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Changes in Body Mass Index and Atherosclerotic Disease Risk Score After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide

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Background. Switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF)-containing antiretroviral therapy (ART) can improve renal function and bone mineral density in people with human immunodeficiency virus (PWH). The switch can also negatively influence cholesterol, but changes in body mass index (BMI) and atherosclerotic cardiovascular disease (ASCVD) risk are unknown.

Methods. This retrospective observational study evaluated BMI and ASCVD risk score changes in virologically suppressed PWH who switched from TDF to TAF without switching other ART regimen components. Adults on TDF for ≥ 1 year with 2 consecutive HIV ribonucleic acid values < 200 copies/mL before a TAF switch were included. Body weight, BMI, cholesterol, and ASCVD risk score were collected for the year before and after the switch. Pre- and postswitch values were compared with the Wilcoxon signed-rank test. Changes in BMI and ASCVD scores were modeled using generalized estimating equations regression.

Results. One hundred ten patients were included. In unadjusted analyses, there were significant increases in weight, BMI, total cholesterol, LDL, HDL, and ASCVD risk score in the year after switching from TDF to TAF (each $P \leq .01$). In regression models, switching from TDF to TAF was associated with a 0.45 kg/m^2 increase in BMI (95% confidence interval [CI], 0.14–0.76) and a 13% increase in ASCVD risk score (95% CI, 4%–23%).

Conclusions. We observed significant BMI and ASCVD score increases in PWH 1 year after switching from TDF to TAF. The mechanism of changes is unclear and requires additional study.

Keywords: BMI; cardiovascular disease risk; HIV; tenofovir alafenamide; weight gain.

Switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF)-containing antiretroviral therapy (ART) can maintain virologic efficacy, while preserving or improving renal function and bone mineral density in people with human immunodeficiency virus (PWH) [1–3]. The switch may also negatively influence cholesterol. Patients that switched to TAF-containing ART in clinical trials had significant increases in total (Tchol) high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) cholesterol levels [3–5]. The impact of these changes on atherosclerotic cardiovascular

disease (ASCVD) risk is unclear [6]. In addition, recent studies suggest that initiating TAF alongside an integrase inhibitor in treatment-naïve patients or switching from TDF to TAF in treatment-experienced patients can lead to weight gain [7, 8]. Patients in the switch study often had changes in other ART regimen components, thereby confounding the ability to analyze TAF alone [7]. The purpose of this study was to determine whether changes in weight, body mass index (BMI), and ASCVD risk score occur after switching from TDF to TAF, without switching other ART regimen components.

METHODS

This was a retrospective, observational study involving virally suppressed PWH who switched from TDF to TAF-containing ART between January 2016 and March 2018 at an urban, academic medical center. Institutional review board approval was obtained before data collection. Adult patients on TDF-containing ART for at least 1 year were included if they had evidence of persistent viral suppression. This was defined as having at least 2 consecutive human immunodeficiency virus (HIV) viral load values < 200 copies/mL and no values > 200

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copies/mL in the year before the TAF switch. Patients were excluded if any other component of their ART regimen changed in the year before or after the TAF switch.

Demographic data including age, sex, and race were extracted from medical records of eligible patients along with preswitch CD4 cell counts, concomitant ART agents, duration of HIV infection, and total years on ART. Any non-ART medications prescribed for chronic use in the year after the TDF to TAF switch were also collected. Each non-ART medication was labeled as being associated with weight gain, weight loss, or no weight change according to package labeling.

To assess the study endpoints, body weight, BMI, Tchol, LDL-C, HDL-C, and triglyceride values were collected for the year before and after the switch. Pre- and postswitch median values for each of these parameters were then calculated.

To determine pre- and postswitch ASCVD risk scores, the 2018 American College of Cardiology/American Heart Association guidelines on treating blood cholesterol were used [6]. According to these guidelines, ASCVD scores can estimate the 10-year risk of a cardiovascular event in patients between 40 and 75 years old. As a result, only patients between these ages with all other necessary data points to perform the ACSVD calculation were assessed. Using age, sex, race, cholesterol, blood pressure, diabetes, and smoking status, ASCVD risk scores were generated for all eligible patients at the time of the ART switch and between 6 and 12 months thereafter for comparison.

Statistical Analysis

Patient demographics were summarized with counts and percentages for categorical variables and summarized with means and standard deviations or medians and interquartile ranges (IQRs) for numeric variables. Unadjusted distributions of the pre- and postswitch values for all study endpoints were summarized with medians and IQRs and compared with Wilcoxon signed-rank tests. To further investigate the association of switching from TDF to TAF with BMI and ASCVD risk score, 2 separate generalized estimating equation regression models were constructed. The covariates selected as candidates for each model included the following: a pre- versus post-TAF switch indicator, age, sex, race, concomitant medications that can cause weight gain, concomitant medications that can cause weight loss, and time since HIV diagnosis. Two-way interactions with covariates and the pre- versus post-TAF indicator were also assessed. Interaction and main effect terms were removed from the model one at a time using a hierarchical variable selection procedure (ie, never removing a main term that is part of an interaction term in the model) with a final retention criterion of 0.05. The ASCVD risk scores were highly right-skewed, so those data were log-transformed before modeling. All the analyses and visualizations were performed and created with SAS 9.4 (SAS Institute Inc., Cary, NC). The significance level of each test was $\alpha = 0.05$.

RESULTS

A total of 110 patients met study criteria and were included in the analysis (Table 1). The majority were African American (58.2%) and male (72.7%) with a mean age of 50 years old. Patients had been living with HIV and receiving ART for a median of 12 and 8 years, respectively, with persistent viral suppression and immunologic recovery in response to ART. Approximately half of the patients were receiving integrase inhibitor-based regimens before their TAF switch.

The majority of subjects (65.5%) were either overweight or obese at the time they switched to TAF. The median patient weight was more than 185 pounds with a BMI of 28 kg/m². In the year after their switch to TAF, patients had significant unadjusted increases in both weight and BMI. On average, patients gained 3 pounds and their BMI increased by 0.5 kg/m² (each $P \leq .01$) (Table 2). In the regression model for BMI, only sex was retained as a covariate. The results of the model were consistent with the unadjusted analysis, suggesting that switching from TDF to TAF was associated with a 0.45 kg/m² mean increase in BMI (95% confidence interval [CI], 0.14–0.76).

Unadjusted analyses also showed significant increases in Tchol, LDL-C, and HDL-C in the year after patients switched from TDF to TAF (each $P \leq .01$) (Table 2). It is notable that, although the total cholesterol to HDL-C ratio did not change significantly after the switch, significant changes in ASCVD risk scores were observed. A total of 91 of 110 patients were between the ages of 40 and 75 and were eligible for ASCVD score calculations. Of these, 68 had all other data necessary to perform the calculations both before and after the switch. For these patients, the median ASCVD score rose from 6.9% to 8.1% after switching to TAF ($P < .01$). Our regression model, adjusting for age, sex, race, concomitant medications that can cause weight gain, and time with HIV, suggested that switching from TDF to TAF was associated with a 13% average increase in ASCVD risk score (95% CI, 4%–23%).

DISCUSSION

We observed significant increases in both BMI and ASCVD risk in PWH who switched from TDF to TAF without changing any other ART regimen components. Importantly, patients in these analyses had longstanding HIV infection that was persistently controlled by ART. Patients were also at or above a normal BMI when switching to TAF. Therefore, it is unlikely that the weight gain patients experienced in this study represented a return to health, which commonly occurs after individuals initiate ART for the first time [9, 10].

In patients with advanced HIV who are underweight before starting ART, weight gain can prolong survival [11, 12]. In contrast, being overweight when initiating treatment or becoming obese on ART can increase a patient's risk for dyslipidemia, diabetes, hypertension, and cardiovascular disease (CVD) [13–15].

Table 1. Demographics and Other Patient Characteristics Summary

Characteristic	All Patients (n = 110)
Age, mean (SD)	50 (11.7)
Sex, n (%)	
Male	80 (72.7)
Female	30 (27.3)
Race, n (%)	
African American	64 (58.2)
White	38 (34.5)
Hispanic	6 (5.5)
Asian	2 (1.8)
Years since HIV diagnosis, median (IQR)	12.0 (11.0)
Years on ART, median (IQR)	8.0 (8.0)
Preswitch CD4 count (cell/mm ³), median (IQR)	627.5 (381.0)
Preswitch BMI category, n (%)	
Underweight	4 (3.6)
Normal weight	34 (30.9)
Overweight	31 (28.2)
Obese	41 (37.3)
Other ART agent, n (%)	
Integrase inhibitor	54 (49.1)
Protease inhibitor	18 (16.4)
Nonnucleoside reverse-transcriptase inhibitor	32 (29.1)
Other	6 (5.4)
Concomitant medication cause weight gain, n (%)	34 (30.9)
Concomitant medication cause weight loss, n (%)	29 (26.4)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

This is concerning because obesity is becoming increasingly prevalent in PWH, and these individuals already carry a disproportionate risk for CVD [16–18]. More than half of the patients in this analysis were overweight or obese at baseline and experienced modest increases in BMI 1 year after switching to TAF. Importantly even modest increases in BMI may be clinically relevant. In a recent analysis of over 9000 PWH enrolled in the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study, the risk of diabetes and CVD increased by approximately 20% per unit of BMI gained in the year after starting ART [13]. The extent to which the BMI changes we observed after

switching ART could influence a patient's risk of developing diabetes or CVD is unclear.

In terms of dyslipidemia, we observed significant increases in Tchol, LDL-C, and HDL-C in our patients after switching to TAF. These findings are consistent with observations from clinical trials. Also consistent with previous trials, we did not observe changes in Tchol/HDL-C ratios. Current guidelines on treating blood cholesterol recommend calculating an ASCVD risk score using cholesterol data in addition to a person's age, sex, race, blood pressure, and smoking status [6]. When performing this assessment for our patients, we observed a 13% increase in ASCVD risk scores after switching to TAF. This resulted in many patients becoming eligible for treatment with a statin medication for ASCVD risk reduction. More specifically, before TAF, the median ASCVD risk score in our sample was 6.9%, indicating that over half (53.3%) of the sample was below the threshold of 7.5% to meet statin eligibility criterion. After switching to TAF, the average 13% increase in ASCVD risk scores shifted 50.7% of our sample over the 7.5% statin criterion. Taken together with the increases in BMI and cholesterol, the changes in ASCVD risk score may indicate an increased risk for CVD in PWH after switching from TDF to TAF.

This study has several limitations. First, as an observational study, the results cannot establish causal relationships between TAF and increases in BMI or ASCVD risk. Second, as a retrospective chart review, we relied on the accuracy and completeness of medical records, but omissions or inaccuracies that influenced the results were possible. In addition, although we made every attempt to control for confounding variables with restrictive inclusion criteria and statistical analyses, it remains possible that data not measured or collected could have influenced our results. For example, we were unable to collect data on patients' caloric intake and physical activity. Finally, our cohort was predominantly African American and male from a single academic center in the Northeastern United States. As a result, the findings may not be generalizable to other populations. Given these limitations, additional investigations will be necessary to determine whether there are causal relationships

Table 2. Unadjusted Outcomes Summary

Outcome Variable	Preswitch (TDF)	Postswitch (TAF)	Change (Post–Pre)	P Value
Weight (lbs), median (IQR)	185.4 (55.8)	190.5 (60.5)	3.0 (9.2)	<.01
BMI (kg/m ²), median (IQR)	28.0 (10.8)	28.2 (10.0)	0.5 (1.4)	<.01
Total cholesterol, median (IQR)	173.8 (44.0)	195.0 (42.0)	12.5 (32.3)	<.01
LDL cholesterol, median (IQR)	98.6 (40.2)	112.1 (46.6)	8.2 (21.0)	<.01
HDL cholesterol, median (IQR)	51.0 (19.0)	55.8 (24.0)	3.0 (12.0)	<.01
Total to HDL cholesterol ratio, median (IQR)	3.5 (1.6)	3.5 (1.7)	0.1 (0.6)	.25
Triglyceride levels, median (IQR)	103.5 (68.0)	109.5 (93.0)	4.0 (64.0)	.28
Atherosclerotic CVD risk score, median (IQR)	6.9 (8.1)	8.1 (10.9)	0.4 (1.9)	<.01
Creatinine clearance, median (IQR)	104.0 (38.0)	102.5 (42.0)	–1.0 (17.0)	.82

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

between TAF exposure and increases in BMI or ASCVD risk. If relationships do exist, the associated mechanisms and any additional risk factors should be determined to optimize treatment for all PWH.

CONCLUSIONS

We observed significant increases in BMI and ASCVD risk in PWH 1 year after a switch from TDF to TAF without changes in other ART regimen components. The mechanisms associated with these metabolic changes are unclear and require additional study.

Acknowledgments

Author contributions. J. J. S. and K. N. S. contributed to study concept and design. J. J. S., K. N. S., J. R. O., and J. A. D. contributed to acquisition, analysis, or interpretation of data. A. S. and S. W. K. performed statistical analysis. J. J. S. and J. R. O. drafted the manuscript. J. J. S., K. N. S., J. R. O., A. S., S. W. K., and J. A. D. critically reviewed and revised the manuscript.

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