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Switching from tenofovir alafenamide to tenofovir disoproxil fumarate improves lipid profile and protects from weight gain

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Background: Switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) increases low-density lipoprotein cholesterol (LDL-C) and body weight. Metabolic effects of the opposite TAF-to-TDF switch are unknown.

Objectives: To investigate the effect of TAF-to-TDF switch on plasma lipids, body weight, and atherosclerotic cardiovascular disease (ASCVD) risk score.

Design: A retrospective chart review.

Methods: One hundred and forty-six patients with TAF-to-TDF switch (Switch group) were compared with 146 patients matched for sex, age, and third antiretroviral agent class who continued unchanged TAF-containing regimen (Control group). Data were collected at approximately 1 year (follow-up FU-1) and 2 years (follow-up FU-2) after baseline values.

Results: In Switch group at FU-1, total cholesterol (TC) and LDL-C decreased 12.1% and 12.4% ($P < 0.001$ in both), respectively. High-density lipoprotein cholesterol (HDL-C) also decreased 8.2% ($P < 0.001$) in Switch group, but TC/HDL-C ratio did not change. No statistically significant changes were observed in Control group in any lipid values. TC remained similarly decreased through FU-2 in Switch group, but LDL-C increased from FU-1 to FU-2 in both groups. ASCVD risk score decreased from 6.3% at baseline to 6.0% at FU-2 ($P = 0.012$) in Switch group but increased from 8.4 to 9.1% ($P = 0.162$) in Control group. Body weight increased from 83.4 kg at baseline to 84.9 kg at FU-2 ($P = 0.025$) in Control group but remained stable in Switch group (83.1−83.7 kg, $P = 0.978$).

Conclusions: TAF-to-TDF switch improved plasma lipid profile and ASCVD risk score, as well as prevented weight gain, when compared with ongoing TAF-based antiretroviral therapy.

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Keywords: body weight, cardiovascular risk score, cholesterol, HIV, tenofovir alafenamide, tenofovir disoproxil fumarate

Introduction

Tenofovir disoproxil fumarate (TDF) has widely been used for treatment of human immunodeficiency virus (HIV) infection for almost two decades, and it remains among the preferred agents in treatment guidelines, together with a newer tenofovir prodrug, tenofovir alafenamide (TAF) [1,2].

Due to pharmacological differences, TAF can be dosed as 1/10th of the TDF dose to reach equivalent intracellular tenofovir concentration [3]. This translates into lower kidney and bone related toxicity when using TAF as compared to TDF [4]. Therefore, TAF has replaced TDF to a large extent in industrialized countries.

Both controlled trials and real-world data have, however, demonstrated worsening of the blood lipid profile after switching from TDF to TAF [5–7]. TDF has been shown to directly decrease blood lipid concentrations [8], whereas the effect of TAF on blood lipids is considered

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neutral [3]. TDF and TAF have also a different effect on body weight. TDF as part of preexposure prophylaxis (PrEP) slightly decreased body weight [9], whereas TAF has been associated with body weight increase [10,11]. Consequently, a switch from TDF to TAF seems to increase body weight [12–15].

According to a recent meta-analysis, the risk of bone and kidney related toxicity of TDF was associated with concomitant use of a pharmacological booster (cobicistat and ritonavir) [16]. If TDF was used without a booster, there were no differences in grade 1–4 adverse events nor in kidney or bone related discontinuation rate compared to TAF [16]. These data and the beneficial metabolic effects of TDF together with the availability of its generic formulations are likely to increase switches back from TAF to TDF. The data, however, are very scarce regarding this switch. To the best of our knowledge, only one uncontrolled study has evaluated TAF-to-TDF switch suggesting a decrease in total cholesterol (TC) and triglyceride (TG) concentrations, but the effects on low-density lipoprotein cholesterol (LDL-C) or body weight were not reported [6].

In the current real-world setting study, we have investigated the effect of switching from TAF to TDF on blood lipids, cardiovascular risk score, and body weight, by comparing participants who switched TAF to TDF with no other changes in the regimen to those who remained on unchanged TAF-containing regimen.

Methods

Study design

This is a retrospective study evaluating the effects of switching from TAF to TDF on plasma lipid concentrations, cardiovascular risk score, body weight, and other laboratory parameters.

Participants

Switch group

All people with HIV (PHIV) attending the HIV Clinic of Helsinki University Hospital between 2017–2020 who switched TAF to TDF without any other changes in their antiretroviral therapy (ART), and had at least one lipid measurement before and after the switch, were included in the study. No other changes in ART were allowed during the study period.

Control group

For each participant in Switch group, a control participant with unchanged TAF-containing ART, matched for sex, age (±10 years), ethnicity, and the third ART class (non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), integrase strand transfer inhibitor (INSTI)) was chosen. The control participants were required to have at least two lipid measurements while taking TAF. No changes in ART were allowed during the study period.

Data collection

The data on laboratory parameters, comorbidities, comedication, body weight, and smoking were collected from medical charts. Participants with changes in lipid-lowering medication during the study period were excluded from the lipid analyses.

Lipid measurements

In Switch group, baseline value (BL) refers to the last lipid measurement while receiving TAF. The first follow-up value (FU-1) refers to the first lipid measurement at least one month after the switch. We conducted also a subanalysis of long-term effect on lipid parameters by collecting the last values (FU-2) of those participants who had more than one postswitch value available while on stable TDF-containing ART.

In Control group, BL value refers to the first lipid measurement after at least one month treatment with TAF. FU-1 value refers to the next consecutive lipid measurement at least 2 months after BL. If control participants had more lipid measurements, FU-2 value refers to the last lipid measurements whilst remaining on the TAF-containing regimen.

Body weight

Data on body weight were collected as follows: in Switch group, BL body weight was the last body weight on TAF and FU-2 value was the last body weight on TDF. In addition, FU-1 value was collected at a temporal midpoint between BL and FU-2.

In the Control group, the last body weight on TAF was first recorded as FU-2 value. Thereafter, in order to have a comparable follow up time with Switch group, we back calculated a matching timepoint for the BL body weight in Control participants. Corresponding to Switch group, FU-1 body weight was collected at a temporal midpoint between BL and FU-2.

Atherosclerotic cardiovascular disease risk estimator

We used atherosclerotic cardiovascular disease (ASCVD) risk estimator by American College of Cardiology and American Heart Association to calculate cardiovascular risk [17]. It estimates 10-year risk for ASCVD, defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke based on age, sex, race, TC, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking. Since the risk estimator is validated only for those without previous ASCVD diagnosis or lipid lowering therapy and with LDL-C

Table 1. Baseline characteristics of the study groups.

	Switch group ($n=146$)	Control group ($n=146$)	P value
Male, *n* (%)	115 (79%)	115 (79%)	1.0
Age (years)	50 (9.6)	55 (9.6)	**<0.001**
Ethnicity, *n* (%)			1.0
Caucasian	132 (90%)	132 (90%)	
Black	8 (6%)	8 (6%)	
Asian	6 (4%)	6 (4%)	
Body weight (kg)	82.4 (18.4)	83.2 (17.7)	0.732
Body mass index (kg/m^2)	26.3 (5.0)	26.9 (5.0)	0.387
Current smokers, *n* (%)	49 (34%)	41 (28%)	0.128
Lipid-lowering agents, *n* (%)	28 (19%)	32 (22%)	0.671
Diabetes medication, *n* (%)	2 (1%)	9 (6%)	0.250
Hypertension medication, *n* (%)	42 (29%)	47 (32%)	0.525

Switch group switched from TAF to TDF. Control group remained on unchanged TAF-containing regimen. The groups were matched for sex, age (±10 years), ethnicity, and third ART class. Data are given as mean (standard deviation).

<190 mg/dl, we included only participants who met these requirements for the ASCVD analysis.

Laboratory measurements

The laboratory samples were collected after an overnight fast. All lipid values, including LDL cholesterol, were measured directly using enzymatic methods from Abbot Laboratories (Lake Bluff, Illinois, USA). Estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Statistical analysis

Descriptive statistics are presented as means with standard deviations (SD), medians with interquartile ranges (IQR), or frequencies with percentages, as appropriate. Independent samples *t*-test or Mann–Whitney *U* test was used for continuous parametric and nonparametric variables, respectively. For categorical variables, chi-squared test was conducted. For the longitudinal analyses, the dependent samples *t*-test, Wilcoxon signed-rank test, repeated measures ANOVA, and the Friedman test were used. For the repeated measures ANOVA, the Mauchly's test of spherity was conducted and the Greenhouse–Geisser correction was applied if necessary. Dependent samples *t*-test and Wilcoxon signed rank test, both with Bonferroni correction, were used as post hoc -analyses for repeated measures ANOVA and Friedman test respectively. For correlation analyses Pearson's *r* and Spearman's ρ were conducted, as appropriate.

Statistical analyses were carried out using SPSS version 27 (SPSS, Inc., Chicago, Illinois, USA). Two-tailed values of $P<0.05$ were considered statistically significant.

Ethics committee/ethical aspects

The study was approved by Helsinki University Hospital. The ethics committee evaluation is not required for this type of retrospective study.

Results

The study comprised 292 PHIV: 146 in Switch and 146 in Control group. Baseline characteristics are shown in Table 1. Due to matching, in both groups 79% of the participants were male and 90% Caucasian. The groups were comparable for body weight, smoking status, and comedications. Control group was approximately five years older than Switch group. There were no significant differences in lipid-lowering medication use between the groups at baseline. In Switch group vs. Control group, 18% vs. 21% of patients used a statin, 1% vs. 1% ezetimibe and 1% vs. 0% fibrate medication.

HIV related characteristics are shown in Table 2. The groups were comparable for HIV transmission mode, time since diagnosis of HIV, and duration of ART. Due to matching, the proportions of third ART classes were identical in both groups, INSTI being the most common third ART, followed by NNRTI and PI. For booster agents, cobicistat was used more frequently in Control than Switch group, whereas ritonavir use was similar between the groups. Detailed information on antiretroviral agents is given in Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C500.

Laboratory parameters at BL and FU-1 are shown in Table 3. There were no statistically significant differences in variables listed in Table 3 between the study groups at baseline, apart from mean (SD) plasma creatinine (P-Cr) (0.919 mg/dl (0.154) in Switch vs. 0.981 mg/dl (0.216) in Control group, $P=0.006$) and mean (SD) eGFR (93.5 ml/min (15.4) vs. 85.3 ml/min (17.5), $P<0.001$, respectively) (Table 2, Supplemental Digital Content, http://links.lww.com/QAD/C501). At BL, the participants had received TAF medication for a median (IQR) of 76 (50–103) weeks vs. 33 (23–51) weeks in Switch vs. Control group, respectively. The median (IQR) time difference between BL and FU-1 values in Switch group was 46 (26–53) weeks and in Control group 50 (31–54) weeks ($P=0.027$). The median (IQR) time between the baseline measurement and TAF-to-TDF switch was

Table 2. HIV related characteristics of the study groups.

	Switch group ($n = 146$)	Control group ($n = 146$)	P value
HIV transmission mode, *n* (%)			0.103
Male-to-male sexual contact	84 (58%)	70 (48%)	
Heterosexual contact	48 (33%)	60 (41%)	
Intravenous drug use	10 (7%)	6 (4%)	
Other/unknown	4 (3%)	10 (7%)	
Time since HIV diagnosis (years)	12 (7.0)	11 (6.3)	0.114
Total duration of ART (years)	9.5 (5.8)	8.5 (5.0)	0.129
Third ART class, *n* (%)			1.0
Participants taking INSTI	104 (71%)	104 (71%)	
Participants taking NNRTI	30 (21%)	30 (21%)	
Participants taking PI	11 (8%)	11 (8%)	
Participants taking NNRTI + INSTI	1 (1%)	1 (1%)	
Boosting agent, *n* (%)			**<0.001**
Cobicistat	2 (1%)	26 (18%)	
Ritonavir	9 (6%)	10 (7%)	
Single tablet users, *n* (%)	9 (6%)	64 (44%)	**<0.001**
$CD4^+$ cell count (10^6/l)	703 (301)	728 (278)	0.448
HIV-1 RNA, *n* (%)			1.0
Participants with <50 copies/ml	138 (94%)	138 (94%)	
Participants with 50–400 copies/ml	7 (5%)	7 (5%)	
Participants with >400 copies/mL	1 (1%)	1 (1%)	

Switch group switched from TAF to TDF. Control group remained on unchanged TAF-containing regimen. The groups were matched for third ART class. Data are given as mean (standard deviation). ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

4.6 weeks (1.6–15.9). We observed a statistically significant decrease in all lipid values in Switch group. The percentage change (median (IQR)) in TC was −12.1% (−20.9–0), in LDL-C −12.4% (−21.7–5.1), in HDL-C −8.2% (−18.2–4.2), and in TG −11.1% (−32.5–11.4). In Control group no statistically significant changes were seen. The TC/HDL-C ratio did not change in either group. Comparison of lipid data between Switch and Control group at FU-1 is given in Table 3, Supplemental Digital Content, http://links.lww.com/QAD/C502.

We observed no statistically significant changes in P-Cr, eGFR, or plasma phosphate (P-Pi) values in either group. Small but statistically significant increases were notified in spot urine sample protein (U-Prot), plasma alanine aminotransferase (P-ALT), and plasma alkaline phosphatase (P-ALP) values in Switch group. Two virologic failures occurred during the study period in Control group but none in Switch group.

The results of the sub-analysis of plasma lipid concentrations among the 193 patients who also had FU-2 values are shown in Fig. 1 and Table 4, Supplemental Digital Content, http://links.lww.com/QAD/C503. The FU-2 values were taken a median of 103 (80–133) weeks after the BL in Switch group and 128 (100–159) weeks in

Table 3. Results of the laboratory parameters at baseline (BL) and follow-up 1 (FU-1).

	Switch group BL	Switch group FU-1	P value*	Control group BL	Control group FU-1	P value#
P-TC (mg/dl)	203.1 (41.7)	181.5 (40.0)	**<0.001**	195.1 (42.1)	194.5 (41.5)	0.816
P-LDL-C (mg/dl)	130.0 (35.9)	117.4 (32.2)	**<0.001**	124.4 (35.8)	123.1 (36.6)	0.512
P-HDL-C (mg/dl)	52.3 (13.2)	47.7 (14.0)	**<0.001**	51.4 (14.6)	52.8 (14.9)	0.083
P-TG (mg/dl), median (IQR)	109.8 (81.5 – 168.9)	101.9 (77.1–147.9)	**<0.001**	115.1 (83.3 – 167.6)	105.8 (82.6 – 158.3)	0.338
TC/HDL-C ratio, median (IQR)	3.8 (3.3–4.8)	3.8 (3.2–4.6)	0.401	3.8 (3.2–4.6)	3.7 (3.0–4.6)	0.208
P-Cr (mg/dl)	0.919 (0.154)	0.929 (0.164)	0.415	0.981 (0.216)	0.966 (0.219)	0.943
eGFR (ml/min)	93.5 (15.4)	92.0 (16.2)	0.172	85.3 (17.5)	85.5 (18.3)	0.452
P-Pi (mg/dl)	2.7 (0.6)	2.7 (0.5)	0.876	2.7 (0.6)	2.7 (0.6)	0.848
U-Prot (mg/l), median (IQR)	71.0 (67.0–98.0)	81.0 (67.0–128.0)	**0.022**	79.5 (67.0–121.0)	83.5 (67.0–140.0)	0.696
P-ALT (U/l), median (IQR)	28.0 (21.8–40.0)	31.0 (23.0–46.5)	**<0.001**	30.0 (21.0–42.0)	29.0 (19.0–39.0)	0.529
P-ALP (U/l), median (IQR)	70.0 (59.3–84.0)	78.5 (65.0–99.8)	**<0.001**	67.0 (54.0–81.5)	68.0 (55.0–82.0)	0.692
P-Gluc (mg/dl), median (IQR)	104.5 (97.3–112.2)	104.5 (99.1–111.7)	0.220	102.7 (95.5–114.0)	104.5 (97.3–117.1)	0.832

Switch group switched from TAF to TDF. Control group remained on unchanged TAF-containing regimen. The laboratory samples were collected after an overnight fast. Data are given as mean (standard deviation) if not stated otherwise.
*P-values for the pairwise comparisons between BL and FU-1 within Switch group.
#P-values for the pairwise comparisons between BL and FU-1 within Control group.
eGFR, estimated glomerular filtration rate (calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation); IQR, interquartile range; P-ALP, plasma alkaline phosphatase; P-ALT, plasma alanine aminotransferase; P-Cr, plasma creatinine; P-Gluc, plasma glucose; P-HDL-C, plasma high-density lipoprotein cholesterol; P-LDL-C, plasma low-density lipoprotein cholesterol; P-Pi, plasma phosphate; P-TC, plasma total cholesterol; P-TG, plasma triglycerides; TC/HDL-C ratio, ratio of total cholesterol to HDL cholesterol; U-Prot, spot urine sample protein.

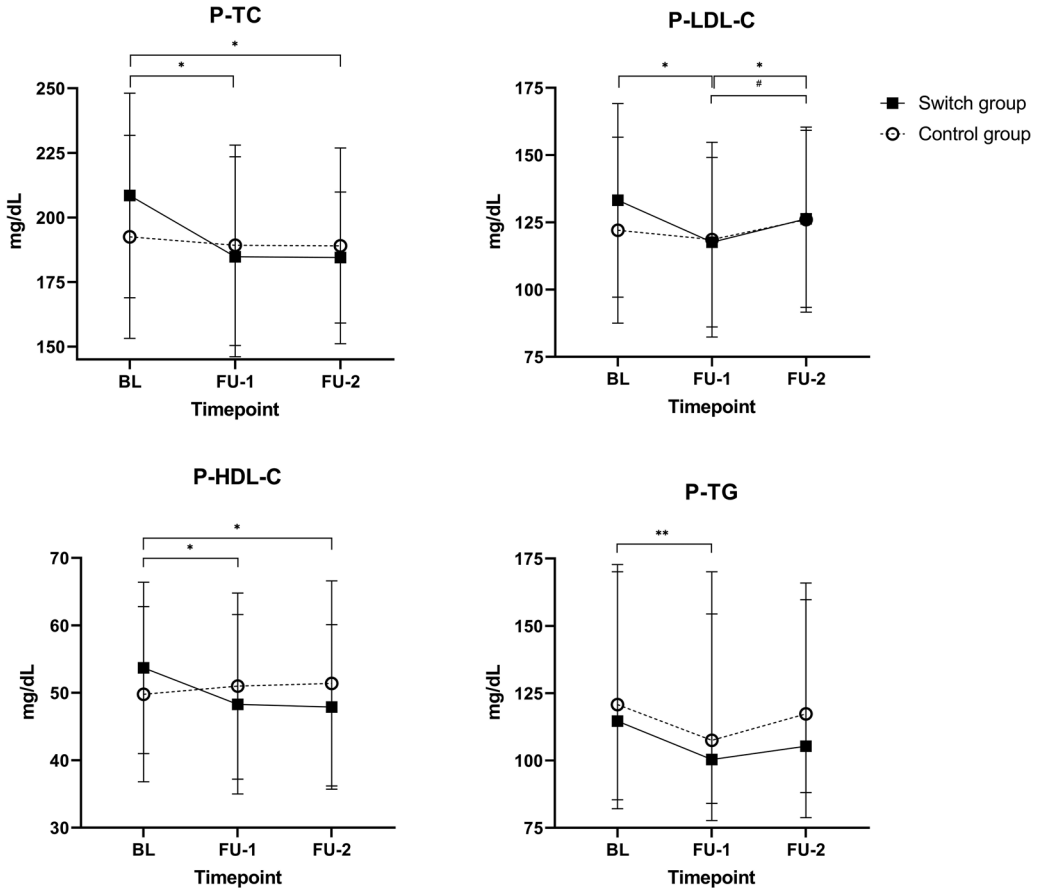

Fig. 1. Plasma lipid values at BL, FU-1 and FU-2 in Switch ($n = 97$) and Control ($n = 96$) groups. P-TC, P-LDL-C and P-HDL-C are mean (±SD). P-TG is median (±IQR). $^{*}P < 0.001$ in Switch group. $^{**}P = 0.024$ in Switch group. $^{\#}P = 0.031$ in Control group. BL, baseline; FU-1, follow-up 1; FU-2, follow-up 2; P-HDL-C, plasma high-density lipoprotein cholesterol; P-LDL-C, plasma low-density lipoprotein cholesterol; P-TC, plasma total cholesterol; P-TG, plasma triglycerides.

Control group. The decrease in TC and HDL-C from BL to FU-2 remained statistically significant in Switch group. For LDL-C, there was a statistically significant increase between FU-1 and FU-2 in both groups. The decrease in LDL-C from BL to FU-2 in Switch group did not reach statistical significance ($P = 0.079$).

During the study period, lipid lowering medication was started for 11 patients in Switch group and for 17 patients in Control group ($P = 0.191$).

In ASCVD risk analysis, the groups were not statistically significantly different at BL ($P = 0.116$). The median (IQR) risk score decreased from 6.3% (2.4–11.5) at baseline to 6.0% (3.2–11.4) at FU-2, $P = 0.012$, in Switch group and increased from 8.4% (3.0–14.8) to 9.1% (4.6– 15.6), $P = 0.162$, respectively in Control group.

Data on body weight are shown in Table 4. The median (IQR) time between BL and FU-1 weight measurements was 52 (50–55) weeks in Switch group and 52 (49–55) weeks in Control group. FU-2 weights were measured a median of 105 (79–131) weeks after the BL in Switch group and 100 (85–108) weeks in Control group. In Control group, we observed a statistically significant increase in body weight between BL weight and FU-1 weight, as well as between BL weight and FU-2 weight. In Switch group, there was no statistically significant weight change during the study period. The percentage change in weight did not correlate with percentage change in LDL cholesterol or other lipid parameters.

To study the potentially confounding effect caused by the baseline age difference between Switch and Control groups, post hoc correlation analyses were conducted. No statistically significant correlations were observed between the baseline age and the within group percentage change in LDL-C, ASCVD risk score or body weight in either group during the study period (data now shown).

Discussion

To the best of our knowledge, this is the first controlled study to report the effects of switching from TAF to TDF

Table 4. Body weight at baseline (BL), follow-up 1 (FU-1), and follow-up 2 (FU-2).

	Weight (kg) at BL	Weight (kg) at FU-1	Weight (kg) at FU-2	*P* value*
Switch group	80.8 (15.5), $n=65$[a]	80.8 (17.7), $n=65$	NA	0.293
Control group	81.9 (17.4), $n=90$[a]	82.8 (17.8), $n=90$	NA	**0.001**
Switch group	83.1 (18.9), $n=95$[b]	NA	83.7 (20.3), $n=95$	0.978
Control group	83.4 (17.6), $n=110$[b]	NA	84.9 (18.6), $n=110$	**0.025**

Switch group switched from TAF to TDF. Control group remained on unchanged TAF-containing regimen. Data are given as mean (standard deviation).
*P-value for the pairwise comparison between BL and FU-1/FU-2 within the study group.
[a]*P*-value for the comparison between Switch and Control group at Baseline was $P=0.686$.
[b]*P*-value for the comparison between Switch and Control group at Baseline was $P=0.922$.
FU, follow up; NA, not applicable.

on detailed plasma lipid concentrations and body weight. This switch caused a statistically significant decrease in plasma lipids, which was reflected in decreased ASCVD score, and was associated with less weight gain compared to Control group that remained on an unchanged TAF containing regimen.

The decrease in LDL cholesterol during the first year after the switch was comparable to the increase observed in previous studies regarding the opposite switch from TDF to TAF [6,7,12]. We could identify only one prior study evaluating the lipid changes caused by TAF-to-TDF switch [6]. In this uncontrolled study, the decrease observed in total cholesterol was similar to that reported in our study, albeit the observation period was shorter than ours. We corroborate and extend these previous findings by the means of including a control group and reporting directly measured LDL cholesterol concentrations.

The numerically higher ASCVD score in Control group at baseline did not translate into higher prevalence of statin use. This may be explained by the similar LDL-C concentrations between the groups at baseline, since the clinicians may have based the initiation of a statin more on LDL-C than ASVD score.

In order to focus on lipid changes directly caused by TAF-to-TDF switch, no other changes in ART were allowed during the follow-up and we excluded participants who changed their lipid lowering medication from the lipid analyses. Since numerically more participants initiated lipid lowering therapy during the study period in Control group, our analysis may slightly underestimate the beneficial lipid effect of TAF-to-TDF switch.

What magnitude of clinical significance may the observed effect on plasma lipids have? Switching TAF to TDF caused a decrease not only in LDL-C and TC but also in HDL-C, hence TC/HDL-C ratio did not change. Nonetheless, LDL cholesterol is considered the main cause of ASCVD [18,19]. The change in cardiovascular risk is directly proportional to the change in LDL cholesterol and the achieved level of LDL cholesterol [18,19]. Studies have also demonstrated that regardless the means by which LDL cholesterol is lowered (e.g. dietary measures or lipid lowering medication) a similar cardiovascular risk reduction is observed [20].

In the subset of participants who had FU-2 measurements available, the decreases in TC and HDL-C remained statistically significant throughout the two-year study period in Switch group. However, in both groups, there was a statistically significant increase in LDL-C between FU-1 and FU-2 timepoints, the reason of which remains unclear. Longer terms studies are needed to confirm the true effect on this ART switch on plasma lipids. Nevertheless, judged from studies on the opposite switch (TDF to TAF), TDF appears to have a long-lasting beneficial lipid-lowering effect, since its withdrawal even after years of exposure led to worsening of lipid profile [7,12].

We also evaluated the effect of TAF-to-TDF switch on ASCVD Score. The ASCVD score was numerically higher in Control than Switch group at baseline. This difference, albeit statistically nonsignificant, was probably driven by the 5-year age difference between the groups. The focus of our study was to monitor the within group changes in both groups. During the 2-year follow-up, we observed a statistically significant decrease in ASCVD risk score from BL to FU-2 in Switch group, whereas Control group had a nonsignificant increase in ASCVD risk score. The decrease in ASCVD score in Switch group regardless of the participants aging two years is in line with the potential cardiovascular benefit of TAF-to-TDF switch.

In recent years, concerns have been raised about increasing obesity rates among PHIV. Despite the reported association of excessive weight gain with the initiation of TAF and INSTIs [10,11], there are no previous data on the effect of switching away from these agents on body weight.

In our study, we observed a stable body weight over 2 years among those who switched TAF to TDF, whereas continuing unchanged TAF-containing regimen led to approximately 1.5 kg weight gain during the same period. In the large OPERA cohort, a switch from TDF to TAF with no other changes in ART was associated with weight

gain of 2.43 kg during the first year, as compared to average weight gain of 0.48 kg/year during previous years whilst receiving TDF. This pronounced weight gain tended to plateau approximately nine months after the switch [15]. As the median duration of TAF-treatment prior to baseline in our study was 33 weeks in Control group, the weight gain between BL and FU-1 may have been enhanced by the less than 9-month duration of TAF-treatment. On the other hand, the weight gain in Control group was of similar magnitude than that observed in PHIV taking ART in general [21], or in general population [22]. This raises the hypothesis that the observed difference in body weight might be due to the weight gain restricting effect of TDF rather than weight increasing effect of TAF.

As the pathogenesis of diabetes mellitus is tightly linked to obesity [23], excessive weight gain among PHIV leads to concerns of rising prevalence of dysglycaemia in this population. Hanttu *et al.* demonstrated that risk of dysglycemia for any given BMI was significantly higher among PHIV compared to the general population, underlining the importance of preventing obesity among these patients [24]. Our study indicates that switching from TAF to TDF could be one tool to control body weight among PHIV. Yet further studies are needed to investigate the unknown mechanisms leading to different effects on body weight and plasma lipids by TDF vs. TAF.

Regarding the safety of TAF-to-TDF switch, we observed no worsening in plasma creatine concentration or eGFR, nor in plasma phosphate concentration. The neutral kidney effect may be explained by the fact that 93% of the participants in Switch group received TDF without ritonavir or cobicistat, as their coadministration increases the risk of kidney and bone toxicity [16]. However, spot urine sample proteinuria increased slightly in Switch group, indicating the importance to monitor kidney function even among these patients. In addition, we noted a small increase in liver enzymes when switching from TAF to TDF. The increase in P-ALT and P-ALP was comparable to the decrease observed in the earlier studies on the opposite TDF to TAF switch [7,25]. The mechanism and clinical importance of these changes are not known.

Regardless the nonrandomized study design, Switch and Control groups were comparable with respect to metabolic parameters at baseline. Control group was five years older than Switch group raising the question about possible confounding effect in the results observed. Nevertheless, no significant correlations were observed between baseline age and the within group changes in primary variables, which was the main focus of our study. These data indicate that the baseline age difference does not explain the results. We matched the study groups for the third ART class, but the individual ART agents were not equally distributed between the groups. Especially the use of elvitegravir/cobicistat, which has been associated with worse lipid profile than other INSTIs was more common in Control group [26]. The number of participants, however, did not allow for sub analyses between the different ART classes or individual agents.

Furthermore, another limitation is the lack of information about participants' dietary or exercise habits that could have affected the change observed both in body weight and plasma lipid concentrations. The specific reasons for the TAF-to-TDF switches were not systemically registered, but it was mainly due to economic reasons after the availability of generic TDF preparations in Finland. Regarding ASCVD risk, the risk calculator is based on American population and the participants in our study were mainly of Finnish origin. In addition, we did not have data on adherence which would have been interesting for the increasing number of tablets in some cases after the switch. However, virologic response, a surrogate marker for adherence, remained excellent in Switch group.

The strength of this study is the fact that all PHIV at our clinic switching from TAF to TDF and meeting the inclusion criteria were included and matched with control participants continuing TAF-based regimen. In addition, we had detailed information about all comedications during the study period.

In conclusion, TAF-to-TDF switch led to decreases in plasma lipid concentrations and was associated with stable body weight, whereas continuous use of TAF increased body weight. These beneficial metabolic effects may have clinical relevance, as a reduction in ASCVD risk estimator showed. Further investigations are needed to explore the mechanisms behind these opposite metabolic effects of TDF vs. TAF.

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K.J.K.: Design of the study, data collection and analysis, manuscript writing.

I.A.: Design of the study, interpretation, manuscript writing.

J.S.: Design of the study, data analysis, interpretation, manuscript writing.

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Conflicts of interest

K.J.K.: None declared.

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