
Renal markers					
Serum creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2
eGFR (mL/min/1.73 m^2)	78.7 ± 17.8	77.9 ± 17.7	77.3 ± 16.4	78.1 ± 17.8	77.1 ± 16.9
Serum cystatin C (mg/L)	0.9 ± 0.1	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2
eGFRcys (mL/min/1.73 m^2)	90.3 ± 18.5	90.2 ± 19.4	93.3 ± 20.8	94.5 ± 20.8	93.2 ± 20.1
Serum phosphate (mg/dL)	3.2 ± 0.5	3.2 ± 0.5	3.3 ± 0.5	3.3 ± 0.5	3.3 ± 0.6
Urine phosphate (mg/dL)	52.2 ± 32.2	59.8 ± 37.8	58.7 ± 40.6	54.4 ± 36.7	59.1 ± 40.3
Tubular reabsorption of phosphate (%)	87.0 ± 5.1	87.0 ± 4.4	86.8 ± 5.7	88.1 ± 5.2	87.4 ± 5.1
Urine protein to creatinine ratio (mg/g creatinine) [median (IQR)]	71 (23–124)	82 (33–140)	86 (47–184)	58 (19–99)	61 (20–118)
Urine protein to creatinine ratio > 200 mg/g creatinine [n (%)]	12 (15)	11 (11)	24 (21)	13 (11)	16 (14)
Urine β_2-microgloburin to creatinine ratio (μg/g creatinine) [median (IQR)]	3.5 (1.7–12.8)	4.0 (1.6–13.3)	4.0 (1.6–14.3)	1.8 (1–4.7)	1.8 (1.1–3.8)
Serum lipid profiles					
LDL-C (mg/dL) [median (IQR)]	99 (83–116)	106 (88.5–119)	108 (86–128)	119 (100–142)	125 (96–145)
Triglyceride (mg/dL) [median (IQR)]	98 (69–162)	110 (75–161)	104 (72–142)	133 (89–209)	134 (95–201)
Body weight (kg)	65.3 ± 11.0	65.3 ± 11.3	65.5 ± 11.0	66.6 ± 11.5	67.4 ± 11.7
Body mass index (kg/m^2)	23.0 ± 3.5	23.0 ± 3.7	23.1 ± 3.5	23.5 ± 3.7	23.8 ± 3.8

Data are means ± standard deviation unless otherwise indicated.
BMD, bone mineral density; eGFRcys, eGFR based on cystatin C; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

total hip [18]. The lower prevalence of decreased bone density in our cohort might reflect the characteristics of our cohort, which predominantly consisted of relatively young Japanese men. In a large cohort study of 3,040 Japanese adults examining prevalence of osteoporosis defined as BMD < 70% of peak bone mass, 2.8% and 6.5% of men younger than 60 years (n = 165) had osteoporosis measured at the lumbar spine and femoral neck, respectively [19]. The prevalence of osteoporosis, particularly in the lumbar spine, in our cohort receiving TDF seems higher than that observed in the HIV-uninfected Japanese cohort of men aged < 60 years. In our cohort, an approximately 2% increase of BMD in the spine was observed at 1 year after switching from TDF to TAF alongside a modest BMD increase in the hip (1.5%). This is in line with previous international phase 3 studies, showing 1.5–1.6% and 1.1–1.5% increase in BMD in the spine and hip, respectively, at 48 weeks after regimen switching [4,5].

Urinary protein and β_2-microglobulin levels significantly decreased after switching from TDF- to TAF-containing regimens. Only 15%, 21% and 14% of patients showed a proteinuria > 200 mg/g creatinine at months −12, 0 and 12, respectively, in this study. However, the median percentage change in the urine protein/creatinine ratio during the TDF period was also significantly higher than the TAF period ratio (50.6% *vs.* −21.9%, P = 0.046), particularly in patients with proteinuria > 200 mg/g creatinine. Similar renal biomarker improvement findings have been reported from international phase 3 switching studies [4,5]. A pooled analysis of 4091 virologically suppressed patients switching from TDF to TAF in five trials showed statistically significant improvements in the urine albumin/creatinine ratio, urine protein/creatinine ratio, and urine β_2-microglobuline/creatinine ratio, as well as in serum creatinine levels and creatinine clearance [11]. However, there was no significant difference in the levels of serum creatinine, eGFR and serum cystatin between the TDF and TAF periods in our study. This may be partly explained by the fact that patients who had developed overt renal dysfunction, such as increased serum creatinine levels or significant proteinuria, with TDF-

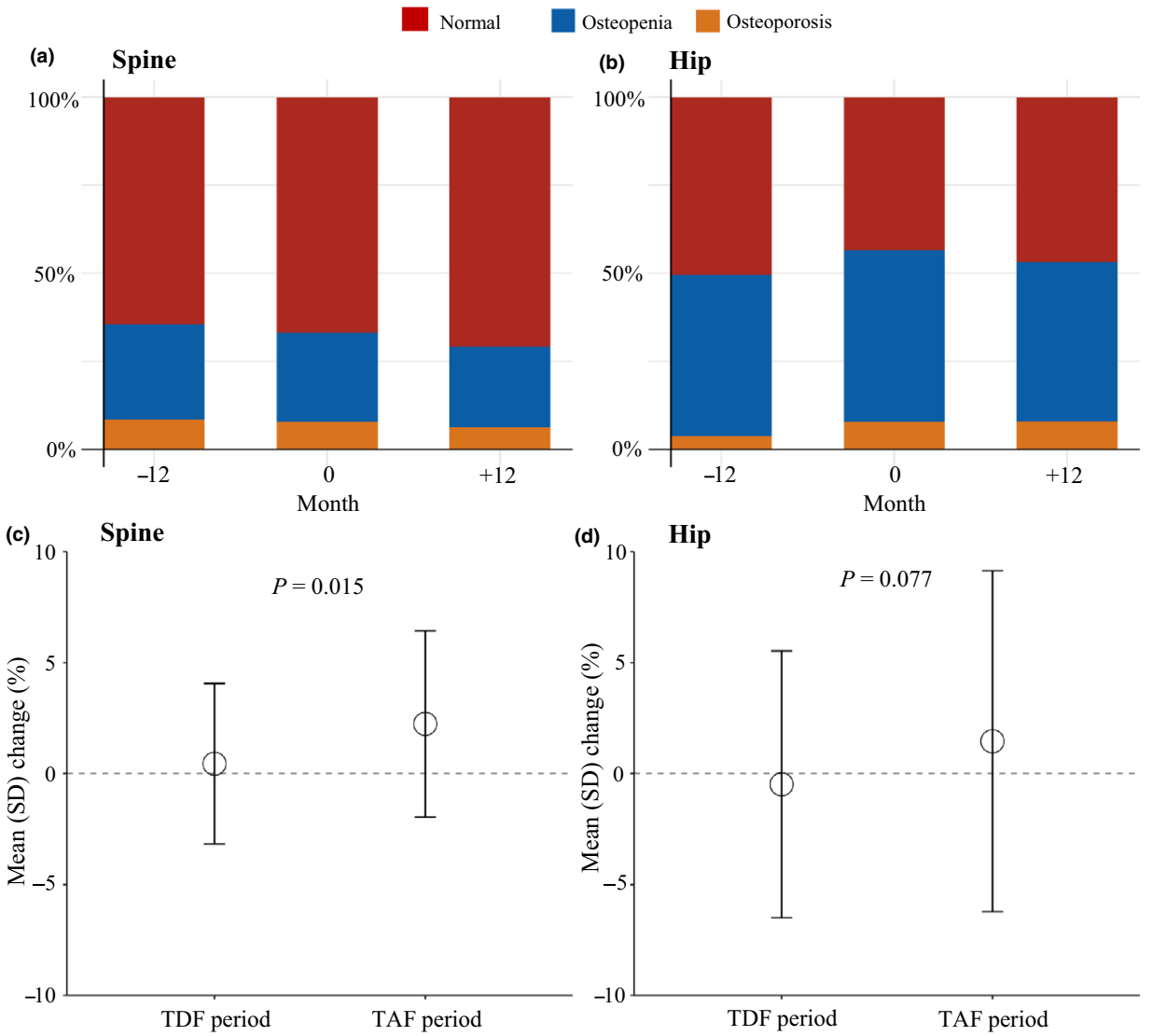

Fig. 1 (a, b) Trends in the frequency of osteopenia and osteoporosis defined by T-score on switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) (month 0), 12 months before (−12) and 12 months after (+12) the switch. Both outcomes were measured at the lumbar spine (a) and hip (femoral neck) (b) levels. (c, d) Percentage change in bone mineral density (BMD) during the TDF (from month −12 to 0) and TAF periods (from month 0 to +12) was measured at the lumbar spine (c) and hip (femoral neck) (d) levels. *P*-values were calculated using two-tailed paired *t*-tests to compare the differences between the two periods. SD, standard deviation. [Colour figure can be viewed at wileyonlinelibrary.com]

containing regimens were unlikely to be included in this study as the regimens would have been switched before study enrolment.

In the present study, significant increases of LDL-C (median = 16 mg/dL) and triglyceride (median = 28 mg/dL) levels were observed at 12 months after the switch to TAF. Furthermore, patients gained a mean of 1.9 kg in body weight during the 1-year period after switching from TDF- to TAF-containing regimens, compared with a mean 0.2 kg increase in body weight during the preceding 1 year of the TDF period. Several recent clinical trials showed the worsening of lipid profiles accompanying TDF switching to TAF [20–22]. A prospective cohort from Ireland reported a significant increase of 9.7 mg/dL of LDL-C and 11.5 mg/dL of triglyceride levels at a median of 24 weeks after switching to TAF, consistent with our result [22]. The mechanism of the changes in lipid profiles is considered due to TDF's lipid-lowering effects [23]. Additionally, body weight gain may also affect the worsening of lipid profiles.

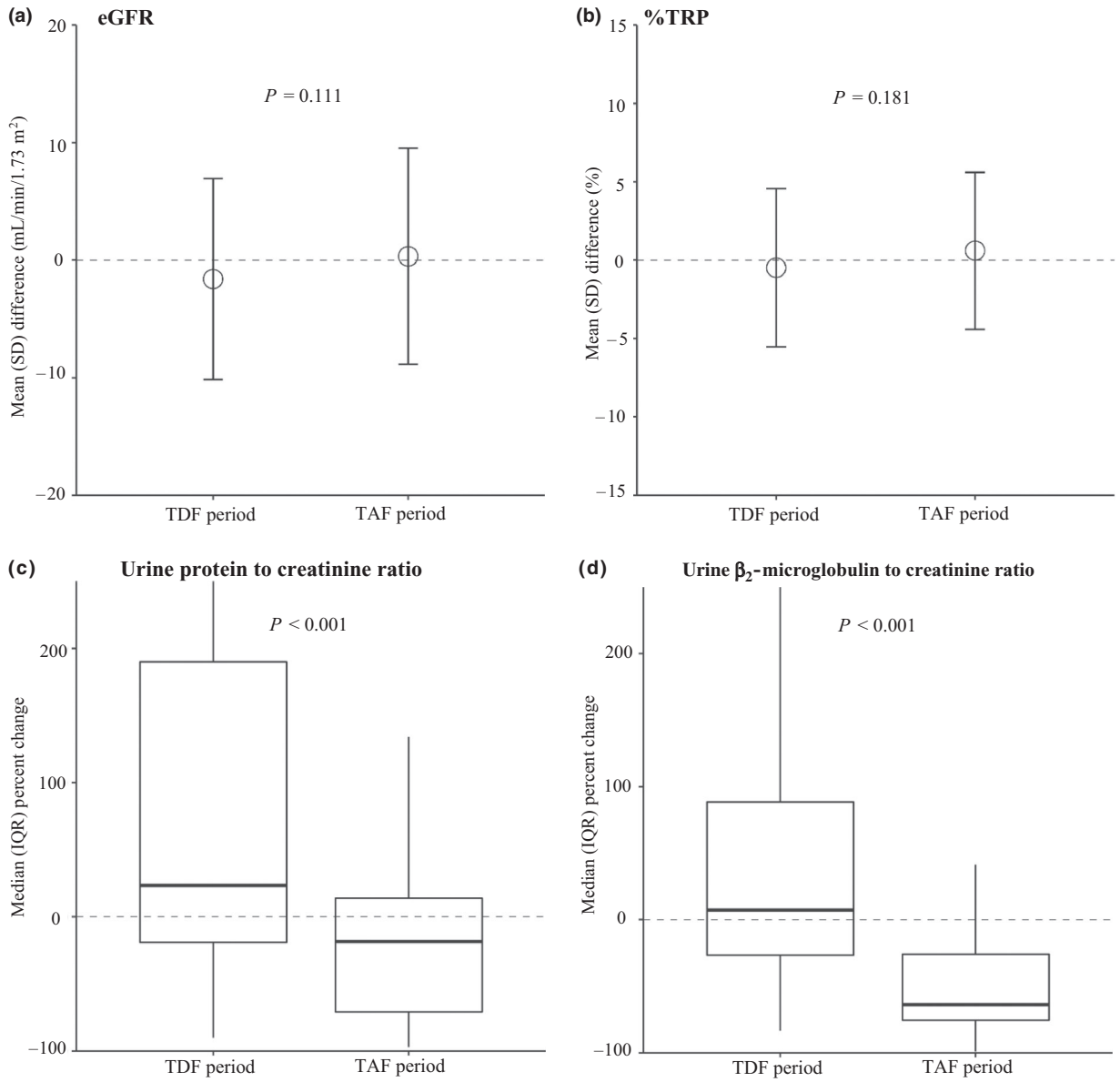

Fig. 2 Changes to renal markers during the tenofovir disoproxil fumarate (TDF) [1-year period before switching from TDF to tenofovir alafenamide (TAF)] and TAF periods (1-year period after switching). (a) Mean (SD) differences in estimated glomerular filtration rate (eGFR); (b) mean (SD) differences in percentage tubular reabsorption of phosphate (%TRP); (c) median [interquartile range (IQR)] percentage changes in the urine protein to creatinine ratio; (d) median (IQR) percentage changes in the β_2-microglobulin to creatinine ratio. *P*-values were calculated using two-tailed paired *t*-tests (a, b) and Wilcoxon signed-rank test (c, d) to compare the differences between the two periods.

Significant body weight gain observed in the present study is in line with recent studies from other countries; absolute weight gains after 1 year from regimen switching have been reported as 3.2 and 1.4 kg in studies from Germany and the United States, respectively [24,25]. The magnitude of weight gain might be affected by multiple factors, including race, ethnicity and antiretrovirals combined with TAF, although data are limited for the Asia-Pacific region. Kuo *et al.* [16] recently reported that a switch from a non-INSTI-containing regimen to an INSTI + TAF-containing regimen (TAF formulated with elvitegravir, cobicistat and emtricitabine) among HIV-infected Taiwanese patients was associated with a moderate weight gain of 1.8 kg at week 48 after the switch. INSTI-associated weight gain has also been reported in comparative studies [14,26]. Additionally, our study

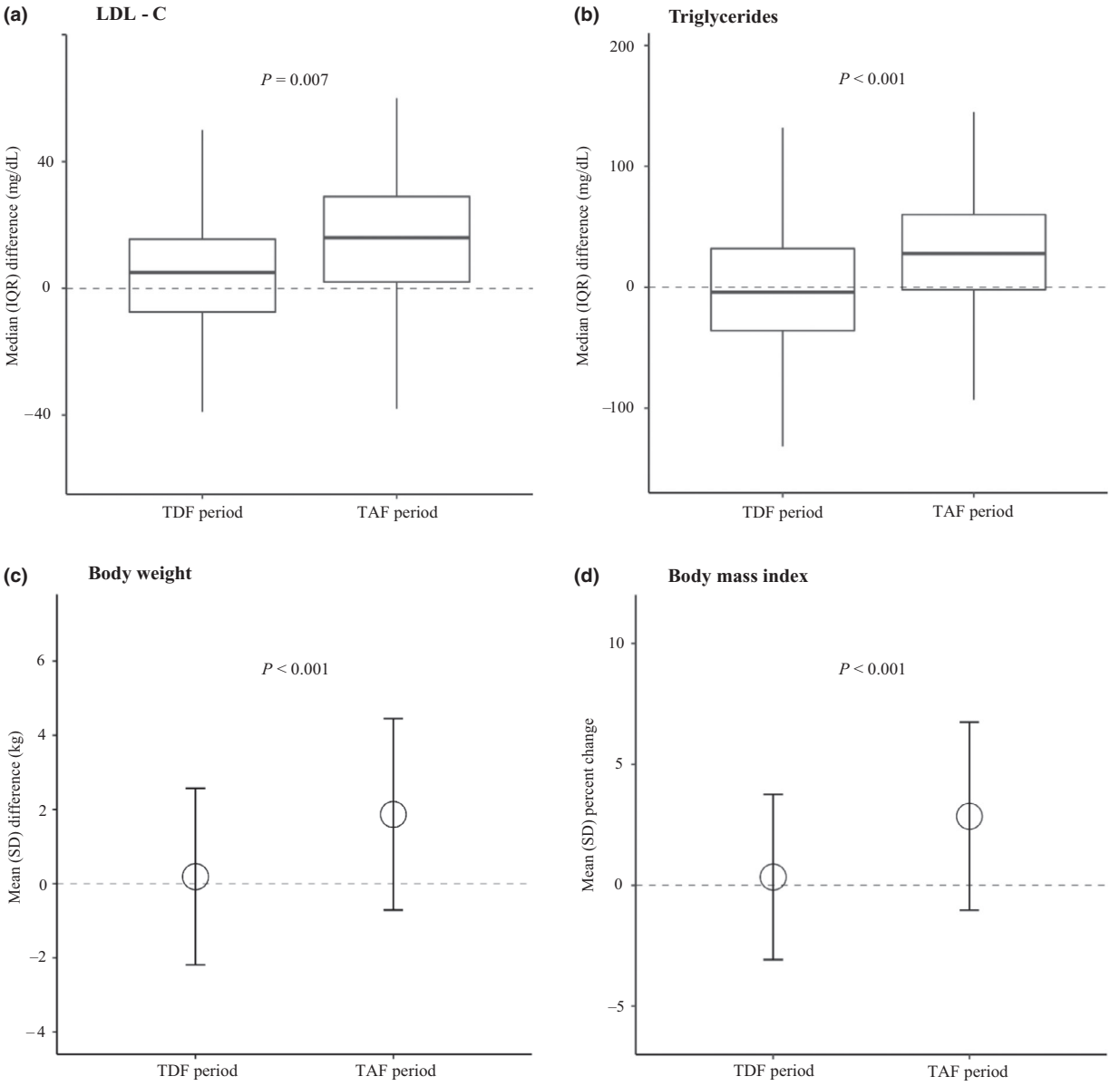

Fig. 3 Changes in lipid profiles and body weight during the tenofovir disoproxil fumarate (TDF) [1-year period before switching from TDF to tenofovir alafenamide (TAF)] and TAF periods (1-year period after the switching). (a) Median [interquartile range (IQR)] differences in low-density lipoprotein cholesterol (LDL-C); (b) median (IQR) differences in triglycerides; (c) mean (SD) differences in body weight; (d) mean (SD) percentage change in body mass index. *P*-values were calculated using Wilcoxon signed-rank test (a, b) and two-tailed paired *t*-tests (c, d) to compare the differences between the two periods. SD, standard deviation.

demonstrated that weight gain was greater among patients taking INSTIs (predominantly dolutegravir) than among those taking PIs or NNRTIs after switching from TDF to TAF. This finding indicated that the combination of TAF and INSTI might have a synergistic, rather than an additive, effect on weight gain. To the best of our knowledge, this synergy has not been reported previously, and the exact mechanism remains unclear. A randomized trial of patients who had switched from TDF + efavirenz (NNRTI) to TDF + dolutegravir or TAF + dolutegravir showed greater weight gain in the TAF + dolutegravir arm (+4.7 kg at week 48) and the TDF + dolutegravir arm (+3.0 kg) than in the standard-care (TDF + efavirenz) arm [7]. This finding also suggests that the combination of TAF and INSTI may have a synergistic or additive effect on weight gain.

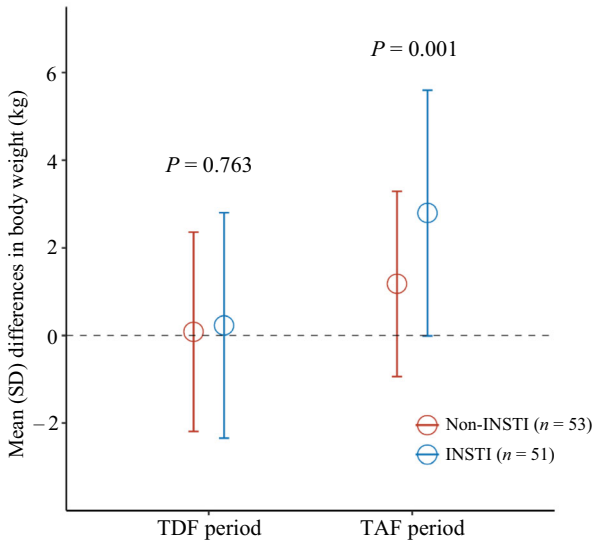

Fig. 4 Changes in body weight during the tenofovir disoproxil fumarate (TDF) [1-year period before switching from TDF to tenofovir alafenamide (TAF)] and TAF periods (1-year period after the switching), stratified by the third antiretroviral agent [integrase inhibitors (INSTIs) *vs.* non-INSTIs). Non-INSTIs comprised protease inhibitors and nonnucleoside reverse transcriptase inhibitors. *P*-values were calculated using two-tailed, two-sample *t*-tests to compare the differences between the two groups. SD, standard deviation. [Colour figure can be viewed at wileyonlinelibrary.com]

There are several limitations to the present study. First, this study had a pragmatic, non-randomized, self-controlled design without a washout period; therefore, the changes observed after switching from TDF to TAF might be due to multiple factors. However, the vast majority [114/118 (97%)] of patients remained on the same third agent throughout the study period, and 98% (116/118) of patients reported no change in their smoking habit, which could have affected BMD or weight. In addition, only one patient reported changes affecting bone metabolism (vitamin D or bisphosphonate). Second, we assessed the impact of regimen change during the 1-year period after the switch. Therefore, the changes after the 1-year period are uncertain. Third, patients who had experienced overt renal dysfunction with TDF-containing regimens were unlikely to be included in this study, as the regimens would have been switched before study enrolment. Fourth, our patients were mostly young men. Therefore, changes seen in our population might not be generalizable to other populations such as older adults or women. Additionally, the sample size was relatively small, meaning the statistical power of the study might have been insufficient to detect changes in some parameters.

In conclusion, in this study with predominantly Japanese patients with HIV infection, renal tubular and bone markers improved, but weight gain increased at 1 year after switching from a TDF- to a TAF-containing regimen. Significantly higher serum lipid concentrations and larger weight gain were associated with TAF- rather than TDF-containing treatments. Concurrent use of INSTIs with TAF was associated with greater weight gain, probably in a synergistic rather than an additive fashion. Further research is needed to evaluate the clinical consequence of these changes in the long term.

Acknowledgments

Financial disclosure: This work was supported in part by the Foundation for Development of the Community (research grant) and MEXT KAKENHI (grant number, 20K07831). The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript or decision to submit the manuscript for publication.

Conflict of interest: None.

Author contributions

SH designed the study. SH, TS, KS and KO conceived the study and collected the data. NK, HO and SH interpreted the data. NK and HO conducted statistical analyses under MM's supervision. SH, KO and NK drafted the manuscript. All authors critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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