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Lipid changes due to tenofovir alafenamide are reversible by switching back to tenofovir disoproxil fumarate

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Short title: Lipids and switch from TDF to TAF and back

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Abbreviations: HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol, PLWH = people living with HIV, TAF= tenofovir alafenamide, TC = total cholesterol, TDF = tenofovir disoproxil fumarate

Conflicts of interest

Ana Milinkovic: honoraria for consultancy and speaker services, as well as support for conference attendance from Gilead Sciences, MSD, Janssen and ViiV Healthcare

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Abstract

Objective: Switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) has shown worsening of lipids, but there is little data exploring changes in lipids switching back from TAF to TDF.

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 (IQR 172-494). After switching from TDF to TAF mean total cholesterol (TC) increased from 186±37 mg/dl at baseline to 206±43 mg/dl 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. Baseline triglycerides increased from mean 153±96 mg/dl to 176±120 mg/dl and 176±124 mg/dl at week 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 (IQR 89-104). At switching back from TAF to TDF mean TC was 202±40 mg/dl and decreased at week 12 and 24 to 183±41 mg/dl and 185±35 mg/dl ($p<0.001$). Mean triglycerides were 163±119 mg/dl and decreased to 145±108 mg/dl and 157±112 mg/dl, respectively ($p<0.005$). Patients with higher increases in TC after switching from TDF to TAF also showed more pronounced decreases after switching back.

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

Key words: HIV, TDF, TAF, cholesterol, lipids.

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, small dense low-density lipoprotein cholesterol (LDL) and low high-density lipoprotein cholesterol (HDL). Research studies also show that lowering cholesterol has a clinical impact 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 the second most frequent cause of death in people living with HIV (PLWH) by now [5]. However, the use of antiretrovirals may be associated with metabolic complications including dyslipidemia and increased cardiovascular events [2, 6, 7, 8, 9, 10]. 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 [11] 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 [12]. But, comparative clinical trial data also indicate that TAF is associated with greater increases in total cholesterol, LDL cholesterol and triglycerides relative to TDF based regimens [13, 14, 15]. 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 [8, 16, 17, 18]. The mechanism by which TDF impacts lipids has not been elucidated so far.

The aim of the present 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 components of ART for all participants were 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 weeks 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 weeks intervals after switch to TDF as part of the clinical routine.

Statistical Analysis

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

Due to the non-interventional and retrospective nature of the study no specific informed consent was required according to German law.

Results:

Data from 385 virologically suppressed people living with HIV (PLWH) were included in the analysis. Mean age at baseline was 49±12 years , 90% were male, 93% Caucasian, with a mean Body Mass Index (BMI) of 23.9±4.3kg/m2 , mean CD4 cell count 752±298 cells/µl. Median TDF exposure before switching to TAF was 317 weeks (IQR 172-494) weeks (Table 1). As a third agent 204/285 (53%) were on integrase inhibitors, 104/385 (27%) on non-nucleoside 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 >240 mg/dl and triglycerides >200 mg/dl were reported in 83/385 (21%). Before switching to TAF, mean total cholesterol was 186±37 mg/dl and it increased to 206±43 mg/dl 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 120±34 mg/dl to 130±36 mg/dl ($p<0.005$) and HDL-cholesterol from 46±13 mg/dl to 52±17 mg/dl ($p<0.001$).

In a logistic regression analysis the odds of having total cholesterol >240 mg/dl after switching to TAF was associated with older age (increased by 2% per year; $p=0.027$), BMI >25 kg/sqm ($p=0.020$) and elevated baseline LDL cholesterol (>160 mg/dl) ($p<0.001$). In the

multivariate model, age >50 years (OR 1.58, p<0.01) and BMI>25 kg/m2 (OR 2.08, p< 0.01) remained independently associated with TC >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 total cholesterol had increased from 188±36 mg/dl to 208 ±43 mg/dl and 203±42 mg/dl at week 12 and 24. Triglycerides increased from 149±95 mg/dl to 185 ±139 mg/dl 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 mg/dl and 157±112 mg/dl at week 12 and 24, respectively (p<0.005).

After switching from TDF to TAF about 1/3 of patients had no or minor increases in total cholesterol (<10 mg/dl), while 65% of patients showed an increase >10 mg/dl. Total cholesterol increased >30 mg/dl in 27% of patients after switching from TDF to TAF.

Patients with higher increases in cholesterol after switching from TDF to TAF (>30 mg/dl compared to < 10 mg/dl) also showed more pronounced decreases after switching back from TAF to TDF (Figure 1). Being on lipid lowering drugs did not affect this observation.

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 total cholesterol >30mg/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/FTC to TAF/FTC containing regimens. These advantages include significant improvement in markers of kidney and bone safety profile [12, 13, 14, 15, 18]. 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 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 [18]. In healthy volunteers total and non-HDL cholesterol are also reduced by TDF and no impact on glucose disposal was observed [19]. Changes observed in cholesterol in our study are similar to those reported with less potent statin agents [20]. 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 [21]. 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 [22].

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 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 to the effect of a BMI change on lipids.

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 total cholesterol and other proatherogenic lipid fractions in a relevant proportion of patients.

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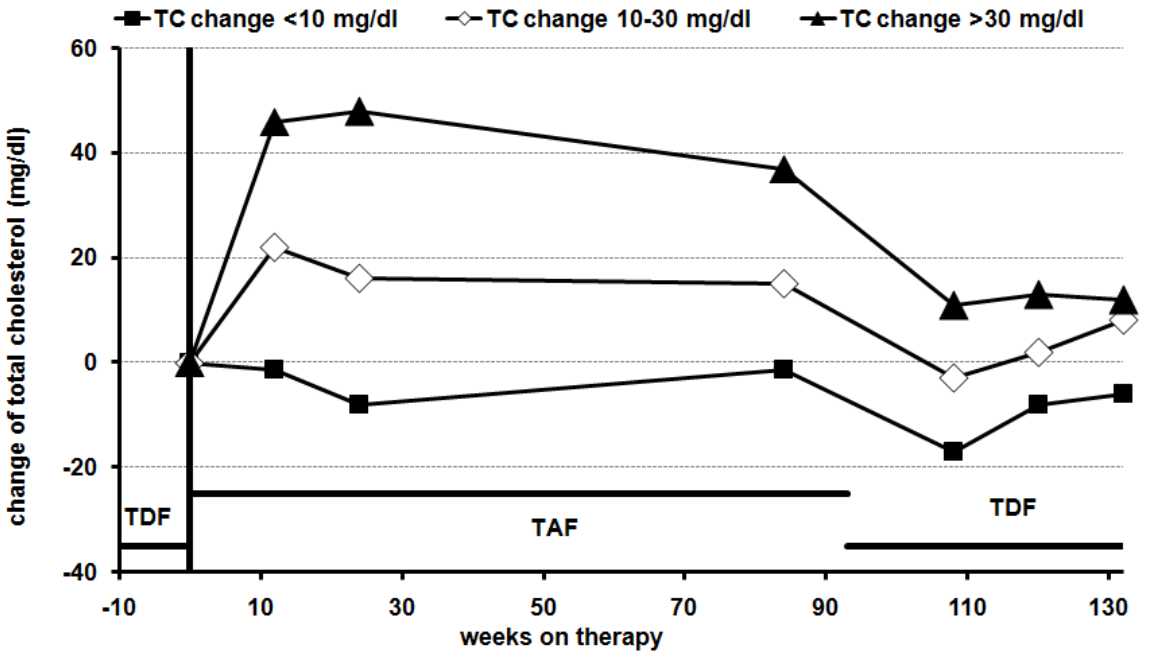
Table 1: Demographics at change from TAF to TDF and from TDF back to TAF

	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 (Caucasian)	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 cp/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%)

Figure 1: Time course of total cholesterol (TC) after switch from TDF to TAF and back according to change in TC (differences, means)



>30 mg/dl	46	45	43	46	37	17
10-30 mg/dl	64	62	60	64	251	20
<10 mg/dl	58	57	56	58	47	24