Reversible effect on lipids by switching from tenofovir disoproxil fumarate to tenofovir alafenamide and back

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Objective: The aim of the current study is to assess the effect of tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) on lipids in patients switching from TDF to TAF and back.

Methods: Retrospective data collection on patients who were initially switched from TDF to TAF and switched back to TDF after generics of TDF became available.

Results: In total, 385 patients were included. Median duration of TDF exposure before switch was 317 weeks (interquartile range 172–494). After switching from TDF to TAF, mean total cholesterol (TC) increased from 186 ± 37 mg/dl at baseline to 206 ± 43 and 204 ± 43 mg/dl at weeks 12 and 24 ($P < 0.001$). The increase in TC was mainly due to an increase in LDL cholesterol. However, ratio of TC/HDL remained unchanged, indicating a simultaneous rise of LDL and HDL cholesterol. Baseline triglycerides increased from mean 153 ± 96 to 176 ± 120 and 176 ± 124 mg/dl at weeks, 12 and 24 ($P < 0.001$). From 385 patients 168 were switched back from TAF to TDF after median duration on TAF of 96 weeks (interquartile range 89–104). At switching back from TAF to TDF, mean TC was 202 ± 40 mg/dl and decreased at weeks 12 and 24 to 183 ± 41 and 185 ± 35 mg/dl ($P < 0.001$). Mean triglycerides were 163 ± 119 mg/dl and decreased to 145 ± 108 and 157 ± 112 mg/dl, respectively ($P < 0.05$). Patients with higher increases in TC after switching from TDF to TAF also showed more pronounced decreases after switching back.

Conclusion: The results demonstrate a reversible effect on lipids by switching from TDF to TAF and back.

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Keywords: cholesterol, HIV, lipids, tenofovir alafenamide, tenofovir disoproxil fumarate

Introduction

Strong evidence links higher lipids to cardiovascular disease and mortality in the general population. Also well established is the association of incident cardiovascular disease and high total cholesterol (TC), small dense LDL cholesterol and low HDL cholesterol. Research studies also show that lowering cholesterol has a clinical impact

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on cardiovascular events [1]. Studies in HIV seropositive populations also tie lipids to cardiovascular morbidity and mortality [2,3].

Continuous antiretroviral therapy dramatically reduces HIV-associated morbidity and mortality [4]. Because of this, cardiovascular events are one of the most frequent causes of death in people living with HIV (PLWH) by now [5–7]. However, the use of antiretrovirals may be associated with metabolic complications including dyslipidemia and increased cardiovascular events [2,8–13]. Possible complications of antiretroviral therapy have gained more importance, as efficacy of antiretroviral therapy is generally high and most modifications of treatment regimen are due to adverse events [14] For this, a specific adverse event profile may guide the choice of antiretroviral regimen and motivate switching therapies.

Tenofovir alafenamide (TAF) has been introduced as an alternative to tenofovir disoproxil fumarate (TDF) with a smaller impact on bone density and a better profile on markers measuring renal tubular function [15]. However, comparative clinical trial data also indicate that TAF is associated with greater increases in TC, LDL cholesterol and triglycerides relative to TDF based regimens [16–18]. Randomized clinical trials suggest that TDF based regimens have less impact on lipids than other nucleoside/nucleotide reverse transcriptase inhibitors and may have even a small lipid-lowering effect [10,19–21]. The mechanism by which TDF impacts lipids has not been elucidated so far.

The aim of the current study is to assess the effect of TAF and TDF on lipids in a cohort of PLWH switched from TDF to TAF and back.

Methods

This is a retrospective data collection on effectively suppressed PLWH initially switched from TDF to TAF-based antiretroviral treatment (ART) as a result of optimization of therapy, in a single site (Center for HIV and Hepatogastroenterology, Düsseldorf, Germany). All patients fulfilling the inclusion criteria as outlined below were included in the cohort from 16 April 2016 to 1 August 2017.

All components of ART for all participants had to be maintained the same with the exception of the single substitution of TDF to TAF. Patients on stable lipid-lowering treatment defined as no changes in lipid-lowering therapy 12 weeks before or any time during follow-up were included in the analysis. Lipids were measured before switch and at 12-week intervals after initiation of TAF.

After the introduction of generic versions of TDF, 168 of 385 patients from the cohort were switched back from TAF to TDF, again keeping all other components of ART and concomitant medication unchanged. Lipid profile was measured at 12-week intervals after switch to TDF as part of the clinical routine.

Statistical analysis

Means, SD, medians and interquartile range were calculated. For univariate analysis, Wilcoxon test for related samples was used. For multivariate analysis, continuous data were summarized and compared using the Mann–Whitney test. In case of data grouped into categories, a chi-square test was used. Significance level was set as $P < 0.05$. Clinically relevant changes were defined as an increase from baseline in TC baseline more than 30 mg/dl. Clinically relevant thresholds were defined as TC more than 240 mg/dl or LDL cholesterol more than 160 mg/dl and were analysed using logistic regression analysis.

Due to the noninterventional and retrospective nature of the study, no specific informed consent was required according to German law.

Results

Data from 385 virologically suppressed PLWH were included in the analysis. Mean age at baseline was 49 ± 12 years, 90% were male, 93% white, with a mean BMI of $23.9 \pm 4.3\,kg/m^2$, mean $CD4^+$ cell count 752 ± 298 cells/μl. Median TDF exposure before switching to TAF was 317 weeks [interquartile range (IQR) 172–494] weeks (Table 1). As a third agent, 204/385 (53%) were on integrase inhibitors, 104/385 (27%) on nonnucleoside reverse transcriptase inhibitors, 62/385 (16%) on protease inhibitors and 15/385 (4%) had two additional third agents. A subset of 51/385 patients (13%) were on stable lipid-lowering drug therapy.

At baseline, 26/385 patients (7%) had TC more than 240 mg/dl and triglycerides more than 200 mg/dl were reported in 83/385 (21%). Before switching to TAF, mean TC was 186 ± 37 mg/dl and it increased to 206 ± 43 and 204 ± 43 mg/dl at weeks 12 and 24 ($P < 0.001$). Mean triglycerides was 153 ± 96 mg/dl and increased to 176 ± 120 mg/dl at week 12 and to 176 ± 124 mg/dl at week 24 ($P < 0.001$).

From 70 patients, additional data on LDL and HDL cholesterol were available at week 12 on TAF and demonstrate an increase of LDL cholesterol from

Table 1. Demographics at change from tenofovir alafenamide to tenofovir disoproxil fumarate and from tenofovir disoproxil fumarate back to tenofovir alafenamide.

	Switch from TDF to TAF	Switch from TAF back to TDF
Number of patients	385	168/385
Weeks on TDF before switch to TAF median (IQR)	317 (172–494)	308 (161–478)
Weeks on TAF before rechange to TDF median (IQR)		96 (89–104)
Sex (male)	345/385 (90%)	145/168 (86%)
Ethnicity (white)	356/385 (93%)	152/168 (86%)
Ethnicity (African/Asian/na)	5%/1%/2%	7%/1%/2%
Age (years)	49 ± 12	49 ± 11
BMI (kg/m^2)	23.9 ± 4.3	24.0 ± 4.4
HIV RNA <40 copies/ml	376/385 (98%)	165/168 (99%)
CD4$^+$ cells(/μl)	752 ± 298	733 ± 282
CD4$^+$ cells (%)	33 ± 9	34 ± 9
CDC stage (A/B/C)	48%/27%/24%	43%/31%/26%
CD4$^+$ nadir (<200/200–499/≥500) cells/μl	37%/44%/19%	43%/39%/18%
Years since HIV diagnosis	12 ± 7.8	12 ± 7.8
Stable lipid-lowering therapy	51/385 (13%)	20/168 (12%)

CDC, US centers for disease control and prevention; IQR, interquartile range; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

120 ± 34 to 130 ± 36 mg/dl ($P < 0.005$) and HDL cholesterol from 46 ± 13 to 52 ± 17 mg/dl ($P < 0.001$).

The ratio TC/HDL remained unchanged with 4.63 ± 1.46 before and 4.56 ± 1.48 at week 12 after switching from TDF to TAF ($P = 0.356$). The ratio triglycerides/HDL was 3.89 ± 2.67 and 4.26 ± 3.57 ($P = 0.426$), respectively.

In a logistic regression analysis, the odds of having TC more than 240 mg/dl after switching to TAF was associated with older age (increased by 2% per year; $P = 0.027$), BMI more than 25 kg/m^2 ($P = 0.020$) and elevated baseline LDL cholesterol (>160 mg/dl) ($P < 0.001$). In the multivariate model, age more than 50 years [odds ratio (OR) 1.58, $P < 0.01$] and BMI more than 25 kg/m^2 (OR 2.08, $P < 0.01$) remained independently associated with TC more than 240 mg/dl.

After generics of TDF were introduced in Germany, 168/385 patients were switched back from TAF to TDF after median 96 weeks (IQR 89–104 weeks) on TAF. A comparison of the baseline demographics of all patients and the patients who were switched back is shown in Table 1. In these 168 patients initially after switching from TDF to TAF, TC had increased from 188 ± 36 to 208 ± 43 and 203 ± 42 mg/dl at weeks 12 and 24. Triglycerides increased from 149 ± 95 to 185 ± 139 and 171 ± 104 mg/dl.

At switching back from TAF to TDF, mean TC was 202 ± 40 mg/dl and it decreased at week 12 to 183 ± 41 mg/dl and to 185 ± 35 at week 24 ($P < 0.001$). Mean triglycerides were 163 ± 119 before switching back from TAF to TDF and decreased to 148 ± 108 and 157 ± 112 mg/dl at weeks 12 and 24, respectively ($P < 0.05$).

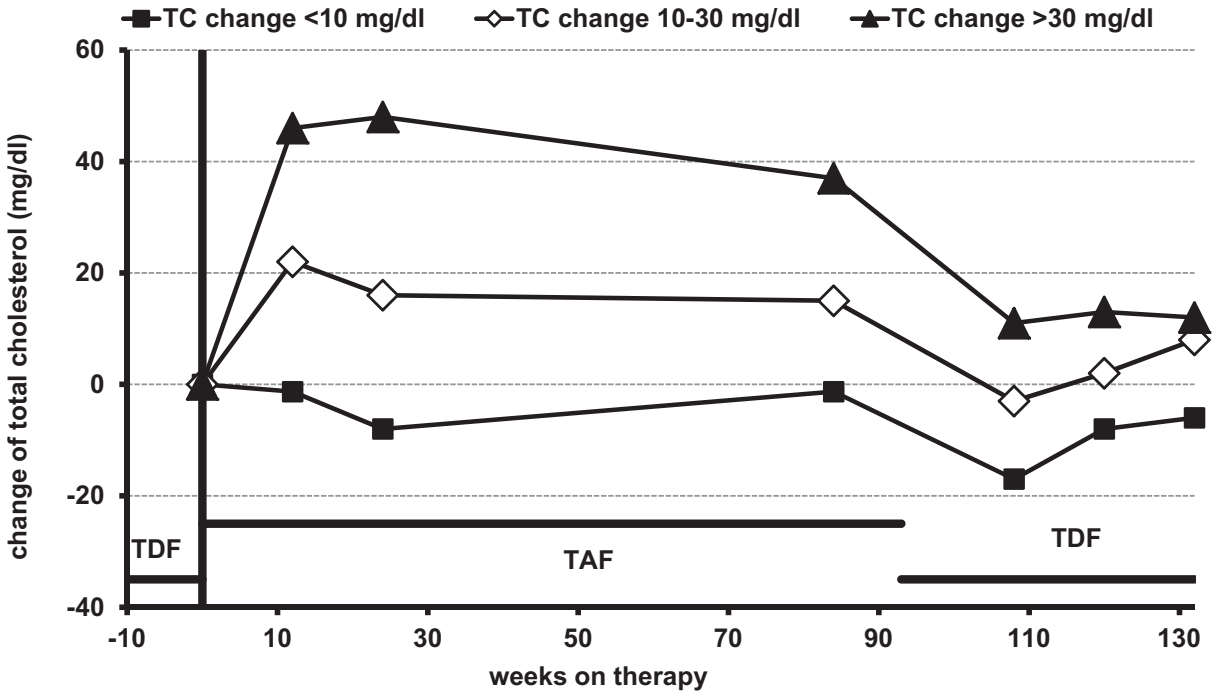
After switching from TDF to TAF, about 1/3 of patients had no or minor increases in TC (<10 mg/dl), while 68% of patients showed an increase more than 10 mg/dl. TC increased more than 30 mg/dl in 31% of patients after switching from TDF to TAF.

Patients with higher increases in cholesterol after switching from TDF to TAF (>30 mg/dl compared with <10 mg/dl) also showed more pronounced decreases after switching back from TAF to TDF (Fig. 1). Being on lipid-lowering drugs or the drug class of the third antiretroviral agent did not affect these results.

Discussion

The results of our study confirm a reversible, pharmacological effect on lipid profile of a switch from TDF to TAF and back. This effect is not a universal phenomenon in all patients, but observed at a level of an increase of TC more than 30 mg/dl and back in about a third of the cohort. In the multivariate analysis, patients with cardiovascular risk factors such as older age and higher BMI were more likely to experience an increase in TC after a switch from TDF to TAF.

Prevention and management of drug-related adverse events and maintenance of adherence remain key challenges to the success of long-term antiretroviral therapy. Previously published studies document several benefits of switching from TDF/emtricitabine (FTC) to TAF/FTC containing regimens. These advantages include significant improvement in markers of kidney and bone safety profile [15–18,21]. However, these may be counteracted by a worsening in cardiovascular risk profile due to discontinuation of TDF/FTC. A possible beneficial impact of the lipid-lowering effect of TDF has not been confirmed with clinical endpoint studies to date, but most situations leading to an increase in LDL



>30 mg/dl	46	45	43	46	37	17
10-30 mg/dl	64	62	60	64	61	20
<10 mg/dl	58	57	56	58	47	24

Fig. 1. Time course of total cholesterol after switch from tenofovir disoproxil fumarate to tenofovir alafenamide and back according to change in total cholesterol (differences, means).

cholesterol have been associated with an increase in cardiovascular events.

In previous studies, TDF has shown a lipid-lowering effect on total and LDL cholesterol [21]. In healthy volunteers, total and non-HDL cholesterol are also reduced by TDF and no impact on glucose disposal was observed [22]. Changes observed in cholesterol in our study are similar to those reported with less potent statin agents [23]. However, changes in lipids observed in our study may not have the same impact on cardiovascular risk as lipid reductions with statin agents due to the anti-inflammatory effects of these agents [24]. In addition, the ratio of TC/HDL remained unchanged after switching from TDF to TAF which indicates a simultaneous rise of LDL and HDL cholesterol. Lastly, the effect of TDF on cardiovascular outcomes has not been assessed prospectively in controlled studies, but in cohort studies the use of TDF was at least not associated with an increased risk of cardiovascular events [25].

However, as TAF compared with TDF has shown a beneficial effect on renal biomarkers and bone density, the possible benefit of lipid changes associated with TDF should be weighed against the possible benefit of TAF for bone and kidney. These different properties should be considered when choosing the specific antiretroviral therapy based on the individual patient profile [15].

Our study has some limitations; predominately, it is of retrospective nature and did not include detailed assessments of other clinical and biomarkers of cardiovascular risk other than lipids. In addition, LDL and HDL cholesterol results are available in only a fraction of the cohort. Another limitation is the lack of data on weight and BMI changes after switching to TAF and back, as this may affect lipid levels. However, the rapid changes of lipid levels observed after a few weeks of exposure to TAF or TDF are more consistent with a pharmacological effect driven by switching from TDF to TAF and back compared with the effect of a BMI change on lipids.

A specific strength of our results is that all patients included in the study had stable third antiretroviral drug and no changes in lipid-lowering therapy through duration of the follow-up, the only change in patients regimen was switch of TDF to TAF and back.

In summary, switching from TDF/FTC to TAF/FTC lead to a marked and reversible increase in TC and other proatherogenic lipid fractions in a relevant proportion of patients.

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Conflicts of interest

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