

Evaluation of the Lipid Concentrations after Switching from Antiretroviral Drug Tenofovir Disoproxil Fumarate/Emtricitabine to Abacavir Sulfate/Lamivudine in Virologically-suppressed Human Immunodeficiency Virus-infected Patients

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Abstract

Objective Recently, tenofovir disoproxil fumarate (TDF)-related side effects, such as renal nephrotoxicity and reduction of bone mineral density, have been reported. Consequently, increased switching from fixed-dose tablet TDF and emtricitabine (TDF/FTC) to abacavir and lamivudine (ABC/3TC) has occurred. Interestingly, while TDF has a lipid-lowering property, one of the ABC-related side effects is hyperlipidemia. Therefore, such switching could cause lipid elevation. To evaluate the change in lipid levels associated with switching from TDF/FTC to ABC/3TC in virologically-suppressed human immunodeficiency virus (HIV)-infected patients.

Methods This is a retrospective, single-center study. We included the HIV-infected patients whose therapy included a drug switch from TDF/FTC to ABC/3TC between September 2009 and December 2012 at Ryukyu University Hospital. The exclusion criteria were HIV-RNA >40 copies/mL on the switching day, and a documented therapy change to a lipid-lowering agent or any other antiretroviral agents within 3 months before or after switching. We compared the low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), and triglyceride (TG) levels before switching to three months after.

Results A total of 18 patients met the inclusion criteria. The LDL, HDL, and TC levels significantly increased three months following the switch ($p < 0.05$), with median (interquartile range) values of 17 (7, 32), 6 (2, 13), and 27 (10, 45) mg/dL, respectively. The TG values did not markedly change.

Conclusion Switching from TDF/FTC to ABC/3TC resulted in significantly increased LDL, HDL, and TC levels.

Key words: tenofovir disoproxil fumarate, abacavir, antiretrovirus therapy, dyslipidemia, human immunodeficiency virus

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Introduction

Since the introduction of combination antiretroviral ther-

apy (cART), the mortality and prognosis of human immunodeficiency virus (HIV)-infected patients have improved (1-3). At the same time, the rates of acute myocardial infarction (AMI) and cardiovascular risk factors have

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also increased compared with the rates in non-HIV patients (4). Dyslipidemia remains an independent risk factor for cardiovascular disease in HIV-infected patients (4). Therefore, lipid management is an important consideration in the cardiac risk modification strategies for the long-term care of HIV patients.

The recommended initial therapy for HIV infection consists of two nucleoside reverse transcriptase inhibitors (NRTIs) combined with a third antiretroviral agent. Among NRTI combinations, the international treatment guidelines list tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as the preferred regimen and abacavir sulfate/lamivudine (ABC/3TC) as an alternative, except when combined with dolutegravir (5, 6). TDF/FTC has superior virologic response to ABC/3TC in patients with a high viral load, and ABC may cause hypersensitivity reactions (7).

However, side effects associated with the long-term use of TDF have been appeared. A meta-analysis concluded that TDF use was associated with a modest loss of renal function, as evidenced by an average reduction in creatinine clearance of 3.9 mL/min (8). The risk was even greater in Japanese patients in particular, in whom the reduction was about four times as high, with an average glomerular filtration rate of 17 mL/min/1.73 m² (8, 9). Given that a low body weight has also been identified as an independent risk factor for tenofovir-associated renal dysfunction (10), the difference between the Japanese and European populations in rates of tenofovir-related renal dysfunction was largely attributed to differences in body weight. Additionally, TDF is associated with a reduction in bone mineral density and increased risk of osteoporotic fracture (11, 12). However, the prevalence of HLA-B*5701, which has a high correlation with ABC-related severe hypersensitivity, is 0.1% in Japanese, which is lower than that in other races (13, 14). This high risk of renal failure and osteoporotic fracture and low risk of hypersensitivity has therefore prompted switching from TDF/FTC to ABC/3TC in Japan.

Interestingly, TDF has a lipid-lowering property (15-18). Withdrawing TDF from cART regimens has been shown to significantly increase total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels by mean degrees of 19, 4, and 11 mg/dL, respectively, over 12 weeks (17). Conversely, ABC might increase the lipid levels. Indeed, according to a Japanese post-marketing survey of ABC/3TC, the incidence of major lipid-related adverse events are 9.5% for hyperlipidemia, 3.4% for hypertriglyceridemia, and 2.2% for an increase in blood triglyceride levels (19). However, to our knowledge, no study has yet examined the incremental fluctuations in lipid levels as a result of switching therapies.

It is therefore regarded that switching TDF/FTC to ABC/3TC would increase the lipid level by abolishing the lipid lowering effect of TDF and by inducing a lipid increasing effect of ABC. However, to the best of our knowledge, no prior study has measured the incremental changes which occur as a result of a change in therapy.

Objective

We herein evaluated the change in lipid levels associated with switching from TDF/FTC to ABC/3TC in virologically-suppressed HIV-infected patients.

Materials and Methods

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards and was approved by the Ethics Committee of Ryukyu University (No. 721).

Study design

This is a retrospective, single-center study. We compared LDL, HDL, TC, and triglyceride (TG) levels before switching and three months after. The baseline data were obtained from the records compiled on the blood sampling day closest to the ABC/3TC initiation. The later data were recorded as “post-three months” and were obtained on the blood sampling day closest to 90 days after switching. To investigate the existence of possible external factors, we also compared LDL, HDL, TC, and TG changes from baseline to post-three months in a control group whose medication was consistently maintained.

Study patients

We evaluated HIV-infected patients switched from a TDF/FTC to an ABC/3TC regimen between September 2009 and December 2012 at Ryukyu University Hospital. The exclusion criteria were HIV-RNA >40 copies/mL on the day of switching and a documented therapy change to a lipid-lowering agent or any other antiretroviral agents within 3 months before or after switching. We also included patients who remained on TDF/FTC therapy as controls, applying the same exclusion criteria described above. These groups were referred to as the “switching” and “non-switching” groups, respectively.

Statistical analyses

The baseline characteristics between the switching and non-switching groups were compared using Fisher's exact test or Mann-Whitney's U test. The p value for intervals from baseline between the two groups were determined using Mann-Whitney's U test. The p value for comparison between the blood concentrations of lipid parameters at baseline and those at post-three months in the switching group were determined using Wilcoxon signed-rank test. The p value for comparison of the changes in lipid levels between the two groups were determined using Mann-Whitney's U test. The proportions of subjects outside the Japan Atherosclerosis Society (JAS) (2012)-recommended lipid levels at baseline were compared with the proportions at post-three months using Fisher's exact test. All of the analyses used a

Table 1. Baseline Characteristics.

	switch group (n=18)	non-switch group (n=19)	p value
Male	18	19	1.000
Median age, years	44 (38 - 68)	39 (24 - 54)	0.423
Japanese, (%)	17 (94)	19	1.000
Median weight, kg	67 (59 - 76)	67 (50 - 89)	0.423
Median TDF/FTC use, months (IQR)	48 (24 , 64)	33 (14 , 63)	0.463
Median CD4+ cells ,/μL (IQR)	551 (347 , 690)	568 (507 , 754)	0.525
CD4+ cells below 200 /μL, (%)	2 (11)	2 (11)	1.000
Comorbidity			
Dyslipidemia, (%)	12 (67)	10 (53)	0.508
Type II diabetes mellitus, (%)	0 (0)	2 (11)	0.486
HCV infection, (%)	2 (11)	1 (5)	0.604
Hemophilia B, (%)	2 (11)	0 (0)	0.230
Smoker, (%)	8 (44)	8 (42)	1.000
Third antiretroviral agent, (%)			
RAL	8 (44)	9 (47)	1.000
EFV	6 (33)	6 (32)	1.000
ATV/r	2 (11)	2 (11)	1.000
LPV/r	1 (6)	1 (5)	1.000
DRV/r	1 (6)	1 (5)	1.000
Stable lipid-lowering treatments at baseline, (%)			
Statins	1 (6)	1 (5)	1.000
Fibrates	2 (11)	1 (5)	0.604
Median lipid parameters, mg/dL (IQR)			
LDL	92 (82 , 105)	97 (83 , 107)	0.456
HDL	43 (36 , 49)	41 (37 , 50)	0.860
TG	166 (100 , 212)	126 (109 , 159)	0.284
TC	159 (143 , 178)	157 (146 , 172)	0.203

p values for comparison between the switch group and the non-switch group are determined by Fisher's exact tests or by Mann-Whitney's U tests. Abbreviations: IQR: interquartile range, HCV: hepatitis C virus, TDF/FTC: tenofovir/emtricitabine, RAL: raltegravir, EFV: efavirenz, ATV: atazanavir, /r: ritonavir, LPV: lopinavir, DRV: darunavir, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, TC: total cholesterol

Table 2. Intervals from Baseline.

	Median Days (interquartile range)		p value
	switch group	non-switch group	
Post three months	88 (84, 98)	84 (84, 91)	0.822

Post three months is defined as the closest day to post 90 days from the baseline measurement. p value for comparison between the switch group and the non-switch group is determined by Mann-Whitney's U test.

two-sided alpha of 0.05. The statistical analyses were performed using the SPSS Statistics software program, ver. 21 (IBM).

Results

A total of 27 patients switched from TDF/FTC to ABC/3TC between September 2009 and December 2012 at Ryukyu University Hospital, and 18 of these were included in this analysis, with 9 excluded (3 for changing to a third antiretroviral agent in the period of three months before switching and three months after, 2 for HIV-RNA >40 copies/mL at baseline, 2 who discontinued ABC/3TC due to nausea, 1 who reduced the dose of mevalostatin at baseline, and 1 who added another antiretroviral agent after switching).

The patient baseline characteristics are shown in Table 1. In the switching group, all of the patients were Japanese ex-

cept for one Caucasian, the median duration of TDF/FTC use was 48 months, and the median CD4⁺ cell count was 551/μL. No significant differences were noted between the groups for any baseline characteristic. Table 2 shows the actual interval of blood sampling between the baseline and the post-three months measurement. The interval in the switching group had a median (interquartile range) of 88 (84-98) days. There were no significant differences in this interval between the groups.

The lipid parameters at the baseline and post-three months in the switching group are shown in Table 3. A significant increase was noted in the LDL, HDL, and TC levels three months after switching. Table 4 shows the lipid changes from baseline to post-three months in both groups. The changes in the LDL, HDL, and TC levels were significantly greater in the switching group than in the non-switching group, although no marked differences were noted in the TG levels between the groups.

In the switching group, the LDL, HDL, and TC levels increased by a median (interquartile range) of 17 (7, 32), 6 (2, 13), and 27 (10, 45) mg/dL, respectively. The Figure shows the proportion of subjects outside the JAS 2012 recommended lipid level. In the switching group, the proportion of patients with an LDL level ≥100 mg/dL at post-three months was significantly higher than at baseline. The proportion of patients with an HDL level <40 mg/dL at post-three months

Table 3. Lipid Parameters at Baseline and Post Three Months in Patients who Switched TDF/FTC to ABC/3TC.

	Median (IQR) n=18		p values
	Baseline	Post three months	
LDL, mg/dL	92 (82 , 105)	114 (97 , 137)	< 0.001
HDL, mg/dL	43 (36 , 49)	48 (41 , 54)	0.001
TG, mg/dL	166 (100 , 212)	142 (111 , 177)	0.948
TC, mg/dL ^α	159 (143 , 178)	184 (174 , 218)	0.009

p values for comparison between blood concentrations of lipid parameters at baseline and those of at post three months are determined by Wilcoxon signed-rank tests. Baseline is defined as the first day when ABC/3TC was prescribed. Abbreviations: IQR: interquartile range, TDF: tenofovir, FTC: emtricitabine, ABC: abacavir, 3TC: lamivudine, ^α TC n=12

Table 4. Lipid Change from Baseline at Post Three Months.

	Median (IQR)		p
	switch group (n=18)	non-switch group (n=19)	
LDL, mg/dL	17 (-6 , 31)	-6 (-11, -1)	< 0.001
HDL, mg/dL	6 (-2 , 13)	1 (-3 , 5)	0.034
TG, mg/dL [†]	-20 (-61 , 31)	-3 (-20, 20)	0.563
TC, mg/dL [‡]	27 (10 , 45)	-1 (-10, 9)	0.002

p values for comparison between the switch group and the non-switch group in lipid changes are determined by Mann-Whitney's U tests. Abbreviations: IQR: interquartile range, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, TC: total cholesterol

[†] TG n=18 in the non-switch group.

[‡] TC n=12 in the switch group, whereas n=15 in the non-switch group.

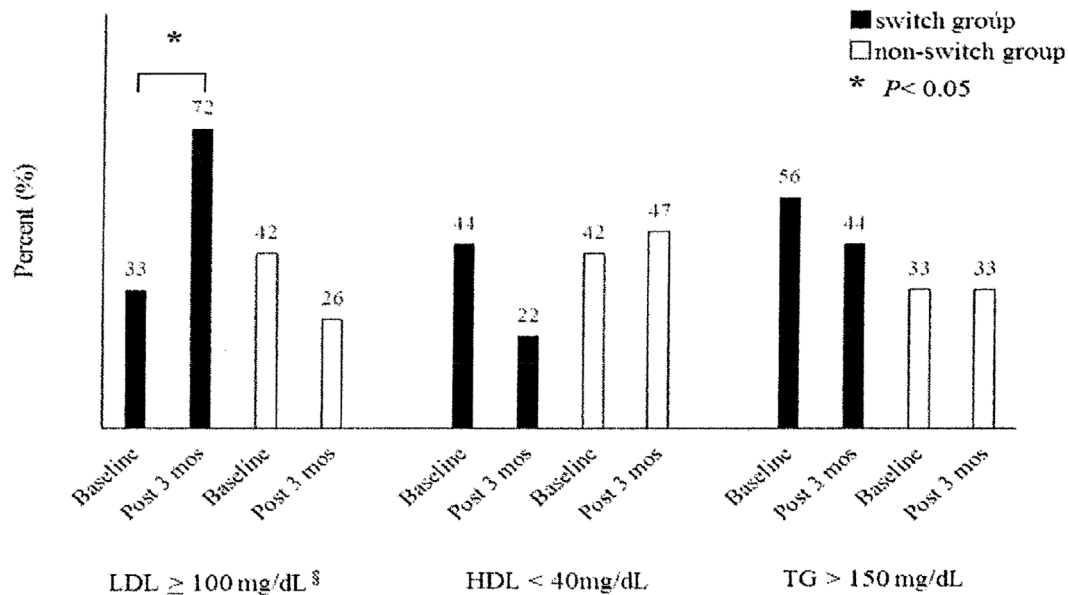


Figure. Proportion of subjects outside JAS (2012) recommended lipid level. Fisher's exact tests were applied to compare proportions at baselines with those of post three months. JAS: Japan Atherosclerosis Society, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride. § recommended as secondary prevention of coronary artery disease.

was lower than at baseline, but not significantly.

Discussion

To the best of our knowledge, this is the first study evaluating the lipid changes associated with switching from TDF/FTC to ABC/3TC in virologically-suppressed HIV-infected patients. In our results, the LDL, HDL, and TC levels significantly increased three months after switching by median (interquartile range) values of 17 (7, 32), 6 (2, 13), 27 (10, 45) mg/dL, respectively. However, the TG levels did not significantly change.

To investigate the potential influence of external factors, such as recovery from low immunity or malnutrition and diet education in outpatient care, we compared the changes in the lipid levels of patients who switched to the changes in those who continuously used TDF/FTC. No significant differences in any baseline characteristic were noted between these groups. The changes in the LDL, HDL, and TC levels-

but not the TG levels - were significantly greater in the switching group than in the non-switching group. We therefore concluded that no external factors had affected our results.

Our findings regarding the changes (or lack thereof) in TC, LDL, HDL, and TG levels agreed with the previous study, which withdrew TDF from cART (17). While the absolute values for the changes in lipids in our study were greater than those in the study that only withdrew TDF from cART, we were unable to compare the fluctuation range between the studies because the preceding study lacked any data on basic statistics, such as the population variance (17).

Observational and clinical studies conducted in Japan have shown that the likelihood of recurrence of cardiovascular disease decreases in association with a decrease in the LDL level to 100 mg/dL (20, 21). Many studies have shown that an HDL level <40 mg/dL is associated with an increased risk of cardiovascular disease compare to a level ≥40 mg/dL (21-26). In the present study, not only TC and

LDL levels but also HDL levels were increased when TDF/FTC was switched to ABC/3TC. In addition, the proportion of patients with LDL levels ≥ 100 mg/dL significantly increased after switching. In contrast, the proportion of patients with HDL levels < 40 mg/dL decreased, but not significantly. This indicates that the increase in the HDL level was not enough to exceed the threshold of 40 mg/dL. Therefore, the increase in lipid levels with drug switching increased the risk of recurrence of cardiovascular disease in our study population.

Several limitations associated with the present study warrant mention. First, our study was retrospective. To reduce the risk of any biases, we initially included all of the patients who switched from TDF/FTC to ABC/3TC and then excluded the inappropriate patients. Second, the number of analyzed patients was small. Our results may therefore not apply to the general population. Third, some patients may have eaten a meal before the blood sampling. Although we attempted to only examine fasting blood samples from HIV-infected outpatients, since we did not record the meal intake status before the sampling, fasting blood sampling might not have been strictly observed in all of the patients. The results from non-fasting blood sampling might have affected our findings, mainly via an observed increase in TG levels. Fourth, we could not clarify the degree to which the discontinuation of TDF or addition of ABC contributed to the lipid change. Resolving this issue will require investigating the change in the lipid levels by adding ABC to virologically-suppressed patients whose regimen does not contain ABC. However, administering unnecessary drugs is ethically inappropriate and could cause adverse events or worsen adherence. In clinical practice, we most often switch TDF/FTC to ABC/3TC since both are fixed-dose tablets. As such, investigating the degree to which each substance contributes to the lipid change is likely not actually meaningful.

A previous study showed the lipid-lowering effects of TDF (15-18) and the incidence of ABC-associated lipid elevation (19). However, our study specifically demonstrated the lipid elevation associated with switching TDF/FTC to ABC/3TC, as well as the fluctuation range. Since HIV-infected patients have increased cardiovascular risk factors and switching from TDF/FTC to ABC/3TC is increasingly common in Japan, thus demonstrating the lipid elevation and the fluctuation range associated with switching therapies is clinically meaningful.

Conclusion

Switching from TDF/FTC to ABC/3TC resulted in an increase in the LDL, HDL, and TC levels.

The authors state that they have no Conflict of Interest (COI).

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