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Weight, anthropometric and metabolic changes after discontinuing antiretroviral therapy containing tenofovir alafenamide (TAF) in people with HIV

José Damas[1], Aline Munting[1], Jacques Fellay[2], David Haerry[3], Catia Marzolini[4], Philip E. Tarr[5], Ana Steffen[6], Dominique L. Braun[7], Marcel Stoeckle[4], Enos Bernasconi[8], Olivier Nawej Tshikung[9], Christoph A. Fux[10], Katharine E.A. Darling[1], Charles Béguelin[11], Gilles Wandeler[11], Matthias Cavassini[1], Bernard Surial[11], *and the Swiss HIV Cohort Study (SHCS)*

[1] Infectious Diseases Service, University Hospital Lausanne, University of Lausanne, Lausanne, Switzerland; [2] School of Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland + Biomedical Data Science Center, University Hospital and University of Lausanne, Lausanne, Switzerland; [3] Chair of the Positive Council, Switzerland; [4] Department of Infectious Diseases, University Hospital Basel, University of Basel, Basel, Switzerland; [5] University Department of Medicine, Kantonsspital Bruderholz, University of Basel, Basel, Switzerland; [6] Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St Gallen, St. Gallen, Switzerland; [7] Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [8] Division of Infectious Diseases, Ente Ospedaliero Cantonale, Lugano, University of Geneva and University of Southern Switzerland, Lugano, Switzerland; [9] Division of Infectious Diseases, University Hospital Geneva, University of Geneva, Geneva, Switzerland; [10] Division of Infectious Diseases, Cantonal Hospital of Aarau, Aarau, Switzerland; [11] Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Corresponding author: José Damas MD MPH**,** Infectious Diseases Service, University Hospital Lausanne, University of Lausanne, Lausanne, Switzerland Email: jose.damas-fernandez@chuv.ch; jose.damasfernandez@unil.ch

Alternative corresponding author: Bernard Surial MD**,** Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland Email: bernard.surial@insel.ch

Background: Antiretroviral therapy (ART)-related weight gain is of particular concern in people with HIV (PWH). While weight gain was observed among PWH receiving tenofovir alafenamide (TAF), little is known about the potential reversibility after TAF discontinuation. We evaluated weight and metabolic changes 12 months after TAF discontinuation in the Swiss HIV Cohort Study.

Methods: We included participants who received at least six months of TAF-containing ART between January 2016 and March 2023. Using multivariable mixed-effect models, changes in weight and lipid levels were compared between individuals who continued TAF and those who switched to one of the following TAF-free regimens: TDF-based ART, dolutegravir/lamivudine (DTG/3TC), or long-acting cabotegravir/rilpivirine (CAB/RPV).

Results: Of 6555 participants (median age 54 years, 24.3% female, 13% Black), 5485 (83.7%) continued and 1070 (16.3%) stopped TAF. Overall, discontinuing TAF was associated with an adjusted mean weight change of -0.54 kg (95% CI -0.98 to -0.11) after 12 months. In stratified analyses, switching from TAF to TDF led to an adjusted mean weight decrease of -1.84 kg (CI -2.72 to -0.97), and to a decrease in mean total cholesterol (-0.44 mmol/L) and triglycerides (-0.38 mmol/L) after 12 months. Switching from TAF-based ART to DTG/3TC (-0.17 kg, CI -0.82 to 0.48) or long-acting CAB/RPV (-0.64 kg, CI -2.16 to 0.89) did not lead to reductions in weight.

Conclusions: Replacing TAF with TDF in PWH led to a decrease in body weight and an improved lipid profile within one year. Weight changes were not observed among individuals who switched to DTG/3TC or long-acting CAB/RPV.

Keywords: antiretroviral therapy, tenofovir alafenamide, tenofovir disoproxil fumarate, weight, HIV

INTRODUCTION

As life expectancy of people with HIV (PWH) is approaching that of the general population, the management and prevention of cardiometabolic conditions, including obesity and cardiovascular disease, have emerged as important issues in the care of PWH[1, 2]. Since the prevalence of obesity is increasing in PWH, antiretroviral therapy (ART)-related weight gain is of particular concern[3-6]. Studies have shown larger weight increases in individuals starting tenofovir alafenamide (TAF) than in those receiving tenofovir disoproxil fumarate (TDF), and weight gain after the switch from TDF to TAF[7, 8]. However, little is known about weight and lipid profile trajectories after stopping TAF-based ART, and whether these metabolic changes are reversible.

The discontinuation of TAF did not lead to a decrease in weight in two randomized trials. In TANGO, no difference in weight changes was observed between individuals who switched away from TAF-based ART to dolutegravir and lamivudine (DTG/3TC), compared to those who remained on TAF[9]. Similarly, weight trajectories in PWH who switched from

bictegravir/TAF/FTC to long-acting cabotegravir(CAB)/rilpivirine(RPV) were similar to those of people continuing bictegravir/TAF/FTC in the SOLAR study[10]. In contrast, replacing TAF with TDF let to a decrease in weight among 70 PWH in South Africa, and to improvements in lipid profiles among 146 individuals Finland, indicating some potential for metabolic improvements after ART modification[11, 12].

The two clinical trials and the observational studies are based on small numbers of participants, which limits their generalizability. Studies from large and well-described cohorts have the potential to inform evidence-based, shared decision-making with persons who become overweight or obese on ART. Therefore, we used data from the nationwide Swiss HIV Cohort Study (SHCS) to evaluate weight and metabolic changes after stopping TAF-based ART and adopting one of four TAF-free strategies: (1) replacing TAF with TDF, (2) switching from TAF-based ART to DTG/3TC, (3) switching to long-acting CAB/RPV, or (4) using other TAF-free ART.

METHODS

Study design

We used data from the SHCS (www.shcs.ch), a prospective cohort established in 1988, which includes close to 80% of PWH who receive ART in Switzerland, and who are followed in one of five University Hospitals, two regional hospitals, 15 affiliated hospitals or by a registered private physicians[13]. Sociodemographic, clinical, laboratory, and behavioural data are prospectively recorded at registration and every six months thereafter using standardized protocols (www.shcs.ch/292-instruction). Assessments at every follow-up visit include weight and anthropometric measurements, documentation of all changes in medication (including ART and comedication), as well as glucose and lipid measurements. Data quality and consistency are ensured by quality checks and regular site visits of participating centres. All centres' local ethical committees approved the cohort study, and all participants provided written informed consent. The reporting of the study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[14].

Eligibility criteria

We considered cohort participants who received at least six months of TAF-containing ART between 1 January 2016, the year in which TAF was approved in Switzerland, and 31 March 2023 (database closure). The index visit was defined as the date of treatment change for participants who discontinued TAF. For individuals who remained on TAF, the index visit was defined as the median date at which participants discontinued TAF (27 July 2021). Female participants who became pregnant during the study period, and participants with missing data on baseline covariables (weight, HIV-1 viral load, CD4 cell count and smoking) were excluded. The

follow-up for participants who discontinued the cohort after the index visit was censored at that time.

Outcomes and Definitions

The primary aim was to compare weight trajectories over time between PWH who continued a TAF-based ART regimen and those who discontinued TAF, and to estimate the difference in weight between the index visit and 12 months thereafter. We performed separate analyses according to the ART regimen after stopping TAF. TAF-free ART regimens were classified into regimens containing tenofovir disoproxil (TDF), dual therapy with DTG/3TC, long-acting CAB/RPV, and other ART combinations. To account for different changes in weight before the index visit, we included all weight measurements 2.5 years before the index visit until the end of each individual's follow-up. The main exposure of interest was discontinuation of TAF compared with continuing TAF. Secondary outcomes were changes in waist-to-hip ratio (WHR), and mean changes in total cholesterol, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and total cholesterol-to-HDL ratio. Weight categories were classified according to BMI as underweight (< 18.5 kg/m^2), normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2) and obese (≥ 30.0 kg/m^2) [15]. Diabetes at index visit was defined as haemoglobin A1c levels ≥ 6.5%, any glucose level above 11 mmol/L or treatment with antidiabetic medication. History of cardiovascular disease included myocardial infarction, stroke, and/or invasive cardiovascular procedures. The occurrence of both diabetes and cardiovascular events were reported by the treating cohort physician using standardized forms.

Statistical analysis

Patient characteristics between individuals who continued and those who discontinued TAF were compared using x^2 and Wilcoxon rank-sum tests. Adjusted mean changes in weight over time in absolute values were estimated using multivariable mixed-effect models, with random intercepts for each individual. In order to allow nonlinear weight trajectories, time was modelled using restricted cubic splines with three knots. Covariates were pre-specified characteristics that are associated with weight changes and/or the decision to discontinue a TAF containing regimen. Multivariable analyses for mean weight changes over time were adjusted for time-fixed values of age, sex, Black people, CD4 cell count at the index visit (cells/mm^3), years on ART, and weight at the index visit (in kilograms), and for time-varying variables, including the use of integrase inhibitors (INSTI, yes/no), physical activity (exercising more than twice a week, one to two times per week, one to four times per month, never or unknown), smoking (yes/no), and use of comedication associated with weight changes (including antidepressants, neuroleptic drugs, corticosteroids, and antidiabetic drugs)[16].

Mean differences in serum lipid levels were estimated similarly to weight analyses using the same random-effects structure and were adjusted for age, sex, Black people, and individual lipid level at the index visit, as well as for the time-varying values of weight, physical activity, and the

use of lipid-lowering drugs (statins, fibrates and nicotinic acid). Observations with missing values in variables of interest were censored (**see appendix figure 1**), except for physical activity where missing values were added as a category (unknown). All statistical analyses were performed using R, version 4.2.3.

Subgroup and Sensitivity analyses

As female PWH and Black people are at particular risk for weight increases on TAF-based ART, we performed pre-specified subgroup analyses in male and female, and in Black people and non-Black people using interaction terms[7, 8]. We repeated the main analysis among individuals with excessive weight gain, defined as an increase of more than 10% of body weight from TAF start until the index visit.

Most participants who switched from TAF to TDF also discontinued INSTI at the same time. To understand whether the changes in weight were driven by the switch to TDF or the discontinuation of an INSTI, we performed a post-hoc analysis of weight changes after switching to TDF in the subset of individuals who did not receive an INSTI until the index visit.

Patient and Public Involvement

A patient and public involvement (PPI) representative from the Swiss HIV Cohort Study (http://www.shcs.ch/315-patient-and-public-involvement-ppi) was involved in the study design, data analysis and critical review of the manuscript, and is included as co-author.

RESULTS

Study population

Of 11'782 participants under follow-up between 1 January 2016 and 31 March 2023, 7'685 received a TAF-containing ART regimen for more than six months. We excluded 995 individuals without any follow-up after the index visit, 59 pregnant females, and 76 participants with missing information on covariates at the index visit (**Figure S1**). The final study population included 6'555 participants**.** The median age was 54 years (interquartile range [IQR], 45.0 to 60.0 years), 24.3% were female, 13.3% were Black people, and 95.1% had a suppressed HIV at index visit. The median weight at the index visit was 76.0 kg (IQR, 67.0 to 87.0 kg), and 50.2% were overweight or obese.

Of the 6'555 participants, 5'485 (83.7%) continued TAF until the end of the study, and 1'070 (16.3%) switched to a TAF-free regimen. Of the individuals who discontinued TAF, 196 (18.3%) participants started a TDF-containing regimen, 565 (52.8%) switched to 3TC/DTG, 115 (10.7%) started long-acting CAB/RPV, and 194 (18.1%) switched to other ART combinations. Among individuals who switched from TAF to TDF, the most common ART regimens used were doravirine/TDF/3TC (n = 642, 60.1%), followed by RPV/TDF/FTC (n = 147, 13.8%).

Compared to individuals who continued TAF, those who discontinued the drug were younger, had received ART for a shorter duration, were more likely to be overweight or obese at index visit, and were less likely to have diabetes or a history of cardiovascular disease. In addition, total cholesterol and LDL levels were slightly higher among individuals who discontinued TAF than in those who continued the drug, while total cholesterol-HDL ratios were similar in both groups (**Table 1**). The median follow-up after the index date was 1.3 years (IQR 1.1 to 1.4) for those continuing TAF, and 1.2 years (IQR 0.6 to 2.3) for those discontinuing TAF.

Changes in weight

In unadjusted analyses, participants who discontinued TAF experienced a mean weight change of -0.24 kg (95% CI, -0.68 to 0.19) in the first 12 months after the index visit, compared with 0.04 kg (95% CI, -0.03 to 0.11) with the continuous use of TAF (between group difference -0.28 kg, 95% CI -0.72 to 0.16). After adjusting for confounders, discontinuing TAF was associated with a mean weight decrease of -0.60 kg (95% CI, -01.03 to -0.16) 12 months after the index visit, compared with 0.03 kg (95% CI, -0.03 to 0.10) with the continuous use of TAF (between group difference -0.63 kg, 95% CI,-1.07 to -0.19, **Figure S2, Table 1**). Decreases in weight after stopping TAF were only observed in individuals who switched to a TDF-containing regimen (mean adjusted weight change after 12 months -1.89 kg, 95% CI -2.76 to -1.01), whereas no changes in weight were observed in individuals who switched to a DTG/3TC, long-acting CAB/RPV or other ART regimens without TAF (**Figure 1, Table 2**).

In subgroup analyses, the decrease in weight was more pronounced among female participants (p-value <0.001 for the interaction with sex, **Figure S2**), and among Black people than non-Black people (p <0.001 for the interaction with ethnicity, **Table 2**). In the subgroup of individuals who experienced a weight gain of more than 10% after starting TAF, individuals who stopped TAF decreased their weight 12 months after index visit (-1.76 kg, 95% CI -3.12 to -0.41), however, a decrease was also observed in individuals who continued TAF (-0.44 kg, 95% CI -0.67 to -0.21, between-group difference -1.32 kg, 95% CI -2.70 to 0.06). In individuals who did not receive an INSTI until the index visit (n = 65), replacing TAF with TDF was associated with a decrease of -1.03kg (95% CI -2.35 to 0.29).

Changes in lipid levels and waist-to-hip ratio

In adjusted analyses, discontinuing TAF was associated with a decrease in total cholesterol, triglycerides and total cholesterol-HDL ratio (**Table 3, Figure S3**). These changes were most pronounced in individuals who switched from TAF to either TDF or 3TC/DTG (**Figure 2, Tables S1-S4**). During follow-up, 172 (3.1%) of PWH continuing TAF-based regiments started a lipid-lowering drug versus 38 (3.6%) who discontinued TAF (-0.4 percentage points, 95% CI -1.7 to 0.8).

Twelve months after index visit, the mean change in WHR was -0.0049 (95% CI -0.0115 to 0.0017) in individuals who discontinued TAF, compared with 0.0021 (95% CI, 0.0010 to

0.0032) in those with continuous use of TAF (between group difference -0.0070, 95% CI, -0.0137 to -0.0003). The difference in WHR between individuals who stopped TAF and those who continued a TAF-containing regimen was larger in male than in female participants (0.0084, 95% CI 0.0004 to 0.0164 vs. 0.0033, 95% CI -0.0090 to 0.0156, **Figure S4)**.

DISCUSSION

In this nationwide cohort study, replacing TAF with TDF led to a decrease in weight and small changes in WHR, whereas no substantial weight changes were noted among individuals who switched to other TAF-free regimens such as CAB/RPV or 3TC/DTG. Changes in weight among individuals who switched to TDF were followed by a decrease in total cholesterol and triglycerides levels. Similar changes in lipid levels were found among PWH switching from TAF to 3TC/DTG.

Our findings of a decrease in weight after switching from TAF to TDF-based ART are in line with those from the CHARACTERISE study[12], a sub study from the ADVANCE trial assessing weight trajectories from 172 PWH following a series of ART changes[8]. In CHARACTERISE, female PWH who switched from TAF/FTC/DTG to TDF/3TC/DTG lost 1.6 kg after 192 weeks of follow-up, whereas no change was present among male participants[12]. In the present study, weight decreases were only observed in individuals who had TAF replaced by TDF, but not in those who switched to other TAF-free ART regimens. These findings together with those from the CHARACTERISE study provide evidence for a weight-suppressing effect of TDF, rather than a weight-promoting impact of TAF. Additional evidence for this hypothesis has been gathered in HIV Pre-Exposure Prophylaxis (PrEP) studies, where participants receiving TDF/emtricitabine were more likely to experience a loss of at least 5% of body weight compared with individuals receiving placebo or CAB[17, 18]. In another study from the ATHENA Cohort, weight trajectories from 115 PWH who experienced excessive weight gain on TAF and/or INSTI-based ART were evaluated after discontinuing TAF, INSTI or both. After 12 months of follow-up, weight loss was most notable among individuals who discontinued both TAF and INSTI (-2.6 kg, 95% CI -5.8 to 0.02), followed by individuals who discontinued TAF (-1.9 kg, 95% CI -3.4 to -0.4) or INSTI alone (-1.9 kg, 95% CI -3.9 to 0.1)[19]. However, a sensitivity analysis in the same study did not found an association of weight loss after TAF, INSTI or both discontinuation with a switch to TDF[19].

We found no differences in weight when TAF-based regimens were switched to either DTG/3TC or CAB/RPV, two common TAF-free ART regimens in clinical practice in Switzerland. These results confirm and extend the findings from the two randomized trials TANGO and SOLAR. In the TANGO trial, 369 PWH receiving TAF gained 2.2 kg after being switched to 3TC/DTG, whereas 371 individuals who remained on TAF gained 1.7 kg (between-group differences 0.49 kg, 95% CI, -0.46 to 1.44)[9]. In the SOLAR trial, no weight change was observed between 277 PWH continuing BIC/FTC/TAF and 454 switched to long-acting CAB/RPV[10]. Weight loss

associated with a switch from TAF to TDF further suggests a weight suppressive effect of TDF[20]. However, in our study, most individuals who switched from TAF to TDF also switched from an INSTI-based to a NNRTI-based ART regimen: 61% switched to doravirine/TDF/3TC, and 13% to RPV/TDF/FTC; with only 12% who continued INSTI-based therapy. The absence of INSTI in most TDF-based regiments may have contributed in part to the reduction of weight that we observed in this subgroup, as INSTI are also associated with weight increase. However, in a post-hoc analysis restricted to individuals who did not receive INSTI-based ART at the index visit, switching from TAF to TDF remained associated with a decrease in weight, indicating that these changes cannot be attributed to the impact of discontinuing INSTI alone.

We observed a decrease of lipid levels after TAF discontinuation. These changes were also mainly driven by participants who switched to TDF-based regimens, which was anticipated as TDF has a favourable impact on lipid profiles[11, 21]. In addition, improvements were observed among individuals who had their TAF-based regimen replaced by 3TC/DTG. These results align well with the findings of the TANGO study, in which participants assigned to the 3TC/DTG arm experienced both a decrease in total cholesterol and triglycerides compared to those assigned to the TAF-based arm[9]. Similarly, an observational study from Spain found a decrease in cholesterol levels among 118 PWH who switched from TAF-based ART to either 3TC/DTG or DTG/RPV[22].

Our study is among the largest to date to evaluate the impact of discontinuing TAF on weight and other metabolic outcomes in PWH. The well-defined and characterised SHCS allowed us to adjust our analyses for a wide range of confounders (including physical activity and weight modifying drugs), and to perform subgroup analyses of clinical interest. However, the follow-up period of one year was relatively short, which limits our ability to grasp the full effect of switching to a TAF-free regimen on longer term weight trajectories. Specifically, CAB/RPV was licensed in Switzerland in March 2022 only, and the analysis of individuals who switched from TAF-based ART to CAB/RPV was based on a small number of individuals with relatively short follow-up. Therefore, we may have been underpowered to detect a potential difference in weight changes between individuals who switched to CAB/RPV and those who remained on TAF. In addition, as only 24% of our study population were female participants, and 13% were Black people, the generalizability of these subgroup analyses remains limited, and confirmation in other studies is warranted. Although we accounted for many confounders including weight trajectories prior to the index visit, some residual confounding by indication could remain, as participants who stopped TAF had a higher weight at baseline compared with individuals who remained on TAF.

In conclusion, replacing TAF with TDF in PWH led to a decrease in body weight, whereas switching to other common TAF-free regimens such as DTG/3TC or CAB/RPV did not lead to substantial weight changes. These findings provide evidence to guide shared decision-making with patients affected by ART-induced overweight or obesity. The potential weight and

metabolic benefits of replacing TAF with TDF must be weighed against the safety profile of TAF, which includes improvements in renal function among individuals with chronic kidney disease, and lower rates of bone demineralization[23-26]. Further studies are needed to assess whether these weight changes are sustained over time, and whether they have an impact on the incidence of weight-related cardiometabolic comorbidities among PWH.

FOOTNOTES

Potential conflicts of interest:

PET received grants, and educational and advisory fees to institution from Gilead, MSD, and Viiv, outside the submitted work. ONT institution received expenses compensation for expert opinion from ViiV Healthcare. KEAD's institution has received research grants from Gilead Sciences and travel grants and lecture fees from Gilead and MSD.

BS reports support to his institution for travel grants from Gilead Sciences and ViiV healthcare.

GW reports unrestricted research grants from Gilead Sciences and Roche Diagnostics, as well as travel grants and advisory board/lecture fees from ViiV, Gilead Sciences and MSD, all paid to his institution.

MC institution received research grants and payment for expert testimony from Gilead, MSD and ViiV.

EB's institution received research grants from MSD, consulting fees from Moderna, payment for lectures from Pfizer AG as well as fees for the participation of EB to advisory boards and/or travel grants from Gilead Sciences, ViiV, MSD, Abbvie, Pfizer, Astra Zeneca, Moderna and Ely Lilly.

CB reports participation on the Gilead advisory board on Bulevirtide.

KD reports grants, payment for lectures and support for meetings and/or travel from Gilead Sciences, as well as payment for expert testimony from MSD.

CAF reports grants from Gilead, as well as Advisory Board attendance support from Gilead, Menarini, Moderna, MSD, and ViiV.

MS reports support for meetings and/or travel from Gilead, participation on an advisory board for Gilead Sciences, Moderna, MSD, and ViiV Healthcare

ONT reports payment or honoraria for lectures from ViiV Healthcare

CM reports speaker honoraria from Gilead, ViiV and MSD

PT reports grants and payment for lectures from Gielad, ViiV, and MSD

DH reports grants from Abbvie, Astra Zeneka, Gilead, GSK, ViiV, MDF, and Pfizer, consulting fees from Astra Zeneca, Gilead, ViiV Healthcare, and Bavarian Nordic, support for travel and/or meetings from Gilead, and payment for leadership or fiduciary role from PFMD and Positive Council

DLB reports payment for lectures, consulting fees ,and participation on advisory board from Gilead, ViiV, MSD, Pfizer, and consulting fees from Astra Zeneka, support for attending meetings from Gilead.

All other authors report no potential conflict of interest.

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***Author's contribution*:** JD, BS, MC and GW conceived and designed the study. JD and BS performed the statistical analyses. JD and BS drafted the initial manuscript. All authors contributed data to the study and to the interpretation of the results and revised the manuscript for substantial content. All authors read and approved the final manuscript.

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Table 1. Characteristics of the study population at the index visit.

Characteristic	Continued TAF (N = 5485)	Stopped TAF (N = 1070)	p-value
Median age, years (IQR)	54.0 (45.0 to 60.0)	50.0 (41.0 to 58.0)	< 0.001
Female, n (%)	1347 (24.6)	243 (22.7)	0.21
Transmission group by sex, n (%)			< 0.001
Heterosexual female	1035 (18.9)	193 (18.0)	
Heterosexual male	906 (16.5)	170 (15.9)	
Injecting drug use female	115 (2.1)	16 (1.5)	
Injecting drug use male	236 (4.3)	18 (1.7)	
Men having sex with men	2728 (49.7)	593 (55.4)	
Other female	65 (1.2)	7 (0.7)	
Other male	118 (2.2)	11 (1.0)	
Missing	282 (5.1)	62 (5.8)	
Black people n (%)	724 (13.2)	131 (12.2)	0.42
Median duration of ART before index visit, years (IQR)	14.5 (8.6 to 23.1)	10.3 (5.4 to 16.7)	< 0.001
Median duration of TAF-containing ART before index visit, years (IQR)	4.3 (3.1 to 5.2)	4.8 (3.8 to 5.4)	< 0.001
Median CD4 count, cells/μL (IQR)	670.0 (497.0 to 874.0)	704.0 (541.3 to 884.7)	0.001
Median CD4 nadir, cells/μL (IQR)	214 (106.0 to 338.0)	264.0 (156.3 to 375.7)	< 0.001
HIV-1 RNA viral load <50 copies/mL, n (%)	5183 (94.5)	1044 (97.6)	< 0.001
ART containing INSTI, n (%)	4139 (75.5)	788 (73.6)	0.19
Bictegravir	2579 (47.0)	278 (26.0)	
Dolutegravir	661 (12.1)	243 (22.7)	
Elvitegravir	732 (13.3)	247 (23.1)	
Raltegravir	167 (3.0)	20 (1.9)	
Self-reported adherence, n (%)			0.32
Missed one dose or more per week	258 (4.7)	43 (4.1)	
Missed one dose per month	464 (8.5)	85 (7.9)	
Never missed a dose	4743 (86.5)	941 (87.9)	
Missing	20 (0.4)	1 (0.1)	
Use of weight-modifying drugs, n (%)	549 (10.0)	85 (7.9)	0.06
Median weight, kg (IQR)	75.0 (66.0 to 86.0)	79.0 (69.3 to 89.0)	< 0.001
Median BMI, kg/m^2 (IQR)	24.9 (22.4 to 27.8)	25.6 (23.2 to 28.9)	< 0.001
BMI category, n (%)			< 0.001
Underweight (<18.5 kg/m^2)	202 (3.7)	21 (2.0)	
Normal (18.5 to 24.9 kg/m^2)	2611 (47.6)	427 (39.9)	
Overweight (25.0 to 29.9 kg/m^2)	1875 (34.2)	413 (38.6)	
Obese (≥30.0 kg/m^2)	797 (14.5)	209 (19.5)	
Diabetes, n (%)	500 (9.1)	63 (5.9)	0.001
History of CVD, n (%)	501 (9.1)	68 (6.4)	0.004
Median eGFR, mL/min (IQR)	84.9 (71.8 to 98.2)	87.3 (74.7 to 100.8)	< 0.001
Smoking, n (%)	1882 (34.3)	299 (27.9)	< 0.001
Median total cholesterol level (IQR)			< 0.001
mmol/L	4.9 (4.2 to 5.6)	5.00 (4.3 to 5.8)	
mg/dl	187.6 (161.6 to 216.6)	193.4 (166.3 to 224.3)	
Median HDL cholesterol level (IQR)			0.40
mmol/L	1.30 (1.1 to 1.6)	1.30 (1.1 to 1.6)	

mg/dl	49.9 (40.6 to 60.3)	50.3 (41.4 to 61.1)	
Median LDL cholesterol level (IQR)			< 0.001
mmol/L	2.7 (2.1 to 3.4)	2.9 (2.2 to 3.5)	
mg/dl	104.8 (80.3 to 130.1)	109.7 (84.8 to 135.8)	
Median triglyceride cholesterol level (IQR)			0.45
mmol/L	1.5 (1.0 to 2.2)	1.4 (1.0 to 2.1)	
mg/dl	131.1 (88.6 to 196.6)	127.9 (88.6 to 188.7)	
Total cholesterol-HDL ratio (IQR)	3.7 (3.0 to 4.6)	3.8 (3.1 to 4.8)	0.05
Receiving lipid-lowering therapy, n (%)	1322 (24.1)	192 (17.9)	< 0.001

TAF = tenofovir alafenamide; **ART** = antiretroviral therapy; **BMI** = body mass index; **CVD** = cardiovascular disease/events; **eGFR** = estimated glomerular filtration rate; **HDL** = high-density lipoprotein; **IQR** = interquartile range; **LDL** = low-density lipoprotein

Table 2. Adjusted changes in weight from index visit to 12 months thereafter in the overall study population and across subgroups[†].

Variable	Continued TAF kg, (95% CI)	Stopped TAF kg, (95% CI)	Difference between the two groups	p-value for difference
Overall	0.03 (-0.03 to 0.10)	-0.54 (-0.98 to -0.11)	-0.58 (-1.02 to -0.14)	0.010
Sex				
Female	-0.06 (-0.20 to 0.07)	-0.89 (-1.69 to -0.09)	-0.83 (-1.64 to -0.1)	0.046
Male	0.07 (-0.01 to 0.14)	-0.43 (-0.94 to 0.09)	-0.49 (-1.01 to 0.02)	0.062
Race				
Black people	-0.05 (-0.24 to 0.14)	-1.24 (-2.40 to -0.08)	-1.19 (-2.37 to -0.01)	0.048
Non-Black people	0.05 (-0.02 to 0.12)	-0.43 (-0.90 to 0.03)	-0.48 (-0.95 to -0.01)	0.046
Subgroup analyses according to TAF-free regimen*				
Switched to TDF	0.05 (-0.02 to 0.11)	-1.84 (-2.72 to -0.97)	-1.89 (-2.76 to -1.01)	< 0.001
Switched to 3TC/DTG	0.05 (-0.02 to 0.11)	-0.12 (-0.77 to 0.53)	-0.17 (-0.82 to 0.48)	0.610
Switched to CAB/RPV	0.05 (-0.02 to 0.11)	-0.58 (-2.11 to 0.94)	-0.64 (-2.16 to 0.89)	0.412
Other	0.05 (-0.02 to 0.11)	0.20 (-0.66 to 1.07)	0.16 (-0.71 to 1.02)	0.724

TAF = tenofovir alafenamide; 3TC = lamivudine; DTG = dolutegravir; CAB = cabotegravir; RPV = rilpivirine; kg = kilograms; CI = confidence interval.
[†]Adjusted for the time fixed covariates age, sex, Black people, weight at index visit, use of integrase strand transfer inhibitor, smoking status, time in antiretroviral therapy, CD4 cell count at index visit, and time-varying physical activity, use of weight-modifying drugs, and HIV-1 viral load. Models include random intercepts for each patient.
*Only applies to the individuals who stopped TAF. The comparator group of individuals who continued TAF remained unchanged. Minor discrepancies in estimates in this group occurred due the model estimation process.

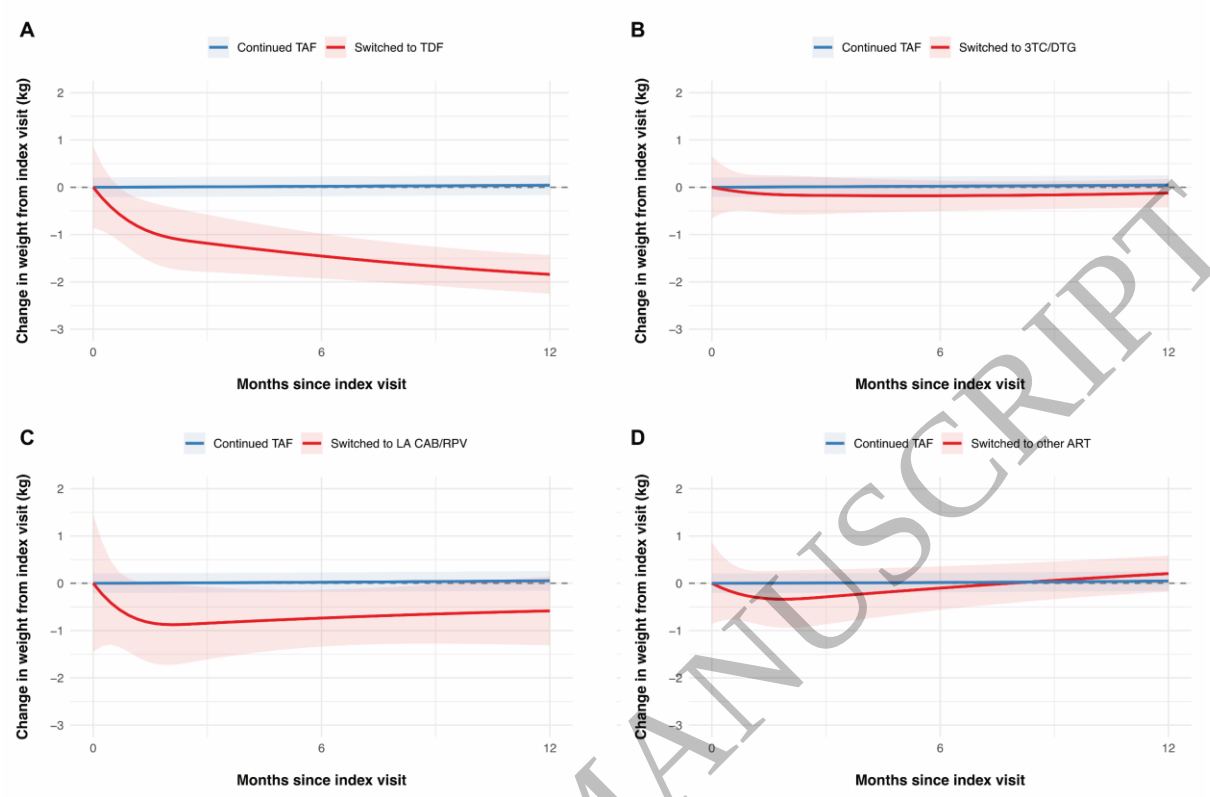
Table 3. Adjusted mean differences of lipid levels after 12 months compared with index visit after discontinuing TAF.

Variable	Continued TAF, (95% CI)	Stopped TAF, (95% CI)	Difference between the two groups	p-value for difference
Total cholesterol				0.005
mmol/L	-0.06 (-0.09 to -0.04)	-0.20 (-0.29 to -0.11)	-0.14 (-0.23 to -0.04)	
mg/dL	-2.5 (-3.4 to -1.5)	-7.7 (-11.2 to -4.1)	-5.2 (-8.9 to -1.6)	
HDL cholesterol				0.543
mmol/L	-0.02 (-0.02 to -0.01)	-0.03 (-0.05 to 0.001)	-0.01 (-0.04 to 0.02)	
mg/dL	-0.07 (-0.9 to -0.4)	-1.0 (-2.1 to 0.1)	-0.3 (-1.5 to 0.8)	
LDL cholesterol				0.644
mmol/L	-0.02 (-0.04 to 0.001)	-0.04 (-0.12 to 0.05)	-0.02 (-0.11 to 0.07)	
mg/dL	-0.7 (-1.5 to 0.2)	-1.5 (-4.8 to 1.5)	-0.8 (-4.2 to 2.6)	
Triglycerides				< 0.001
mmol/L	-0.07 (-0.10 to -0.03)	-0.30 (-0.43 to -0.17)	-0.23 (-0.36 to -0.10)	
mg/dL	-5.9 (-8.9 to -2.9)	-26.2 (-37.8 to -14.7)	-20.4 (-32.3 to -8.5)	
Total cholesterol-HDL ratio	-0.02 (-0.06 to 0.02)	-0.18 (-0.33 to -0.03)	-0.16 (-0.31 to -0.01)	0.036

TAF = tenofovir alafenamide; **HDL** = high-density lipoprotein; **IQR** = interquartile range; **LDL** = low-density lipoprotein

Models adjusted for time fixed covariables age, sex, ethnicity, individual lipid level at baseline: and time-varying physical activity, weight, and use of lipid-lowering drugs

Figure 1. Weight changes over time after index visit, stratified by the TAF-free antiretroviral therapy (ART) regimen



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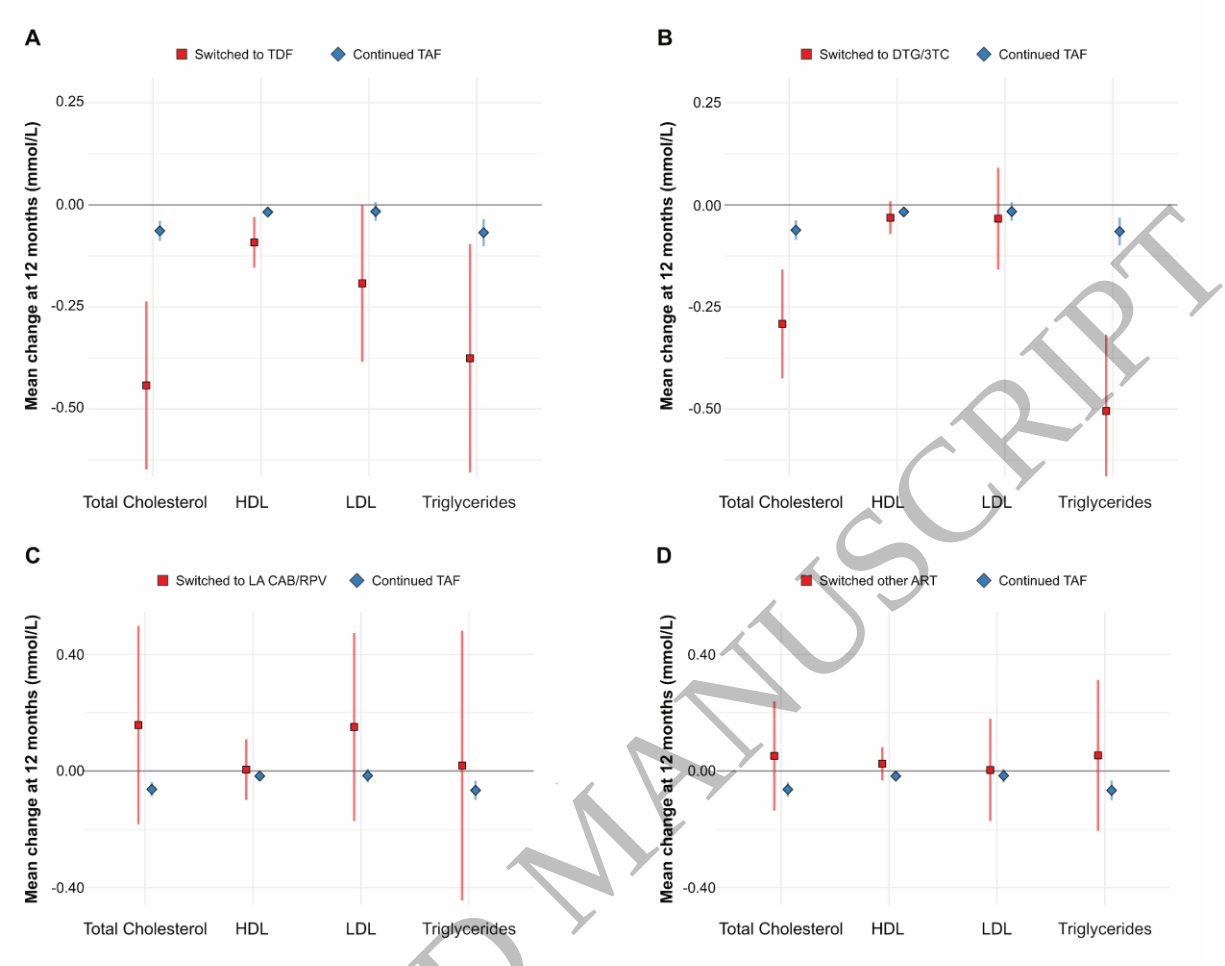
Mean changes in weight (line) and corresponding 95% CIs (shaded area) of continuing TAF-based antiretroviral therapy (ART, **blue** line) compared with (**A**) switching to TDF-based ART, (**B**) switching to dolutegravir and lamivudine (DTG/3TC), (**C**) switching to long-acting cabotegravir and rilpivirine (LA CAB/RPV), or (**D**) switching to other ART (**red** lines). All models were adjusted for age, sex, ethnicity, CD4-cell count, use of integrase inhibitors, physical activity, smoking status and use of weight-modifying drugs. The model includes random intercepts for each individual. A total of 6282 PWH were included in the analyses. **CIs** = confidence intervals; **TAF** = tenofovir alafenamide.

Figure 2. Changes in lipid levels 12 months after the index visit, stratified by the TAF-free antiretroviral therapy (ART) regimen



Mean changes in lipid levels (squares and diamonds) and corresponding 95% CIs (vertical line) after 12 months of continuing TAF-based antiretroviral therapy (ART, in **blue**) compared with (**A**) switching to TDF-based ART, (**B**) switching to dolutegravir and lamivudine (DTG/3TC), (**C**) switching to long-acting cabotegravir and rilpivirine (LA CAB/RPV), or (**D**) switching to other ART (all in **red**). All models were adjusted for age, sex, ethnicity, individual lipid level at baseline, and time-varying physical activity, weight, and use of lipid-lowering drugs. The model includes random intercepts for each individual. **HDL** = High density lipoprotein, **LDL** = low density lipoprotein, **TAF** = tenofovir alafenamide.

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