Changing Trends in Lipid Profile and Biomarkers of Renal Function and Bone Metabolism Before and After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide: a Prospective Observational Study

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Research

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Abstract

Background

Antiretrovirals, including tenofovir, can suppress human immunodeficiency virus (HIV) infection but cannot completely eradicate it. Patients with HIV infection are administered antiretroviral drugs over a long term; thus, managing consequent adverse drug reactions, such as renal dysfunction and bone mineral loss, is important. Currently, highly sensitive biomarkers that can detect adverse drug reactions early have not been well studied.

Methods

This single-center, prospective, observational study explored changes in the biomarkers of renal function, bone metabolism, and lipid profile before and after switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) in patients with HIV infection.

Results

All 31 enrolled patients had been treated with antiretrovirals for more than 5 years. The urinary liver-type fatty acid binding protein (L-FABP)/creatinine ratio was significantly decreased at 3 and 6 months after switching to TAF compared with that before switching to TAF (-0.5 μg/gCr at 3 months, and -0.8 μg/gCr at 6 months; \( p < 0.005 \) for both at 3 and 6 months). The urinary N-terminal telopeptide (NTx)/creatinine ratio decreased over the study period, and the ratios were significantly different between 3 months and 6 months (-11 nmol/mmol Cr at 3 months, -15.2 nmol/mmol Cr at 6 months; \( p = 0.0069 \) at 3 months, \( p < 0.0001 \) at 6 months). Low density lipoprotein-cholesterol level significantly increased at 3 (+26 mg/dL) and 6 months (+13 mg/dL) compared with that at the baseline (\( p < 0.0001 \)).

Conclusions

Switching from TDF to TAF decreased the levels of renal and bone biomarkers, such as urinary L-FABP and NTx, but increased low density lipoprotein-cholesterol levels. Highly sensitive markers, such as urinary L-FABP and NTx, might be useful tools to predict adverse drug reaction early.

Background

Antiretrovirals (ARVs) have been successfully used to suppress human immunodeficiency virus (HIV) infection, and the life expectancy of the HIV-infected patients treated with ARVs has considerably increased, comparable to that of HIV-uninfected patients (1). However, ARVs cannot completely eradicate HIV; therefore, lifelong therapy with ARVs is still required.

Long-term therapy with ARVs can cause adverse drug effects. Tenofovir disoproxil fumarate (TDF) was used since 2001 in the world and since 2004 in Japan. TDF has recommended as a part of initial regimens for most treatment naïve patients(2). The adverse drug effects commonly caused by TDF...
include renal dysfunction and bone density loss (3). Tenofovir alafenamide (TAF), a prodrug of tenofovir, was approved in Japan in 2017. TAF has improved permeability into the lympho-reticular cells and reduces the systemic concentration of tenofovir by 10% compared to TDF (4). Clinical trials have shown that switching from TDF to TAF has improved the estimated glomerular filtration rate (eGFR) and levels of creatinine, urinary protein, and urinary biomarkers such as retinol-binding protein (RBP) (5, 6). A pooled analysis of 26 clinical trials have also supported the improved renal safety of TAF compared to TDF (7).

Although switching to TAF from TDF showed renal improvement with potent viral suppression, highly sensitive biomarkers that indicate these subclinical changes after switching to TAF are not well-identified.

The urinary liver-type fatty acid binding protein (L-FABP) is expressed in the human proximal tubules, and its excretion via urine reflects tubulointerstitial damage (8). L-FABP could be a prognostic biomarker for the development of renal dysfunction in HIV-infected patients (9).

Among the biomarkers of bone metabolism, bone-specific alkaline phosphatase (BAP) is a glycoprotein on the surface of osteoblasts that is released during bone formation. The N-terminal fragments of telopeptide (NTx) of type 1 collagen after degradation of the bone matrix is considered a resorption marker (10). These markers have been evaluated in several studies (11–13) in patients on a TDF-containing regimen of antiretrovirals.

In this study, we aimed to explore the changing trends in biomarkers of renal function and bone metabolism, and lipid profile while switching from TDF- to TAF-containing regimen in HIV-infected patients.

Methods

Patients and setting

This observational study was conducted prospectively at the University of Tokyo Hospital, a 1217-bed tertiary-care teaching hospital in Tokyo, Japan. The study was approved by the research ethics committee of the Faculty of Medicine of the University of Tokyo. All the patients have provided written informed consent.

HIV-infected adult (20 years old and more) patients were enrolled in the study from July 2017 to June 2018. The enrollment criteria were as follows: 1) patients who had already received TDF-containing antiretroviral regimen for at least a year, 2) patients who could visit the outpatient clinic, and undergo blood and urine tests at least once every three months, and 3) if the physician had determined that the patients preferred TAF over TDF as treatment.

The study period of all the patients was for 6 months. Additional urine samples, and venous blood samples were collected for testing in a commercial laboratory during the study period.

Data collection and selection
The collected patient data included age, sex, body weight, height, underlying disease (diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease (CKD), chronic hepatitis C virus infection, and chronic/history of hepatitis B virus infection), a history of acquired immunodeficiency syndrome (AIDS), and the prescribed antiretroviral regimen by medical chart review. Chronic kidney disease was defined as eGFR < 60 mL/min/1.73 m$^2$ during the study period or previous diagnosis by their respective doctors. Body mass index was calculated as weight in kilograms divided by the square of height in meters: weight (kg)/height (m$^2$).

The following laboratory data were reviewed using the medical charts: CD4$^+$ lymphocyte count, plasma HIV RNA level, complete blood count, serum phosphate level, low and high density lipoprotein cholesterol levels, triglyceride (TG) level, urinalysis, and serum creatinine level. Glomerular filtration rate (GFR) was calculated with serum creatinine and cystatin C levels.

In addition, serum and urine samples were tested for the following in a commercial laboratory (LSI Medience Corporation): urinary liver-type fatty acid binding protein level (U-L-FABP; latex agglutination immunoturbidimetric assay), urinary phosphate level, urinary N-acetyl-beta-D-glucosaminidase (U-NAG), cystatin-C, urinary N-terminal telopeptide (U-NTx; enzyme immunoassay), and serum BAP (chemiluminescent enzyme immunoassay). Using this data the following creatinine ratios were calculated: U-L-FABP/creatinine (Cr), U-NAG/Cr, and U-NTx/Cr. The rate of tubular reabsorption of phosphate (percent tubular reabsorption of phosphate; %TRP) was calculated according to the following formula:

\[ \%\text{TRP} = \left\{1 - \frac{\text{urine-phosphate} \times \text{serum creatinine}}{\text{serum phosphate} \times \text{urine- creatinine}}\right\} \times 100 \]

Proteinuria was defined by a value of $\geq 1 +$ by dipstick urinalysis.

**Statistical analysis**

The Wilcoxon signed-rank test was performed using the JMP Pro software version 14.2.0 (SAS institute Inc., Cary, NC, USA) to analyze trends of biomarkers before and after switching from TDF to TAF. The significance level of the two-tailed test was set at 0.05.

**Results**

Thirty-one patients were enrolled in our study. The patients' characteristics are shown in Table 1. All the patients were men, and the median age was 45 years. The average BMI was 23.6, and 5 patients had low body weight (< 55 kg). Thirty patients were Japanese, and one was an African. All the patients had been treated with ARVs for more than 5 years. Half of the TDF-containing antiretroviral regimens also consisted of integrase inhibitors, such as dolutegravir and raltegravir. Among all the ARVs, only TDF was changed during the study period. Two patients in the study had baseline CKD. Eleven patients were diagnosed with hyperlipidemia, among which, two of them received statin treatment before switching to TAF.
| Patients' characteristics | Comorbidity          |
|--------------------------|----------------------|
| Age: median (range)      | Chronic kidney disease | 2 |
| Sex: male:female         | Diabetes mellitus     | 2 |
| BMI: average (range)     | Hypertension          | 5 |
|                          | Hyperlipidemia        | 11|
|                          | HCV infection         | 3 |
| History of AIDS          | HBV infection         | 20|
| PCP                      | 5                     |
| Lymphoma                 | 2                     |
| CMV retinitis            | DRV/r                 | 10|
| Candida esophagitis      | RAL                   | 8 |
| Kaposi's sarcoma         | DTG                   | 8 |
| Disseminated MAC         | EFV                   | 4 |
| Cryptococcus meningitis  | FPV/r                 | 1 |
| Duration of ART          |                       |
| less than 5 years        | 11                    |
| 5–10 years               | 19                    |
| more than 10 years       | 1                     |

BMI: body mass index [calculated as weight in kilograms divided by the square of height in meters: weight (kg)/height (m²)], AIDS: acquired immunodeficiency syndrome, PCP: Pneumocystis pneumonia, CMV: cytomegalovirus, MAC: Mycobacterium avium complex, HCV: hepatitis C virus, HBV: hepatitis B virus, DRV/r: darunavir/ritonavir, RAL: raltegravir, DTG: dolutegravir, EFV: efavirenz, FPV/r: fosamprenavir/ritonavir, ART: antiretroviral therapy

There was no significant change in CD4⁺ T cell count, and a rate of successful viral suppression was maintained. The median CD4⁺ T cell counts were 448, 385, and 442 cells/µL at 0, 3, and 6 months, respectively, after switching from TDF to TAF. The rates of HIV RNA suppression (less than 100 copies/mL) were 93.5%, 90.3%, and 100% at 0, 3, and 6 months, respectively. All patients remained on ART during the study period. No events of bone fractures, acute coronary syndrome, and renal failure was occurred.
Biomarkers of renal function

The biomarkers of renal function such as the eGFR values calculated using creatinine, and with cystatin-C did not show any statistical change during the study period (Table 2). The rate of proteinuria decreased significantly after starting TAF-containing antiretroviral regimen.
Table 2

Analysis of serum and urine biomarkers before and after changing to tenofovir alafenamide among 31 patients

| Median                        | Duration after switching | p value |            |            |
|-------------------------------|--------------------------|---------|------------|------------|
|                               | 0 months | 3 months | 6 months | 0 months | 6 months |
| Serum creatinine (mg/dL)      |          |          |          |            |          |
|                               | 0.89 (0.68– 1.16)        | 0.90 (0.66– 1.11) | 0.89 (0.6– 1.25) | 0.179      | 0.098    |
| Estimated GFR using creatinine | 73.1(50.1– 108.4)        | 72.6 (53.2– 110.2) | 74.8 (47.2– 123.3) | 0.238      | 0.098    |
| Estimated GFR using cystatin-C | 91.2 (50.2– 130.5)        | 91.5 (56.4– 131.6) | 92.3 (56.4– 136.2) | 0.833      | 0.226    |
| Urine-NAG/urine-creatinine (U/g·Cr) | 3.72 (0– 56.9)          | 5.31 (0.83– 28.6) | 3.93 (0– 29.4) | 0.723      | 0.739    |
| Urine-L-FABP/urine-creatinine (μg/g·Cr) | 2.3 (0.6– 63.9)          | 1.8 (0.6– 31.2) | 1.5 (0.3–15) | 0.0166*   | 0.0002*  |
| %TRP                          | 85.1 (73.7– 92.7)        | 87.7 (73.6– 97.7) | 86.9 (74.2– 94.2) | 0.043*     | 0.200    |
| Serum inorganic phosphorus (mg/dL) | 3.1 (2.5–4.1)          | 3.0 (2.1–4.3) | 3.1 (2.2–4.7) | 0.992      | 0.841    |
| Proteinuria (%)               | 13.3             | 6.67        | 6.67        | 0.023*     | 0.023*    |
| Urine occult blood: Positive (%) | 6.7             | 6.7         | 10          | 0.573      | 0.973    |
| Serum LDL-cholesterol (mg/dL) | 106 (67–159)          | 132 (84–199) | 119 (82–207) | <0.0001*   | <0.0001* |
| Serum Triglyceride (mg/dL)    | 144 (41–874)         | 146 (47–700) | 175 (43–669) | 0.192      | 0.273    |
| Serum BAP (μg/L)              | 10.8 (7.0–21.6)       | 11.7 (6.2–21.1) | 11.0 (7.4–19.8) | 0.894      | 0.150    |
| Urine NTx/Urine Cr (nmol/mmol Cr) | 48 (27.4–84.9)         | 37 (20.2–83.4) | 32.8 (14.7–67.4) | 0.0034*   | <0.0001* |

* Urinalysis data were obtained from 30 of the 31 patients. GFR: glomerular filtration rate, NAG: N-acetyl-beta-D-glucosaminidase, L-FABP: liver-type fatty acid binding protein, TRP: tubular reabsorption of phosphate, LDL: low density lipoprotein, BAP: bone-specific alkaline phosphatase, NTx: N-terminal fragments of telopeptide

U-L-FABP/Cr ratios had significantly decreased at 3 and 6 months after switching to TAF, compared to the value before switching to TAF, as shown in Fig. 1a) (-0.5 μg/g·Cr at 3 months, and − 0.8 μg/g·Cr at 6
months; \( p = 0.0166 \) at 3 months, \( p = 0.0002 \) at 6 months). U-NAG/Cr ratios did not show any statistical change during the study period.

The value of %TRP had significantly increased at 3 months (\( p = 0.026 \)), but the rate of change in each patient was low.

**Lipid profile and biomarkers of bone metabolism**

Low density lipoprotein-cholesterol (LDL-C) levels significantly increased at 3 months and 6 months compared to the baseline (+26 mg/dL at 3 months, and +13 mg/dL at 6 months; \( p < 0.0001 \)) (Fig. 1b)). The significance was maintained regardless of co-administration with other ARVs, or hyperlipidemia at baseline.

BAP levels had not changed during the study period. The U-NTx/Cr ratios decreased during the study period, and there were statistical significances between all the points (-11 nmol/mmol Cr at 3 months, -15.2 nmol/mmol Cr at 6 months; \( p = 0.0069 \) at 3 months, \( p < .0001 \) at 6 months) (Fig. 1c)).

**Discussion**

In this study, we reported the changes in biomarkers of renal function and bone metabolism, and lipid profile when switching from TDF to TAF in HIV-infected patients. During the study, all the patients continued the TAF-containing regimen of ARVs that showed potent viral suppression. There were no serious adverse effects in the first 6 months after switching to TAF-containing regimen.

There were no noticeable changes in the eGFR calculated using creatinine levels, and cystatin-C levels during the study period. The L-FABP levels and the rate of proteinuria were significantly decreased. These results might be subclinical for majority of the participants without having CKD. However, it has been reported that the renal function in Japanese HIV-infected patients decreased depending on the duration of treatment with TDF, especially in patients with low body weight (14). Another observational study of a 12-year period also showed that decreased eGFR occurred after 3 months of TDF-containing regimen of ARVs, which was also related to low body weight (15).

Because L-FABP was reported as a potential marker of CKD for patients without albuminuria(16), the detection of subclinical changes using urinary L-FABP prior to the progression to CKD is important in patients taking TAF, especially in those with low body weight.

The elevation of biomarkers of lipids such as LDL-C was observed to have significance. Previous studies have also shown the elevation in the LDL-C and TG levels, but the range of elevation depended on the observational period, and the characteristics of the participants (17–19). One of the major risks for hyperlipidemia that was identified after switching to TAF was the elevation at beginning in TG or LDL-C levels (20) although opposite results also reported (21). In our study, LDL-C levels increased regardless of the hyperlipidemia at baseline. This risk population, that needs lipid-lowering drugs after switching TAF from TDF, must be extensively studied in the future.
Among the biomarkers of bone metabolism, U-NTx significantly decreased in our study. Previous study showed TDF-sparing regimen decreased the level of biomarkers of bone metabolism such as osteocalcin and bone alkaline phosphatase (13), and switching from TDF to TAF also improved bone mineral density (22). Although it is unclear whether tenofovir directly influences osteoblasts, a change in gene expression was observed with tenofovir exposure in vitro (23). Because U-NTx levels related bone mineral density levels in older men and women(24), U-NTx could also be used to predict current osteoporosis in TDF-exposure patients.

Here, the renal function and bone metabolism had improved within 6 months after switching to TAF. However, attention must be drawn to whether the lipid metabolism could be elevated up to the level that needs statin treatment.

According to patients’ genetic background (25, 26) the presence of various comorbidities, and body weight (14), clinicians might be required to determine whether to continue TDF or switch to TAF to prevent the progression to renal tubular dysfunction or metabolic disorders, using biomarkers such as urinary L-FABP and NTx. Its tailor-made design would help lives without disabilities of HIV-infected patients on ARVs.

Nevertheless, there were some limitations to our study. First, the information on the changes in lifestyle, such as new exercise habits and dietary patterns, were not collected using a questionnaire, although the treating physicians had recorded the changes in lifestyle and adherence to ARVs during each visit and no other drugs was changed. Second, the study did not have long observational period. Finally, this study was a single-centered observational study, and all except one was Japanese.

**Conclusions**

The TAF-containing regimen of ARVs could be safe with potent viral suppression for 6 months after switching from a TDF-containing regimen of ARVs. Switching from TDF to TAF decreased the levels of biomarkers such as urinary L-FABP and NTx but increased LDL-C levels. These biomarkers might be useful to detect serious adverse drug reaction early.

**Abbreviations**

HIV – Human immunodeficiency virus

ARV – Antiretrovirals

TDF – Tenofovir disoproxil fumarate

TAF – Tenofovir alafenamide

eGFR – Estimated glomerular filtration rate
Declarations

Ethics approval and consent to participate

The study was approved by the research ethics committee of the Faculty of Medicine of the University of Tokyo. All the patients provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MI designed this study, acquired and analyzed the patients’ data and samples, and was a major contributor in writing the manuscript. YW and SO enrolled the patients in this study and collected the samples. KO, SY, SO, and KM revised the manuscript. All authors have read and approved the final manuscript.

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Figures
Figure 1

Rate of change in biomarkers before and after switching from tenofovir disoproxil to tenofovir alafenamide. Vertical axis represents the rate of change (%) of each biomarker compared to the baseline (before switching antiretrovirals) a) Rate of change in urine-liver-type fatty acid binding protein/creatinine (L-FABP/Cr) levels b) Rate of change in low-density lipoprotein cholesterol (LDL-C) levels c) Rate of change in urine-N-terminal telopeptide/creatinine (U-NTx/Cr) levels