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Weight and Metabolic Changes After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in People Living With HIV

A Cohort Study

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Background: Tenofovir-based antiretroviral therapy (ART) has become first-line in all major HIV treatment guidelines. Compared with tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) has a favorable renal and bone safety profile, but concerns about metabolic complications remain.

Objective: To assess weight changes, the development of overweight/obesity, and changes in lipid levels 18 months after replacing TDF with TAF.

Design: Cohort study.

Setting: 5 university hospitals, affiliated hospitals, and private physicians in Switzerland.

Participants: 4375 adults living with HIV who received TDF-containing ART for 6 months or longer.

Measurements: Changes in weight and lipid levels were assessed using mixed-effect models. Differences in proportions of newly overweight/obese participants were calculated using 2-proportions *Z* tests.

Results: 4375 individuals were included, with follow-up between 1 January 2016 and 31 July 2019. Median age was 50 years (interquartile range, 43 to 56 years), 25.9% were female, and 51.7% had a normal body mass index (BMI); 3484 (79.6%) switched to TAF and 891 (20.4%) continued TDF. After 18 months, switching to TAF was associated with an adjusted mean weight increase of 1.7 kg (95% CI, 1.5 to 2.0 kg), compared with 0.7 kg (CI, 0.4 to 1.0 kg) with the continued use of TDF (between-group difference, 1.1 kg [CI, 0.7 to 1.4 kg]). Among individuals with a normal BMI, 13.8% who switched to TAF became overweight/obese, compared with 8.4% of those continuing TDF (difference, 5.4 percentage points [CI, 2.1 to 8.8 percentage points]). Switching to TAF led to increases in adjusted mean total cholesterol (0.25 mmol/L [9.5 mg/dL]), high-density lipoprotein cholesterol (0.05 mmol/L [1.9 mg/dL]), low-density lipoprotein cholesterol (0.12 mmol/L [4.7 mg/dL]), and triglyceride (0.18 mmol/L [16.1 mg/dL]) levels after 18 months.

Limitation: Short follow-up, small subgroup analyses, and potential residual confounding.

Conclusion: Replacing TDF with TAF is associated with adverse metabolic changes, including weight increase, development of obesity, and worsening serum lipid levels.

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Tenofovir plays an important role in antiretroviral therapy (ART) for people living with HIV (PLWH) and is recommended as part of the first-line regimens in all major HIV treatment guidelines (1–4). Tenofovir disoproxil fumarate (TDF) has been associated with proximal renal tubulopathy and loss of bone mineral density (5–7). The more favorable bone and renal safety profile of tenofovir alafenamide (TAF) (8–10) led to the replacement of TDF with TAF in most ART guidelines (2–4). However, TAF is not part of the World Health Organization's preferred first-line regimens due to concerns about metabolic side effects (1). In treatment-naive patients, TAF was associated with rising blood lipid levels and an increased need for lipid-lowering therapy compared with TDF (11), and recent data indicate that TAF leads to a substantially larger increase in weight compared with TDF in PLWH initiating ART (12, 13).

So far, weight and metabolic changes have been assessed mainly in ART-naive patients, which makes the interpretation of results challenging. Because effective HIV treatment reduces the infection-associated catabolism, and thereby leads to weight increases in the first months after starting ART (14), it is difficult to differentiate between metabolic changes due to the return to health and adverse drug reactions in individuals initiating ART. In addition, most data on weight and metabolic changes were gathered among selected participants in clinical trials, and data from well-described real-world cohorts are scarce. We used data from the Swiss HIV Cohort Study (SHCS) to assess weight changes and metabolic outcomes in PLWH receiving stable ART who switched from TDF to TAF.

See also:
Summary for Patients

METHODS

Study Population

The SHCS (www.shcs.ch) is an ongoing, nationally representative cohort study that was established in 1988. It includes close to 80% of all PLWH receiving ART in Switzerland who are followed in 1 of 5 university hospitals, 2 regional hospitals, or 15 affiliated hospitals or by 1 of 36 private physicians (15). Laboratory values, sociodemographic data, and clinical data are prospectively recorded at registration and every 6 months thereafter using a standardized protocol (http://shcs.ch/292-instructions). Assessments at every follow-up visit include weight measurement, documentation of all changes in medication (including ART and comedications), and glucose and lipid measurements at accredited laboratories (https://shcs.ch/173-laboratories). Data quality and consistency are ensured by quality checks and regular site visits of participating centers. All centers' local ethical committees approved the cohort study, and all patients provided written informed consent.

For the present study, we considered all participants with follow-up between January 2016, the year in which TAF was approved in Switzerland, and 31 July 2019 (database closure). We included patients who were receiving a TDF-containing treatment for at least 6 months and either continued TDF until the end of the study period or had TDF replaced by TAF. We defined the index visit as the switching date for patients who had TDF replaced with TAF, and a random sample of these switching dates was selected and assigned to individuals who continued TDF. All individuals with any follow-up after the index visit were included, and follow-up of individuals who stopped TAF before the end of the observation period was censored at that time. We excluded patients who received different nucleoside reverse transcriptase inhibitors (NRTIs) between the use of TDF and TAF and women who were pregnant during the study period.

Outcomes and Definitions

The primary aims were to compare weight trajectories over time between individuals who continued TDF and those who had TDF replaced by TAF and to estimate the differences in weight between the index visit and 18 months thereafter. To account for different changes in weight before the index visit, we included all weight measurements from 2.5 years before that date until the end of each individual's follow-up. The main exposure of interest was switching from TDF to TAF. Secondary outcomes were the proportion of individuals who became overweight or obese (body mass index [BMI] >25 kg/m^2), mean changes in lipid levels (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides, and total cholesterol–HDL ratio), and the incidence of diabetes after the index visit. Weight categories were classified according to BMI as normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), obese (≥30 kg/m^2), and underweight (<18.5 kg/m^2) (16). Diabetes at the index visit was defined as a hemoglobin A_{1c} level of 6.5% or greater or treatment with antidiabetic medication, and history of cardiovascular disease included myocardial infarction, cerebral infarction, coronary angioplasty or stenting, coronary artery bypass grafting, or any procedure on peripheral arteries. Incident diabetes was defined as a hemoglobin A_{1c} level of 6.5% or greater, a fasting glucose level greater than 7.0 mmol/L, or random glucose levels greater than 11.0 mmol/L on at least 2 visits or the start of use of any antidiabetic drug after the index visit. The occurrence of cardiovascular events or elevations of hemoglobin A_{1c} are reported by the treating cohort physician using standardized forms.

Statistical Analysis

Patient characteristics were compared between individuals who continued TDF and those who switched to TAF using χ^2 and Wilcoxon rank-sum tests. Crude weight trajectories over time were presented using locally estimated scatter plot smoothing. Adjusted mean changes in weight over time in absolute values were estimated using 2-level multivariable mixed-effect models, with random intercepts for each individual nested within the corresponding cohort site and random slopes for time on the individual level. To allow the weight trajectories to be nonlinear, time was modeled using restricted cubic splines with the numbers of knots chosen to minimize Bayesian information criteria. The first knot was positioned at the index visit because trajectories were expected to change at that time, and the remainder of the knots were evenly spaced at percentiles 33.3 and 66.6 of the available follow-up time thereafter (0, 7.1, and 14.8 months). Because all individuals were receiving TDF before the index visit, and crude weight trajectories before the index visit were similar between individuals who continued TDF and those who switched to TAF after the index visit, preindex weight trajectories for both groups were combined to improve model fit. Covariates were prespecified characteristics that were potentially associated with weight increase, the decision to switch to TAF, or both. Multivariable analyses for weight were adjusted for sex, African origin, age, time since ART initiation, CD4 cell count, and index visit values of weight and estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula). In addition, we included the third ART drug component used after the switch, categorized as integrase strand transfer inhibitors (INSTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs). The self-reported use of weight-modifying drugs (for example, antidiabetics, neuroleptics, systemic corticosteroids [17]), smoking status (yes or no), and physical activity (exercising more than twice a week, 1 to 2 times per week, 1 to 4 times per month, or never) were included as time-varying covariates. We assessed model fit with Bayesian information criteria and compared models using likelihood ratio tests. Because there was evidence for effect modification by weight at the index visit, we included an interaction term with this variable and showed trajectories stratified by 3 weight categories based on index weight tertiles. In exploratory analyses, the joint effect of sex and African origin and the influence

of the third drug used in the ART regimen after the index visit on the association between the main exposure variable and weight was assessed using interaction terms. Interactions with sex, African origin, and the third drug did not improve model fit, so these variables were included only as covariates in the final model. Differences in proportions of individuals who became overweight or obese were calculated using 2-proportions *Z* tests.

Mean differences in serum lipid levels were estimated similarly to weight analyses using the same random-effects structure and were adjusted for age, sex, African origin, and individual lipid level at the index visit and for the time-varying values of weight, physical activity, and the use of lipid-lowering drugs (including statins, fibrates, and nicotinic acid). Analyses on incidence rate ratios of new-onset diabetes were restricted to individuals without diabetes at the index visit and were calculated using quasi-Poisson regression adjusted for age, sex, African origin, and BMI, including an offset for the total number of follow-up years. All statistical analyses were performed using R, version 4.0.0 (18).

Sensitivity Analyses

Weight analyses restricted to individuals with at least 6 and 12 months of follow-up were performed to examine potential attrition bias. To limit the effect of replicating HIV infection on weight, we conducted a sensitivity analysis restricted to individuals with an HIV viral load of less than 50 copies/mL during the prior year and throughout follow-up. To minimize confounding by other ART components, we performed an analysis restricted to individuals who had TDF replaced with TAF, with the rest of the regimen left unchanged. We repeated the weight analysis in those who switched from an abacavir (ABC)–containing ART to TAF to investigate whether weight changes are associated with starting TAF or stopping TDF, as a protective effect of the latter on serum lipid levels has been shown previously (19).

Role of the Funding Source

The present study was funded by the SHCS, supported by the Swiss National Science Foundation. The funders had no role in the study design, data collection, analysis, interpretation, or writing of the manuscript. The corresponding author had full access to all of the data and was responsible for the decision to submit this article.

RESULTS

Study Population

Of 10 674 participants under follow-up, 8047 had received TDF for more than 6 months. We excluded 3149 individuals who switched from TDF to a different NRTI, 474 without follow-up after the index visit, and 49 women who became pregnant. The study population included 4375 individuals; the median age was 50 years (interquartile range [IQR], 43 to 56 years), 25.9% were female, and 51.7% had a normal BMI. Of the 4375 participants, 891 (20.4%) continued TDF until the end of the study and 3484 (79.6%) switched to TAF (**Appendix Figure 1**, available at Annals.org). Patients who switched to TAF were more likely to be male and men having sex with men, were less likely to be of African origin, had a lower estimated glomerular filtration rate, and were more likely to receive INSTI-based regimens than those who continued TDF (**Table 1**). The median follow-up was 17.1 months (IQR, 9.6 to 21.3 months) in individuals who switched to TAF and 17.5 months (IQR, 13.0 to 21.2 months) in those who continued TDF. Individuals in both groups were assessed at a median of 3 follow-up visits after the index visit, and 20 (2.2%) who continued TDF and 60 (1.7%) who switched to TAF were lost to follow-up. Observations were missing in less than 2% of visits for all covariates (**Appendix Table 1**, available at Annals.org).

Changes in Weight

Crude weight trajectories were similar before the index visit and diverged thereafter (**Figure 1**, *top*; **Appendix Figure 2**, available at Annals.org). In unadjusted analyses, switching to TAF was associated with a mean weight increase of 1.8 kg (95% CI, 1.6 to 2.0 kg) 18 months after the index visit, compared with 0.7 kg (CI, 0.4 to 1.0 kg) with the continuous use of TDF (between-group difference, 1.1 kg [CI, 0.7 to 1.4 kg]). These estimates remained similar after adjustment for confounders (**Table 2**; **Figure 1**, *middle*; **Appendix Table 2** and **Appendix Figure 3**, available at Annals.org). **Figure 1** (*bottom*) describes changes in BMI categories at 18 months compared with the index visit in all patients with available weight measurements. Among individuals with a normal BMI at the index visit and available follow-up at 18 months, 211 of 1529 (13.8%) who switched to TAF became overweight or obese after 18 months, compared with 35 of 419 (8.4%) who continued TDF (difference, 5.4 percentage points [CI, 2.1 to 8.8 percentage points]).

The use of TAF was associated with statistically significant increases in adjusted mean weight regardless of sex or origin (**Table 2**). Between-group weight differences of TAF compared with TDF were most pronounced among women of African origin (1.5 kg [CI, 0.4 to 2.5 kg]), followed by women of non-African origin (1.4 kg [CI, 0.2 to 2.7 kg]) and men of non-African origin (1.1 kg [CI, 0.7 to 1.5 kg]), and were not significant among men of African origin ($P < 0.001$ for the joint interaction with African origin and sex). Weight increases while receiving TAF were observed regardless of the third drug used after the index visit ($P = 0.055$ for interaction [**Table 2**]), and the magnitude of weight increases diminished with higher index visit weight and BMI (**Figure 2**; **Table 2**; **Appendix Figure 4**, available at Annals.org).

Sensitivity Analyses of Weight Changes

Analyses based on individuals with at least 6 and 12 months of follow-up showed similar weight changes as the main analysis (**Appendix Table 3**, available at Annals.org). In an analysis restricted to individuals with continuously suppressed HIV viral load, switching to TAF remained associated with an adjusted weight increase of 1.8 kg (CI, 1.6 to 2.1 kg), compared with 0.5 kg (CI, 0.2 to 0.8 kg) in those continuing TDF (**Appendix Figure 5**, available at

Table 1. Characteristics of the Study Population at the Index Visit

Characteristic	Continued TDF (*n* = 891)	Switched to TAF (*n* = 3484)	*P* Value
Women, *n (%)*	272 (30.5)	861 (24.7)	<0.001
Median age (IQR), *y*	49 (42–55)	50 (43–56)	0.017
African origin, *n (%)*	180 (20.2)	462 (13.3)	<0.001
Transmission group, *n (%)*			<0.001
Men having sex with men	373 (41.9)	1732 (49.7)	
People who inject drugs	77 (8.6)	356 (10.2)	
Other	441 (49.5)	1396 (40.1)	
Median CD4 count (IQR), *cells/μL**	637 (485–824)	658 (498–859)	0.097
Median CD4 nadir (IQR), *cells/μL**	221 (109–323)	215 (113–325)	0.98
Median duration of ART before index visit (IQR), *y*	11.3 (6.5–18.3)	11.4 (6.6–19.3)	0.54
Median duration of TDF therapy before index visit (IQR), *y*	7.7 (5.1–11.0)	8.2 (5.2–11.0)	0.21
Median eGFR, (IQR), *mL/min*	96.0 (82.0–107.0)	87.9 (74.8–101.1)	<0.001
Diabetes, *n (%)*	38 (4.3)	186 (5.3)	0.23
History of CV disease, *n (%)*	49 (5.5)	240 (6.9)	0.157
Smoker, *n (%)*	331 (37.1)	1309 (37.6)	0.138
Receiving lipid-lowering therapy, *n (%)*	130 (14.6)	555 (15.9)	0.35
Median weight (IQR), *kg*	74 (65–84)	74 (65–84)	0.52
Median BMI (IQR), *kg/m²*	24.5 (22.1–27.5)	24.4 (22.1–27.3)	0.49
BMI category at the index visit, *n (%)*			0.147
Normal (18.5–24.9 kg/m²)	445 (49.9)	1816 (52.1)	
Overweight (25–29.9 kg/m²)	272 (30.5)	1097 (31.5)	
Obese (≥30 kg/m²)	122 (13.7)	405 (11.6)	
Underweight (<18.5 kg/m²)	37 (4.2)	132 (3.8)	
Third drug used at index visit, *n (%)*			<0.001
INSTI	189 (21.2)	1333 (38.3)	
PI	84 (9.4)	741 (21.3)	
NNRTI	606 (68.0)	1390 (39.9)	
Median total cholesterol level (IQR)			0.73
mmol/L	4.9 (4.2–5.5)	4.8 (4.2–5.5)	
mg/dL	186 (16–214)	186 (162–214)	
Median HDL cholesterol level (IQR)			0.070
mmol/L	1.3 (1.1–1.6)	1.3 (1.0–1.6)	
mg/dL	50 (41–61)	49 (39–60)	
Median LDL cholesterol level (IQR)			0.136
mmol/L	2.8 (2.2–3.4)	2.7 (2.2–3.4)	
mg/dL	108 (87–132)	106 (83–130)	
Median triglyceride level (IQR)			<0.001
mmol/L	1.2 (0.9–1.9)	1.4 (1.0–2.1)	
mg/dL	108 (80–168)	124 (89–186)	
Median total cholesterol–HDL ratio (IQR)	3.7 (3.0–4.6)	3.8 (3.1–4.7)	0.039

ART = antiretroviral therapy; BMI = body mass index; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; INSTI = integrase strand transfer inhibitor; IQR = interquartile range; LDL = low-density lipoprotein; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
* To convert to SI units (× 10^9 cells/L), multiply by 0.001.

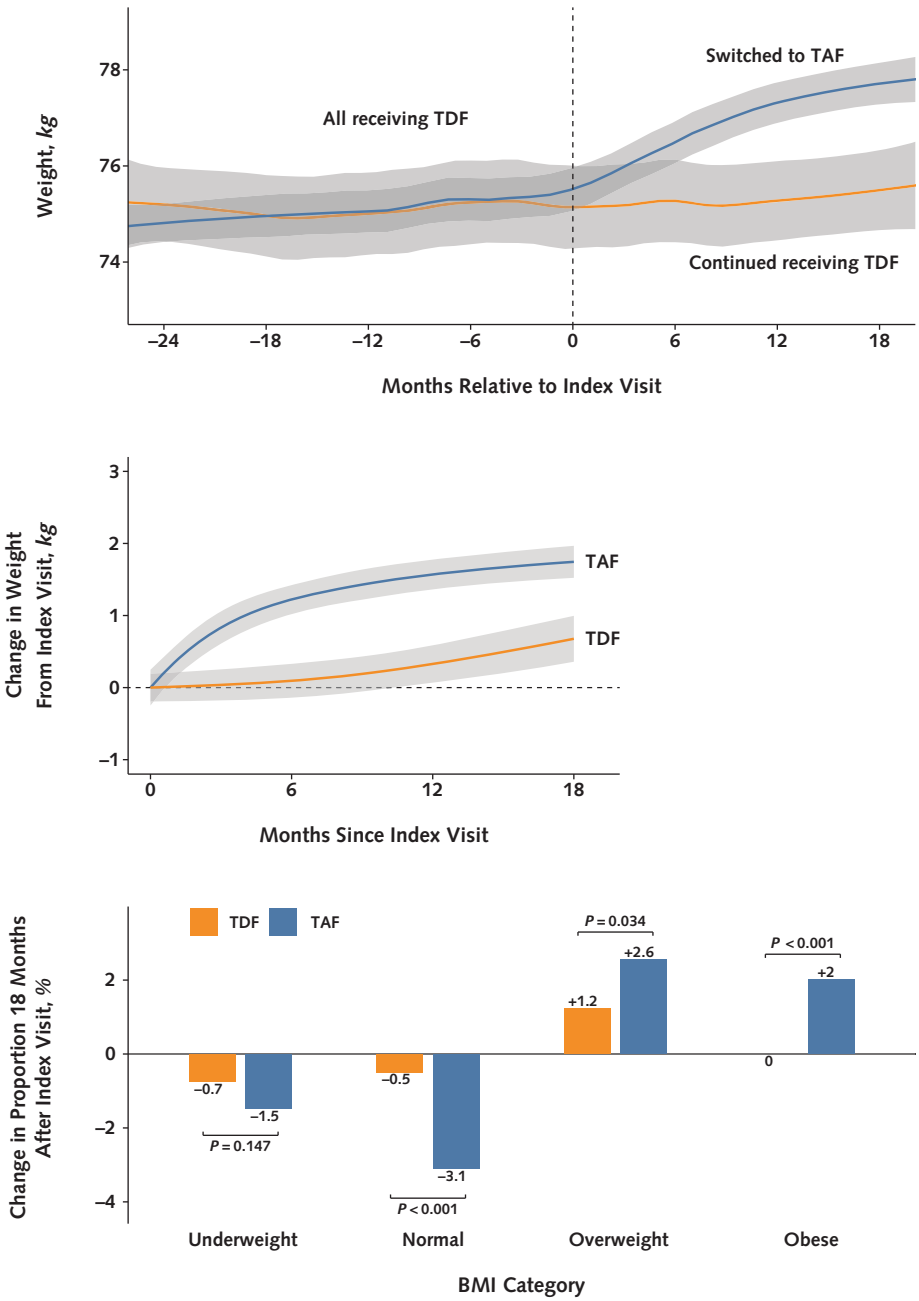
Annals.org). When including only individuals who had TAF replaced by TDF without further changes in ART, TAF remained associated with significant increases in weight, regardless of the third drug used (**Appendix Table 4**, available at Annals.org). Finally, switching from ABC to TAF was associated with a weight increase of 1.7 kg (CI, 1.0 to 2.4 kg) after 18 months, compared with 0.5 kg (CI, 0.3 to 0.7 kg) with the continuous use of ABC (between-group difference, 1.2 kg [CI, 0.5 to 1.9 kg]) (**Figure 3**).

Lipid and Glucose Levels

At the index visit, triglyceride levels and total holesterol–HDL ratios were slightly higher in individuals who switched to TAF than in those who continued TDF, whereas total cholesterol, HDL cholesterol, and LDL cholesterol levels were similar between groups (**Table 1**). Observations were missing in less than 2.5% of all follow-up visits (**Appendix Table 1**). Eighteen months after the index visit, switching to TAF was associated with increases in total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels, whereas decreases in total cholesterol and LDL cholesterol levels were observed with the continuous use of TDF (**Figure 4**; **Appendix Table 5**, available at Annals.org). During follow-up, 127 individuals (3.6%) who switched to TAF started a new lipid-lowering treatment, compared with 30 (3.4%) who continued using TDF (difference, −0.3 percentage point [CI, −1.7 to 1.1 percentage points]).

Among 4151 individuals without diabetes at the index visit, 4150 (99.9%) contributed to 5616 person-years of follow-up. The crude incidence rate of new-onset diabetes among individuals who switched to TAF was 1.1 per 100 person-years compared with 0.9 per 100 person-years among those who continued TDF (unadjusted incidence rate ratio, 1.2 [CI, 0.6 to 2.6]). After adjustment for age, sex, African origin, and BMI at the index visit, the incidence rate ratio for new-onset diabetes was 1.3 (CI, 0.7 to 2.8) (**Appendix Table 6**, available

Figure 1. Changes in weight and BMI categories over time.



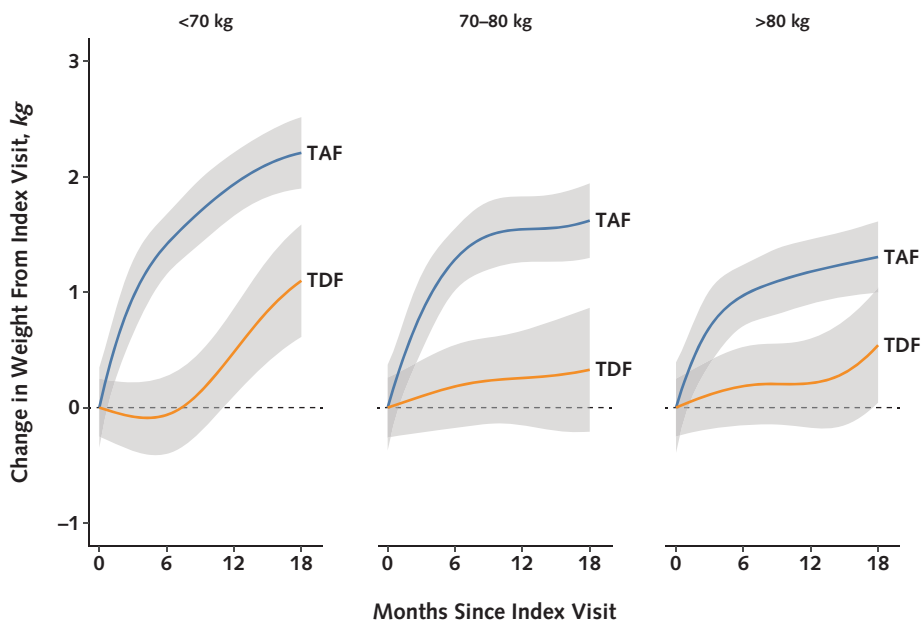
BMI = body mass index; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate. **Top.** Crude mean weight trajectories (*line*) and 95% CIs (*shaded area*) before and after the index visit for individuals who continued TDF and those who switched to TAF, derived using locally estimated scatter plot smoothing. **Middle.** Mean changes in weight (*line)* and 95% CIs (*shaded area*) compared with the index visit after switching to TAF versus continuing TDF. Adjusted for sex; African origin; age; CD4 cell count; time since antiretroviral therapy initiation; index visit values of weight and estimated glomerular filtration rate; third drug used after the index visit; and time-updated use of weight-modifying drugs, smoking status, and physical activity. The model includes random intercepts for each patient nested within cohort site and a random slope for time on the individual level. Because all individuals were receiving TDF before the index visit, and preindex trajectories of individuals who switched to TAF and those who continued TDF were similar, their preindex visit trajectories were combined in the multivariable model. A total of 4291 individuals were included in the models. Knots were positioned at 0, 7.1, and 14.8 mo. **Bottom.** Unadjusted changes in the proportion of BMI categories after 18 mo compared with the index visit, stratified by whether individuals switched to TAF or continued TDF. Analysis restricted to individuals with available weight measurements at 18 mo (n = 2484).

Table 2. Adjusted Changes in Weight From the Index Visit to 18 Months Thereafter in the Overall Sample and Across Subgroups*

Variable	Change in Weight After 18 mo of TDF (95% CI), *kg*	Change in Weight After 18 mo of TAF (95% CI), *kg*	Difference Between TAF and TDF (95% CI), *kg*	*P* Value for Difference
Overall sample	0.7 (0.4 to 1.0)	1.7 (1.5 to 2.0)	1.1 (0.7 to 1.4)	<0.001
Sex and origin				
Women of non-African origin	−0.1 (−1.1 to 0.9)	1.4 (0.6 to 2.2)	1.4 (0.2 to 2.7)	0.026
Men of non-African origin	0.6 (0.2 to 0.9)	1.7 (1.4 to 2.0)	1.1 (0.7 to 1.5)	<0.001
Women of African origin	1.0 (0.2 to 1.8)	2.4 (1.7 to 3.2)	1.5 (0.4 to 2.5)	0.009
Men of African origin	0.9 (-0.2 to 2.1)	1.6 (0.5 to 2.6)	0.6 (-1.0 to 2.2)	0.44
Third drug used				
INSTI	0.1 (-0.5 to 0.7)	1.8 (1.5 to 2.1)	1.7 (1.0 to 2.4)	<0.001
NNRTI	0.8 (0.5 to 1.2)	1.9 (1.4 to 2.4)	1.1 (0.4 to 1.7)	0.001
PI	0.8 (-0.2 to 1.7)	1.8 (1.2 to 2.4)	1.1 (0.0 to 2.1)	0.061
Weight at index visit				
<70 kg	1.1 (0.6 to 1.6)	2.2 (1.8 to 2.6)	1.1 (0.5 to 1.7)	<0.001
70–80 kg	0.3 (-0.2 to 0.8)	1.6 (1.2 to 2.0)	1.3 (0.7 to 1.9)	<0.001
>80 kg	0.5 (0.1 to 1.0)	1.3 (0.9 to 1.7)	0.8 (0.1 to 1.4)	0.015

INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
* Adjusted for age, sex, African origin, body mass index, and CD4 cell count at the index visit; time since antiretroviral therapy initiation; third drug used after the index visit; and time-updated use of weight-modifying drugs, smoking status, and physical activity. Models include random intercepts for each patient nested within cohort site and a random slope for time on the individual level.

Figure 2. Changes in weight over time, stratified by the weight at the index visit.



Mean changes in weight (*line*) and corresponding 95% CIs (*shaded area*) after switching to TAF compared with continuing TDF, stratified by the weight at the index visit. Results are based on a multivariable model adjusted for sex; African origin; age; CD4 cell count; time since antiretroviral therapy initiation; index visit values of weight and estimated glomerular filtration rate; third drug used after the index visit; and time-updated use of weight-modifying drugs, smoking status, and physical activity. The model includes random intercepts for each patient nested within cohort site and a random slope for time on the individual level. Because all individuals were receiving TDF before the index visit, and preindex trajectories of individuals who switched to TAF and those who continued TDF were similar, their preindex visit trajectories were combined in the multivariable model. A total of 4291 individuals were included in the model. Knots were positioned at 0, 7.1, and 14.8 mo. TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

at Annals.org). There was no evidence that switching from TDF to TAF increased incidence of diabetes among individuals with a higher BMI at the index visit (*P* for interaction = 0.95) (**Appendix Figure 6**, available at Annals.org).

Discussion

In this nationwide cohort study, individuals switching from TDF to TAF experienced a larger weight increase than those who continued TDF over 18 months of follow-up. The largest difference between groups was observed among women of African (1.5 kg) and non-African (1.4 kg) origin. Compared with individuals who continued TDF, those who switched to TAF were more likely to become overweight and to experience worsening of serum lipid levels. Our estimates were robust across subgroups of patients regardless of whether TAF was administered together with PIs, NNRTIs, or INSTIs. Taken together, our results highlight the need for continuous monitoring of metabolic comorbid conditions during TAF-containing ART and for further exploring the mechanisms leading to metabolic changes in this population.

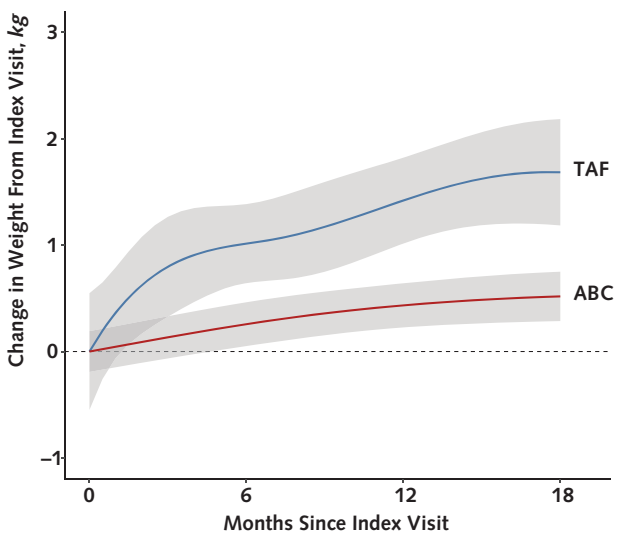
Compared with previous publications (identified by an English-language MEDLINE search to "[TAF or tenofovir alafenamid*] AND HIV AND weight"), the weight increase observed in our study is in line with 2 retrospective studies of patients switching from TDF to TAF (20, 21). However, compared with our study, the sample sizes were small (241 and 305, respectively), and the analyses were not adjusted for important confounders. In our study, switching to TAF compared with continuing TDF translated into a larger proportion of individuals with a normal BMI at the index visit who became overweight or obese during the study period, which might further contribute to increasing obesity rates among PLWH (22). The absolute increase in weight on TAF was largest among women of African origin, a finding that was also shown in a large pooled analysis of 8 clinical trials including 5680 treatment-naive PLWH (13). Whereas the underlying mechanisms remain unclear, women of African origin were also at higher risk for obesity among PLWH in a study from the United Kingdom (23). Although less marked than among women of African origin, weight increases among other demographic groups receiving TAF were statistically significant, generally exceeding 1.5 kg after 18 months.

In our study, weight increase while receiving TAF was observed with the concurrent use of all major third drug classes (PIs, NNRTIs, and INSTIs). Whereas a study in treatment-experienced patients showed similar weight changes regardless of the third drug class (24), studies from treatment-naive patients showed larger weight increases among patients receiving INSTI-based regimens (12, 13). Although an additional influence of other drugs, such as INSTI, cannot be excluded, the consistency of our findings across treatment regimens speaks for the important role of switching from TDF to TAF in driving weight increases. Increases in weight while receiving TAF without other ART components have also been observed in a study evaluating TAF–emtricitabine for HIV preexposure prophylaxis (25). Finally, our observation that switching from ABC to TAF was also associated with weight increases further suggests that the increases seen after the replacement of TDF by TAF cannot only be attributed to stopping TDF.

We observed increased lipid levels among individuals who switched to TAF compared with those who continued TDF. These findings confirm and extend observations from registration trials and cohort studies, which consistently showed worsening lipid profiles (9, 26, 27) and an increased demand for lipid-lowering therapy with TAF (11). Several studies indicate that the increase in lipid levels in individuals switching from TDF to TAF might be attributed to stopping TDF, which has an intrinsic lipid-lowering effect (19). Although weight increase and dyslipidemia can affect insulin resistance, we found no clear evidence for increased rates of new-onset diabetes with the use of TAF during the study. Neither TDF nor TAF itself led to insulin resistance among healthy volunteers (28, 29). However, follow-up data from the ADVANCE trial indicate that the large increases in weight observed with the use of TAF led to increased rates of diabetes (30).

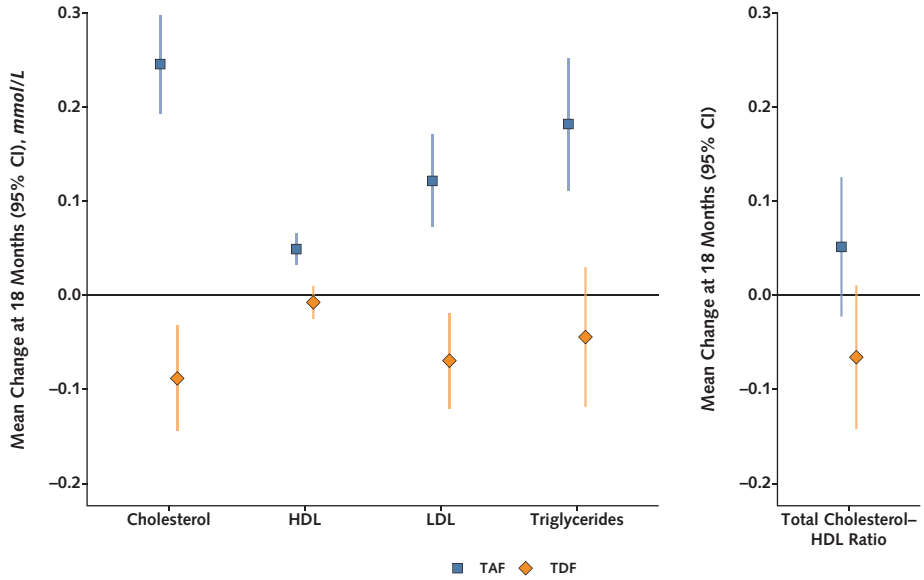
Our study is among the largest to date investigating the effect of switching from TDF to TAF on weight and metabolic outcomes within a well-defined and nationally

Figure 3. Changes in weight over time, analysis of patients who received ABC and continued ABC (*n* = 2560) or switched to TAF (*n* = 427).



Mean changes in weight (*line*) and corresponding 95% CIs (*shaded area*) after switching to TAF compared with continuing ABC, adjusted for sex; African origin; age; CD4 cell count; time since antiretroviral therapy initiation; index visit values of weight and estimated glomerular filtration rate; third drug used after the index visit; and time-updated use of weight-modifying drugs, smoking status, and physical activity. The model includes random intercepts for each patient nested within cohort site and a random slope for time on the individual level. Because all individuals were receiving ABC before the index visit, and preindex trajectories of individuals who switched to TAF and those who continued ABC were similar, their preindex visit trajectories were combined in the multivariable model. Knots were positioned at 0, 7.1, and 14.8 mo. ABC = abacavir; TAF = tenofovir alafenamide.

Figure 4. Adjusted mean changes (95% CIs) in lipid levels from the index visit to 18 months thereafter.



Mean changes (*squares and diamonds*) and 95% CIs (*vertical line*) in blood lipid values from the index visit to 18 mo thereafter, adjusted for age; sex; African origin; individual lipid levels at the index visit; and time-varying physical activity, weight, and use of lipid-lowering drugs. The models include random intercepts for each patient nested within cohort site and a random slope for time on the individual level. A total of 4290 individuals were included in the models. HDL = high-density lipoprotein; LDL = low-density lipoprotein; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

representative cohort. Assessing these outcomes among treatment-experienced PLWH allowed us to avoid the influence of the return to health, which inherently complicates the interpretation of studies among treatment-naive individuals. We adjusted our analyses for a wide range of confounders, including time-updated physical activity and comedications, and our findings remained robust across several sensitivity analyses, including an analysis among patients who switched from ABC to TAF.

Some limitations of our study should be noted. Follow-up was relatively short to grasp the full effect of TAF on new-onset diabetes and lipid metabolism. In addition, subgroup analyses in specific demographic groups were based on small numbers, which limited our ability to detect differences. Information on physical activity and use of weight-modifying drugs was self-reported, and misclassification of these covariates may have affected our results. Although most individuals had replaced TDF with TAF at a time when no published evidence for a treatment-associated weight increase was available, confounding by indication cannot be fully excluded. Assuming that individuals who were more prone to weight increase continued TDF to avoid metabolic side effects of TAF, the difference in weight increase between TDF and TAF would have been underestimated. Third drug classes at the index visit differed markedly between groups, and our methods might have been insufficient to fully adjust for these imbalances. However, a sensitivity analysis restricted to individuals who only replaced TDF with TAF without further ART modifications showed results consistent with our primary analysis. Finally, unmeasured residual confounding cannot be excluded in this observational study. Accordingly, weight increases after switching from TDF to TAF should also be explored in large-scale randomized controlled trials with sufficient follow-up.

In conclusion, our results indicate that switching from TDF to TAF is associated with metabolic adverse events, including obesity and dyslipidemia. Recommendations on the use of TAF should balance its advantages (renal and bone safety) with its potential harms, including metabolic complications. The decision to prefer TAF over TDF as a component of ART should be individualized and accompanied by the repeated assessment of cardiometabolic risk factors, including weight and lipids. Further studies are needed to provide more insight into the mechanisms of weight increase and metabolic effects of modern HIV drugs, to identify individuals at highest risk for such metabolic complications, and to assess the effect of these metabolic complications on clinical outcomes.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-4853.

Reproducible Research Statement: *Study protocol and data set:* Not available. *Statistical code:* Parts of the statistical code can be made available on reasonable request; contact Dr. Surial (e-mail, bernard.surial@insel.ch).

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Obtaining of funding: B. Surial, G. Wandeler, A. Rauch.
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Appendix: Members of the Swiss HIV Cohort Study

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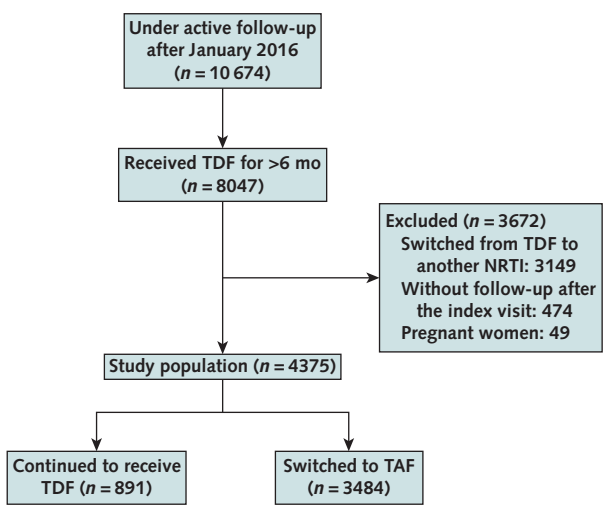
* Members of the Swiss HIV Cohort Study who contributed to this work but did not author it.

† Members of the Swiss HIV Cohort Study who authored this work.

Appendix Figure 1. Selection of the study population.



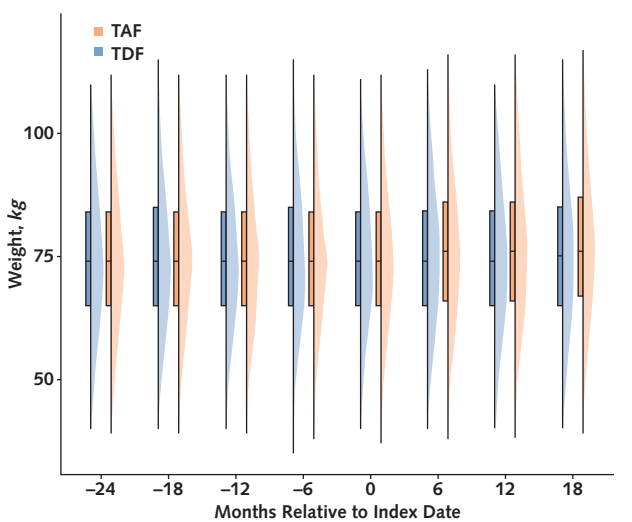
NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Appendix Table 1. Missing Observations at Index Visit and Among All Follow-up Visits for Weight and Lipid Analyses

Variable	TDF, *n* (%)	TAF, *n* (%)
Index visit assessments	891	3484
TDF vs. TAF	0	0
Sex	0	0
African vs. non-African origin	0	0
Weight	15 (1.7)	34 (1.0)
BMI	15 (1.7)	34 (1.0)
Age	0	0
Years since ART initiation	0	0
Third drug class switched to	12 (1.3)	16 (0.5)
Renal function (eGFR)	0	0
CD4 at index date	6 (0.7)	16 (0.5)
Smoker	1 (0.1)	0
Cholesterol	11 (1.2)	26 (0.7)
HDL cholesterol	17 (1.9)	75 (2.2)
LDL cholesterol	22 (2.5)	96 (2.8)
Triglycerides	16 (1.8)	47 (1.3)
Total–HDL cholesterol ratio	17 (1.9)	78 (2.2)
Follow-up visits	6246	25 009
Weight measurement	96 (1.5)	229 (0.9)
Physical activity	51 (0.8)	108 (0.4)
Weight-modifying drug	0	0
Smoking status	29 (0.5)	140 (0.6)
Total cholesterol	7 (0.1)	24 (0.1)
HDL cholesterol	37 (0.6)	106 (0.4)
LDL cholesterol	61 (1.0)	234 (0.9)
Triglycerides	24 (0.4)	125 (0.5)
Total cholesterol–HDL ratio	39 (0.6)	126 (0.5)
Use of a lipid-lowering drug	0	0

ART = antiretroviral therapy; BMI = body mass index; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Appendix Figure 2. Unadjusted distribution of weight over time.



Kernel density and box-and-whisker plots showing the distribution of weight measurements between TDF and TAF over time. TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

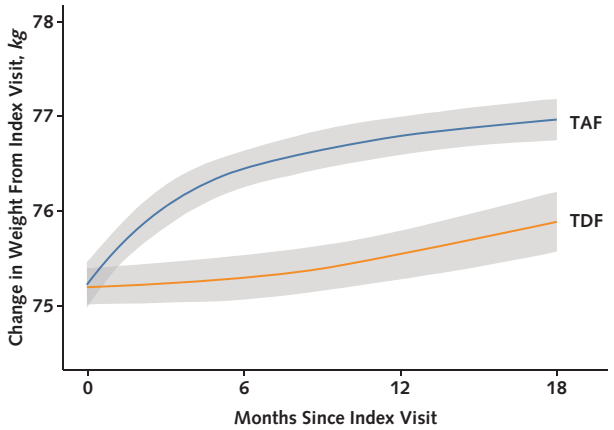
Appendix Table 2. Estimates of the Multivariable Mixed-Effects Model for Weight Over Time

Fixed Effects	Estimate	SE	Statistic
Intercept	6.87	0.64	10.78
Time (years) 1	−6.5	0.66	−9.85
Time (years) 2	8.04	2.51	3.2
Time (years) 3	−32.24	9.61	−3.35
Time (years) 4	−55.67	19.68	−2.83
TAF vs. TDF	−16.79	64.99	−0.26
Index weight (per 10 kg)	8.96	0.06	148.07
Female vs. male	−0.42	0.1	−4.06
Non-African vs. African origin	−0.03	0.13	−0.26
Smoking vs. not smoking	−0.52	0.07	−7.63
Age per 10-y increase	0.09	0.05	1.91
Time since ART initiation (per year)	−0.01	0.01	−0.9
NNRTI vs. INSTI	−0.04	0.09	−0.51
PI vs. INSTI	−0.06	0.12	−0.49
CD4 at index date (per 100 cells/μL)	0.02	0.01	1.7
Physical activity: 1–4 times/mo vs. never	0.07	0.07	0.99
Physical activity: 1–2 times/wk vs. never	−0.24	0.06	−3.86
Physical activity: >2 times/wk vs. never	−0.39	0.06	−6.57
Use of weight-modifying drug	−0.04	0.12	−0.31
eGFR at index date (per 10-mL/min change)	0.04	0.02	1.51
Time (years) 1: TAF vs. TDF	19.52	64.59	0.3
Time (years) 2: TAF vs. TDF	6.45	37.8	0.17
Time (years) 3: TAF vs. TDF	44.27	124.63	0.36
Time (years) 4: TAF vs. TDF	48.42	36.12	1.34
Time (years) 1: Index weight (per 10 kg)	0.94	0.09	10.96
Time (years) 2: Index weight (per 10 kg)	−0.87	0.33	−2.64
Time (years) 3: Index weight (per 10 kg)	4.81	1.26	3.82
Time (years) 4: Index weight (per 10 kg)	8.06	2.58	3.13
TAF vs. TDF: Index weight (per 10 kg)	−2.34	8.41	−0.28
Time (years) 1: TAF vs. TDF: Index weight (per 10 kg)	2.16	8.36	0.26
Time (years) 2: TAF vs. TDF: Index weight (per 10 kg)	1.96	4.89	0.4
Time (years) 3: TAF vs. TDF: Index weight (per 10 kg)	2.58	16.14	0.16
Time (years) 4: TAF vs. TDF: Index weight (per 10 kg)	−4.51	4.71	−0.96

Random Effects	SD
Patient ID nested in cohort center (random intercept)	2.18
Cohort center (random intercept)	0.08
Years (random slope)	1.52
Residual	2.76

ART = antiretroviral therapy; eGFR = estimated glomerular filtration rate; INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Appendix Figure 3. Adjusted mean absolute weight over time.



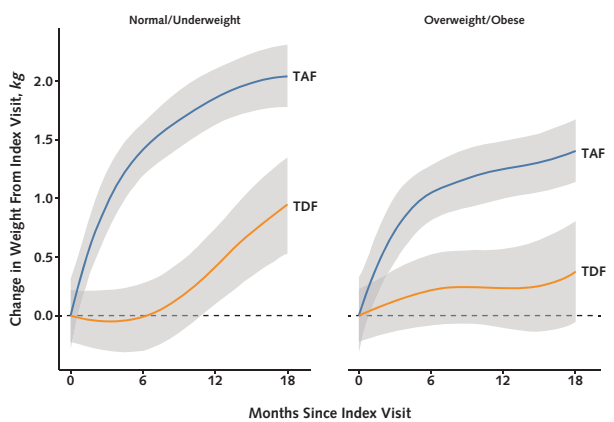
Mean weight changes over time after switching to TAF compared with continuing TDF. Adjusted for sex; African origin; age; CD4 cell count; time since antiretroviral therapy initiation; index visit values of weight and estimated glomerular filtration rate; third drug used after the index visit; and time-updated use of weight-modifying drugs, smoking status, and physical activity. The model includes random intercepts for each patient nested within cohort site and a random slope for time on the individual level. A total of 4291 individuals were included in the models. TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Appendix Table 3. Sensitivity Analyses of Patients With at Least 6 and 12 Months of Follow-up

Variable	Change in Weight After 18 mo of TDF (95% CI), *kg*	Change in Weight After 18 mo of TAF (95% CI), *kg*	Difference Between TAF and TDF (95% CI), *kg*	*P* Value for Group Difference
At least 6 mo of follow-up (*n* = 3821)	0.7 (0.4–0.9)	1.8 (1.6–2.0)	1.2 (0.8–1.5)	<0.001
At least 12 mo of follow-up (*n* = 3127)	0.6 (0.3–0.9)	1.9 (1.6–2.1)	1.2 (0.9–1.6)	<0.001

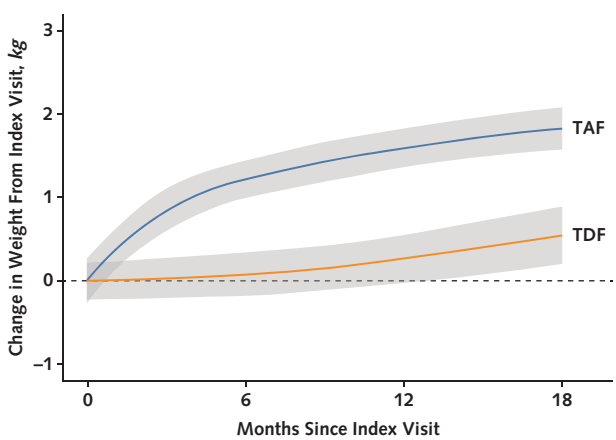
TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Appendix Figure 4. Adjusted mean weight over time, stratified by BMI category at the index visit.



Mean weight changes over time after switching to TAF compared with continuing TDF, stratified by BMI categories at the index visit. Adjusted for sex; African origin; age; CD4 cell count; time since antiretroviral therapy initiation; index visit values of weight and estimated glomerular filtration rate; third drug used after the index visit; and time-updated use of weight-modifying drugs, smoking status, and physical activity. The model includes random intercepts for each patient nested within cohort site and a random slope for time on the individual level. A total of 4291 individuals were included in the models. BMI = body mass index; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Appendix Figure 5. Changes in weight over time, analysis restricted to patients who had a suppressed HIV viral load 1 y before baseline and through follow-up (includes 758 who continued TDF and 2930 who switched to TAF).



According to a multivariable model, adjusted for sex; African origin; baseline body mass index, age, and CD4 cell count; time since antiretroviral therapy initiation; third drug used after baseline; and time-updated use of weight-modifying drugs, smoking status, and physical activity. The model includes random intercepts for each patient nested within cohort site and a random slope for time on the individual level. TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Appendix Table 4. Sensitivity Analysis of Patients Who Had Only TDF Replaced With TAF, Without Further Changes in Antiretroviral Therapy*

Variable	Change in Weight After 18 mo of TDF (95% CI), *kg*	Change in Weight After 18 mo of TAF (95% CI), *kg*	Difference Between TAF and TDF (95% CI), *kg*	*P* Value
Overall	0.6 (0.3 to 0.9)	1.6 (1.3 to 1.9)	1.0 (0.6 to 1.4)	<0.001
INSTI	0.0 (−0.6 to 0.6)	1.5 (1.1 to 1.9)	1.5 (0.7 to 2.2)	<0.001
NNRTI	0.8 (0.5 to 1.1)	1.9 (1.4 to 2.5)	1.1 (0.5 to 1.8)	0.001
PI	0.8 (−0.1 to 1.8)	1.9 (1.2 to 2.5)	1.0 (−0.1 to 2.1)	0.081

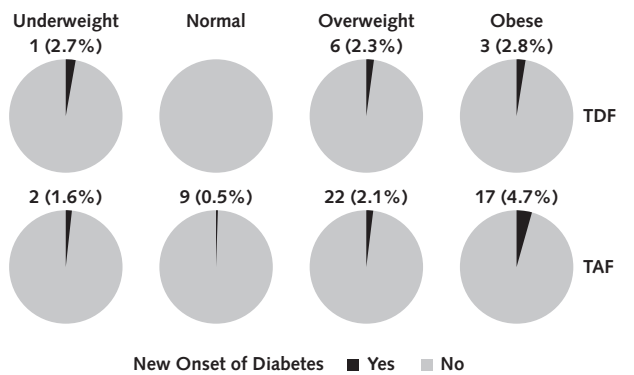
INSTI = integrase strand transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
* Includes 885 who continued TDF and 2022 who switched to TAF.

Appendix Table 5. Adjusted Mean Differences of Lipid Levels After 18 Months Compared With the Index Visit After Switching From TDF to TAF or Continuing TDF*

Variable	Mean Difference in Those Who Continued TDF (95% CI)	Mean Difference in Those Who Switched to TAF (95% CI)
Total cholesterol		
mmol/L	−0.09 (−0.15 to −0.03)	0.24 (0.19 to 0.30)
mg/dL	−3.5 (−5.6 to −1.3)	9.5 (7.4 to 11.5)
HDL cholesterol		
mmol/L	−0.01 (−0.03 to 0.01)	0.05 (0.03 to 0.06)
mg/dL	−0.3 (−1.0 to 0.3)	1.9 (1.2 to 2.5)
LDL cholesterol		
mmol/L	−0.07 (−0.12 to −0.02)	0.12 (0.07 to 0.17)
mg/dL	−2.7 (−4.7 to −0.8)	4.7 (2.8 to 6.6)
Triglycerides		
mmol/L	−0.05 (−0.12 to 0.03)	0.18 (0.11 to 0.25)
mg/dL	−4.0 (−10.6 to 2.5)	16.0 (9.8 to 22.3)
Total cholesterol-HDL ratio	−0.07 (−0.14 to 0.01)	0.05 (−0.02 to 0.12)

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
* Adjusted for age; sex; African origin; each lipid level at the index visit; and time-varying physical activity, weight, and use of lipid-lowering medication. The models include random intercepts for each patient nested within cohort site and a random slope for time on the individual level.

Appendix Figure 6. Numbers of individuals (percentages) with new onset of diabetes among persons without diabetes at the index visit stratified by index visit BMI category (n = 4150).



BMI = body mass index; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Appendix Table 6. Incidence Rate Ratios of New-Onset Diabetes Among Individuals Without Preestablished Diabetes at the Index Visit*

Variable	IRR (95% CI)	*P* Value
TAF vs. TDF	1.3 (0.7–2.8)	0.49
Age (per 10-y increase)	1.5 (1.2–1.9)	<0.001
Women vs. men	0.4 (0.2–0.9)	0.037
Non-African vs. African origin	0.6 (0.3–1.6)	0.31
BMI at baseline (per 5-kg/m^2 increase)	1.9 (1.5–2.2)	<0.001

BMI = body mass index; IRR = incidence rate ratio; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
*n = 4150, adjusted for all categories in the table.