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Tenofovir Disoproxil Fumarate-Lowering Lipid Effects Moderately Protect Liver during Long-Term Antiretroviral Therapy in HIV-Infected Patients

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Abstract

Background: Non-alcoholic fatty liver disease is prevalent in HIV-infected patients and dyslipidemia is the main cause of long-term toxicities of current antiretroviral therapy (ART). Tenofovir disoproxil fumarate (TDF) is a commonest antiretroviral of ART. It has been reported to have lipid-lowering effects.

Objectives: In this study, the influences of the lipid-lowering effects of TDF on fatty liver, liver function profiles and renal toxicity were further investigated in mono-HIV-infected patients during long-term ART up to five years.

Methods: 115 and 38 HIV-infected, ART-naive patients who respectively received TDF- and zidovudine (AZT)-based regimens for 5 years were enrolled. The differences in lipid profiles, liver functions and renal toxicity between those two groups of patients and the correlations among these observed indicators were retrospectively analyzed.

Results: After 5 years of ART, no increase in plasma triglyceride (TG) and only moderate increase in total cholesterol (TC) were found in TDF group. As for plasma TG and TC, the increments in the fifth year and the level changes over time in TDF group were all much less serious than those in AZT group. The new occurrence rates of hypercholesterolemia, fatty liver and abnormality of alanine aminotransferase (ALT) were significantly lower in TDF group. The mean estimated glomerular filtration rate (eGFR) was comparable between two groups except 4 patients who were excluded due to renal toxicity in TDF group. The further analyses showed that there were close correlations between TG and BMI, BMI and ALT, TC and ALT, and TC and AST, but no correlations between eGFR and TG or TC in patients treated with TDF-based regimen.

Conclusion: The lipid-lowering effect of TDF had moderate protective effects on liver functions via reducing liver fat. In the era of tenofovir alafenamide fumarate and integrase inhibitors, TDF-based regimens may remain to be the first choice for young HIV-infection patients with dyslipidemia, fatty liver and obesity.

Keywords: AIDS • Highly active antiretroviral therapy; Lipid metabolism • Liver and kidney function • Fat decay index

Introduction

The number of human immunodeficiency virus (HIV)-infected patients is rapidly increasing. The global number of individuals living with AIDS (acquired immune deficiency syndrome)/HIV increased up to 37.9 million by the end of 2018 [1]. Antiretroviral therapy (ART) has significantly increased the survival rate and life span of those patients [2,3]. However, long-term use of ART is correlated with side effects and non-AIDS-related comorbidities such as dyslipidemia and cardiovascular, kidney or liver diseases [4-6]. Dyslipidemia, hypertriglyceridemia and/or hypercholesterolemia, is very common in patients receiving ART, which is closely associated with hepatic steatosis [6], and the outcome of severe cardiovascular disease (CVD) [7-9]. In addition, non-alcoholic fatty liver disease (NAFLD) is significant with a prevalence of up to 50% in HIV-infected patients [10]. NAFLD may progress to non-alcoholic steatohepatitis (NASH), fibrosis, and even end-stage liver disease [11,12]. The main drivers of fatty liver seem to be insulin resistance, mitochondrial dysfunction and dyslipidemia, which are contributed by both HIV infection itself and ART [9,13].

Tenofovir disoproxil fumarate (TDF), an ester prodrug of tenofovir, is the first-line antiviral drug recommended by most guidelines and World Health Organization (WHO) [14,15]. Recently, tenofovir alafenamide fumarate (TAF), a phosphonate prodrug of tenofovir is under consideration to replace TDF [16,17]. Among common antiretrovirals (ARVs) including TAF and integrase inhibitor dolutegravir (DTG), TDF is the only one that has been evidenced to be favorable for lipid metabolism in HIV-infected patients. TDF-based regimen, compared with non-TDF one, had lower risks of hypertriglyceridemia and hypercholesterolemia in HIV-infected patients after two years of treatment [18]. Compared with TAF-treated group, TDF- treated patients are significantly less great in weight gain and in increases in lipids [19,20]. The switching from TDF-based to TAF based or non-tenofovir regimens is correlated with weight gain [21], or the low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol (TC) levels significantly increase three months after the switching [22]. In contrast, the switching back or TDF addition can significantly improve the lipid profiles rapidly [23-25]. Of course, TDF also improve the lipid profiles in patients with chronic hepatitis B [26].

Besides dyslipidemia, impaired liver function is also a common (48.1%) adverse event of ART [5]. Compared with other common ARVs, TDF in spite of low incidence of dyslipidemia does not show any advantage in reduction of ART-related impaired liver functions in studies with follow-up from 12 months to 120 weeks [5,27], and even like most ARTs is independently associated with increased end-stage liver disease/hepatocellular carcinoma rates during a median follow-up of 8.4 years [28]. Thus, it is not yet known whether the advantages of TDF in lipid metabolism lead to benefits for liver function, fibrosis

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or NAFLD/NASH, especially in long-term therapy. On the other hand, long-term use of TDF has potential renal toxicity, including proximal renal tubular lesions and bone density reduction [29,30]. Compare with TDF, TAF has better viral suppression rate and renal safety [17,31,32]. However, TDF with boosters other than ritonavir (RTV) or cobicistat (COBI) has similar viral suppression rate and renal safety to TAF, implying that the health economic value of TAF versus low-cost generic TDF may be limited when these drugs are used without RTV or COBI [17]. Therefore, in the era of TAF and integrase inhibitors and the face of increasing number of NAFLD in HIV-infected patients, it is difficult to decide whether TDF should be insisted or given up due to its orphan advantage in lipid metabolism and outstanding safety concerns, especially in moderate-income areas where either renal toxicity or dyslipidemia can been minimized by kidney function monitoring or prescription of lipid-lowing drugs.

In order to provide more bases for decision making about TDF, we further respectively analyzed, i) Whether the advantage in lipid metabolism of TDF leads to benefits for fatty liver and liver function profiles; ii) Whether the advantage in lipid metabolism is independent on renal toxicity, based on a long-term follow-up cohort of 153 mono-HIV-infected patients receiving TDF- and Zidovudine (AZT)-based regimes.

Materials and Methods

Subjects and study design

A total of 204 mono-HIV-1-infected patients who firstly started ART in the Love Outpatient Department of The Fifth Affiliated Hospital of Sun Yat-sen University were enrolled from January 2012 to May 2015. All patients met the diagnostic criteria of AIDS Diagnosis and Treatment Guidelines. The age was limited from 18 to 45 years old in order to minimize the influences of age or aging-related lipid metabolism disorders on the evaluations of TDF advantages in lipid metabolism. At enrollment, patients with acute infections, severe cardiopulmonary or liver and kidney dysfunctions, serious mental and neurological diseases, drug allergy, and pregnant and lactating women were excluded. During ART, treatment with lipid-lowering agents and switching to other ART regimen due to renal toxicity were registered in medical records. All patients were followed up in the love outpatient department of our hospital with an interval of 3-6 months. All patients had signed the informed consent. This study has been approved by the ethics committee of the Fifth Affiliated Hospital of Sun Yat-sen University.

Data collection

Demographic and baseline clinical data of all patients were obtained by reviewing the electronic case system. The occurrences of diabetes and hypertension, the usages of lipid-lowering drugs, CD4+ T cell count, serum creatinine (Cr), glomerular filtration rate (eGFR), TC, triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and liver controlled attenuation parameter (CAP) were collected 0, 0.5, 1, 2, 3, 4 and 5 years from the onset of ART. Hypercholesterolemia and hypertriglyceridemia were defined as TC > 5.2 mmol/L and TG > 1.7 mmol/L [33]. The CAP showed as dB/M. CAP > 240 dB/M was defined as fatty liver. The eGFR was calculated using MDRD modified formula [34]. Renal dysfunction was divided into mild (60-90), moderate (30-60) and severe (< 30 mL × min^{-1} × 1.73 m^2) types according to eGFR [22].

Data analysis

Continuous variables were expressed as Mean ± SD, while categorical variables are described by numbers and percentages. Paired t-test or T-test was used to analyze normal continuous variables, and Mann-Whitney U test was used for comparison of non-normal data. The differences between two groups were compared by ANOVA using repeated measurement design. The correlation analyses were conducted by Spearman rank sum test. The logistic regression test was used to analyze the risk factors for lipids, liver and renal profiles among TDF group of patients. Factors with significant associations (P <0.10) in the univariate analysis were included in multivariate analysis. The influences of drugs (TDF vs AZT) on CAP were evaluated by matching the duration of ART. Statistical significance was defined by a conventional P value of 0.05 (two-tailed). SPSS 25.0 (StataCorp, College Station, TX, USA) was used for all data statistical analysis. Graphics was built by using GraphPad Prism 6.0 software (GraphPad Software Inc. San Diego, CA, USA).

Results

Baseline characteristics of study populations

The flow diagram of patients throughout the course of the study was shown in Figure 1A. A total of 204 mono-HIV-infected patients were initially enrolled. The selection of ART regimens was made based on clinical criteria and recommendations of the national clinical practice guidelines at that time of enrollment. TDF was recommended as a first-line drug by WHO guideline in 2011, but was not recommended by Chinese guideline until 2015. During the specific time window, 51 patients selected AZT-based and 153 patients selected TDF-based regimens (Figure 1B), which provided a chance to evaluate the superiority of TDF-based regimen over AZT-based regimen in lipid metabolism. Thirty-two patients were excluded for final analysis due to loss to follow-up and incomplete data. Twelve patients were excluded due to opportunistic infections. Seven patients were switched to other ART regimens. Among them, 4 patients were due to eGFR below 60 ml × min^{-1} × 1.73 m^2, a diagnostic criterion of CKD as reported [29]. The distribution of invalid cases between the regimen groups was not significantly different (Figure 1A). A total of 153 valid patients, 115 patients treated with TDF-based regimen (TDF group) and 38 patients treated with AZT-based regimen (AZT group), were included for further analyses in the study. The demographic and baseline clinical data were summarized in Table 1. All indicators including the uses of lipid-lowing drugs were of no difference between TDF and AZT groups.

Virological and immunological responses

After 5 years of ART, the HIV RNA level in 94.8% (145/153) of patients was below the lower limit of detection. No significant difference in virological response was found between TDF and AZT groups. CD4+ T cell count significantly increased from 276.00±138.35 to 519.41±142.12 (P <0.05) in TDF group and from 271.41±88.35 to 594.50±146.56 (P <0.05) in the AZT group. The CD4+ T cell counts of last follow up were slightly lower in TDF group than those in AZT group (519.41±142.12 vs 594.50±146.56, P <0.05).

Changes in serum lipids and liver fat CAP

The levels of TG and TC between baseline and the fifth year during ART in TDF and AZT groups were shown in Table 2. The TG level only in AZT group, but the TC levels in both groups significantly increased after 5 years of ART. The increments in TDF group were much smaller than those in AZT group in both TG (0.19±1.47 VS 1.52±2.66, P<0.001) and TC (0.40±0.87 VS 0.95±1.51, P <0.05). Compared with baseline, ART for five years had more hypercholesterolemia, but similar hypertriglyceridemia in both groups (Table 2). As for their changes over time during ART, the TG level from the first year (Figure 2A) and the TC level in the third and fifth years (Figure 2B) in TDF group were significantly lower than those in AZT group. Compared with AZT group, TDF group had a significant lower new occurrence rate of hypercholesterolemia, but the rate of hypertriglyceridemia decreased without statistical significance (Figure 2C). The prevalence of fatty liver in the fifth year in TDF-group was lower than that in AZT-group after excluded fat liver patients at baseline (Figure 2C). Since the FibroTouch test was not available until September 2016, we only obtained complete liver fat CAP data of last three years from 110 patients. Liver fat CAP between the third year and the fifth year during ART in both groups was not significant (Table 2), but the CAP in the first 3.5 years in TDF group significantly lower than that in AZT (Figure 2D).

Changes in liver and renal functions

The levels of ALT and AST between baseline and the fifth year during ART in TDF and AZT groups were shown in Table 2. ALT levels increased in both groups, but only the increase in TDF group was significant even though its average was lower than that in AZT group and the abnormal rates of both ALT and AST were similar in these two groups (Table 2). As for their changes over time during ART, there was no significant difference in ALT and AST levels

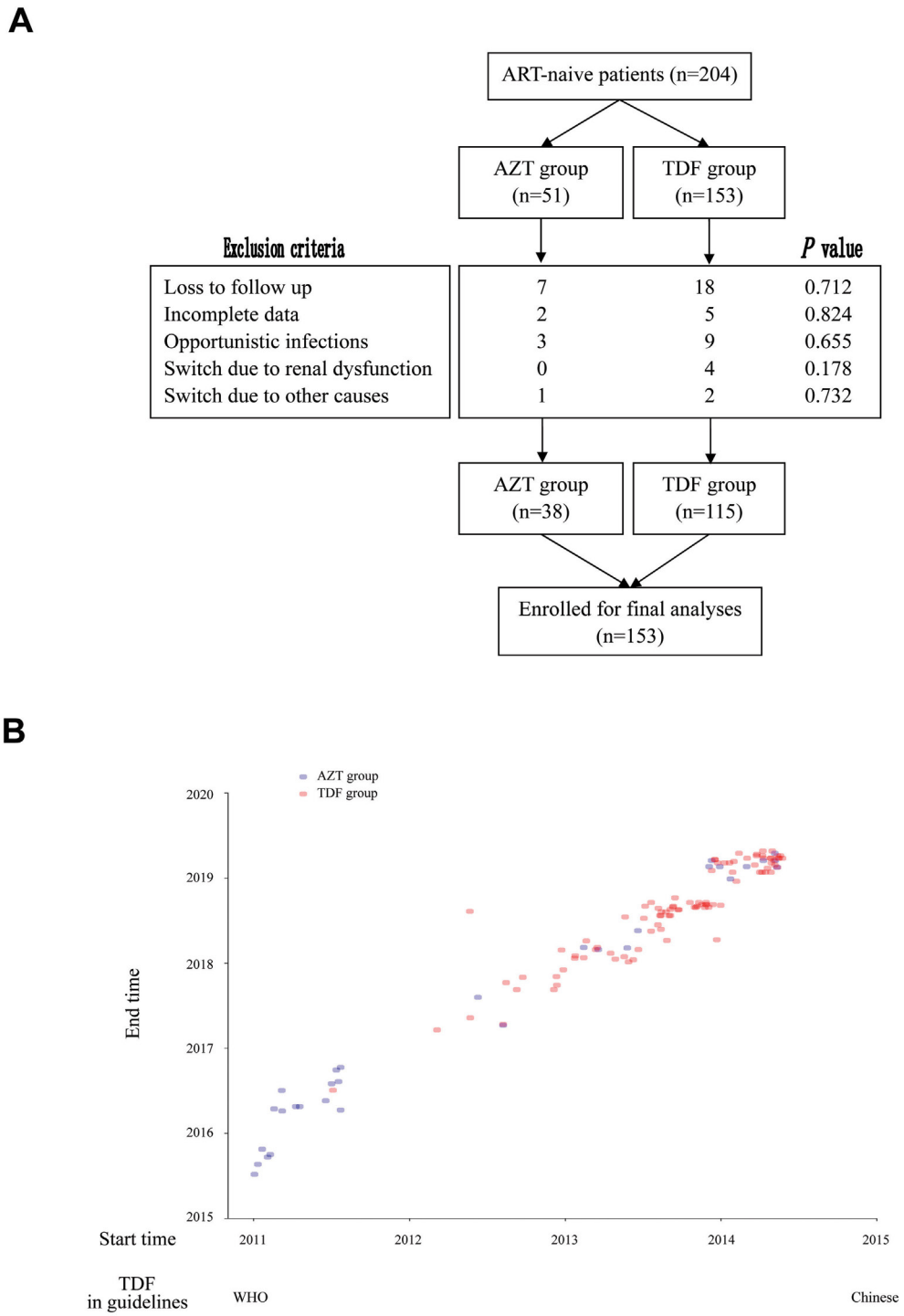

Figure 1. Patient managements. ATR, antiretroviral therapy; AZT, Zidovudine; TDF: Tenofovir Disoproxil Fumarate. (A) The flow diagram of patients throughout the course of the study. (B) The distributions of ART start and end times of patients (Red, TDF; Blue, AZT) and the relationships between regimen selections and major guidelines.

between the TDF and AZT groups. However, the prevalence of abnormal ALT in TDF group was lower than that in AZT group after excluded those patients with abnormal ALT at baseline (Figure 3C). The levels of eGFR between baseline and the fifth year during ART in TDF and AZT groups were shown in Table 2. The eGFR did not decrease as expected. In contrast, it increased in both groups and the increase in TDF group was significant. Except for 4 patients in TDF group who were excluded due to eGFR below 60 ml × min^{-1} × 1.73 m^2, no cases with serious renal dysfunction occurred in both groups. In addition, the prevalence of eGFR below 60 ml × min^{-1} × 1.73 m^2 was similar (Figure 3C), and there were no significant difference at any time point between those two groups (Figure 3D).

Correlation and risk factor analyses of lipid, liver and renal profiles with general clinical data in patients treated with TDF-based regimen

The correlation analyses of lipid, liver and renal profiles with general data in patients treated with TDF-based regimen based on the data of 5 years of ART were shown in Figure 4. TG was positively correlated with BMI and CD4+ T cell counts, while TC was only positively correlated with CD4+ T cell counts. The risk factor analyses of hypertriglyceridemia and hypercholesterolemia also showed that it was hypertriglyceridemia that was marginally correlated BMI (Tables S1 and S2). The CD4+T cell counts, however, were associated with

Table 1. Baseline characteristics and uses of lipid lowing drugs in 153 patients enrolled for analyses in this study (Mean ± SD/ n (%)).

Indicators	AZT group (n=38)	TDF group (n=115)	*P* value
Age (years)	32.2 ± 7.6	32.6 ± 6.7	0.398
Sex			
Male	33 (86.8)	106 (92.2)	0.323
Female	5 (13.2)	9 (7.8)	
Marriage			
Unmarried	20 (52.6)	72 (62.6)	0.072
Married	10 (26.3)	30 (26.1)	
Divorced	6 (15.8)	13 (11.3)	
Death of a spouse	2 (5.3)	0	
Transmission route			
Intravenous drug use	0	2 (1.7)	0.398
MSM	29 (76.3)	95 (82.6)	
Heterosexual	9 (23.7)	18 (15.7)	
Diabetes			
Yes	1 (2.6)	4 (3.5)	0.799
No	37 (97.4)	111 (96.5)	
Hypertension			
Yes	2 (7.9)	3 (5.2)	0.425
No	36 (92.1)	112 (94.8)	
Dyslipidemia			
Hyper-TG	9 (23.7)	35 (30.4)	0.425
Hyper-TC	1 (2.6)	13 (11.3)	0.108
TG (mmol/L)	1.52 ± 1.08	1.65 ± 1.25	0.550
TC (mmol/L)	4.05 ± 0.80	4.16 ± 0.84	0.480
Height (cm)	170.7 ± 6.80	169.8 ± 5.70	0.624
Height (cm)	170.4 ± 7.58	169.9 ± 5.71	0.624
BMI	22.35 ± 2.48	21.40 ± 2.71	0.058
CD4+ T cell (cells/μL)	271.4 ± 88.4	276.0 ± 138.4	0.813
eGFR (ml*min^{-1}*1.73 m^2)	110.0 ± 21.5	106.2 ± 20.2	0.321
ALT (U/L)	28.8 ± 18.9	23.6 ± 14.7	0.080
AST (U/L)	26.5 ± 11.4	24.9 ± 10.8	0.449
Lipid-lowing drugs			
Statins	0	2 (15.4)	0.696
Fibrates	1 (11.1)	8 (22.9)	0.514

SD: Standard Deviation; BMI: Body Mass Index; eGFR: Estimated Glomerular Filtration Rate; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; TG: Triglyceride; TC: Total Cholesterol; Hyper-TG: Hypertriglyceridemia; Hyper-TC: Hypercholesterolemia.

Table 2. Changes in lipid, liver and kidney profiles after 5 years of ART in HIV-infected patients (Mean ± SD/ n (%))

Indicators	AZT group (n=38)			TDF group (n=115)		
	Baseline	5 years	*P* value	Baseline	5 years	*P* value
TG	1.52 ± 1.08	3.04 ± 2.71	0.001	1.65 ± 1.25	1.84 ± 1.10	0.17
TC	4.05 ± 0.80	5.01 ± 1.48	<0.001	4.16 ± 0.84	4.56 ± 0.83	<0.001
Hyper-TG	9 (23.7)	16 (42.1)	0.087	35 (30.4)	43 (37.4)	0.265
Hyper-TC	1 (2.6)	14 (36.8)	<0.001	13 (11.3)	25 (21.7)	0.033
CAP*	241.1 ± 19.6	236.7 ± 24.2	0.264	237.6 ± 19.7	233.6 ± 30.4	0.153
Fatty Liver	8 (21.4)	16 (42.1)	0.086	28 (24.4)	29 (25.2)	0.857
ALT	28.8 ± 18.9	34.8 ± 21.9	0.16	23.6 ± 14.7	30.9 ± 14.9	<0.001
AST	26.5 ± 11.4	27.4 ± 17.3	0.769	24.9 ± 10.8	26.6 ± 8.83	0.192
Abnormal ALT	7 (18.4)	10 (25.8)	0.943	9 (7.8)	10 (8.7)	0.737
Abnormal AST	4 (10.5)	5 (12.9)	0.759	7 (6.1)	13 (11.3)	0.184
eGFR	110.0 ± 21.5	117.2 ± 21.3	0.019	106.2 ± 20.2	113.3 ± 21.7	<0.001
Abnormal eGFR	8 (21.1)	5 (13.2)	0.221	22 (19.1)	13 (11.3)	0.125

* Data in the third year were served as baseline; AZT, Zidovudine; TDF: Tenofovir Disoproxil Fumarate; TG: Triglycerides (mmol/L); TC: Total Cholesterol (mmol/L); Hyper-TG: Hypertriglyceridemia; Hyper-TC: Hypercholesterolemia; CAP: Controlled Attenuation Parameter; ALT: Alanine Aminotransferase (U/L); AST: Aspartate Aminotransferase (U/L); eGFR: Estimated Glomerular Filtration Rate (ml × min^{-1} × 1.73 m^2).

neither hypertriglyceridemia nor hypercholesterolemia. ALT was significantly correlated with sex, transmission routine, BMI and blood glucose, while AST was correlated with blood glucose and CD4+ T cell counts (Figure 4). The eGFR was only negatively correlated with age in those patients treated with TDF-based regimen (Figure 4).

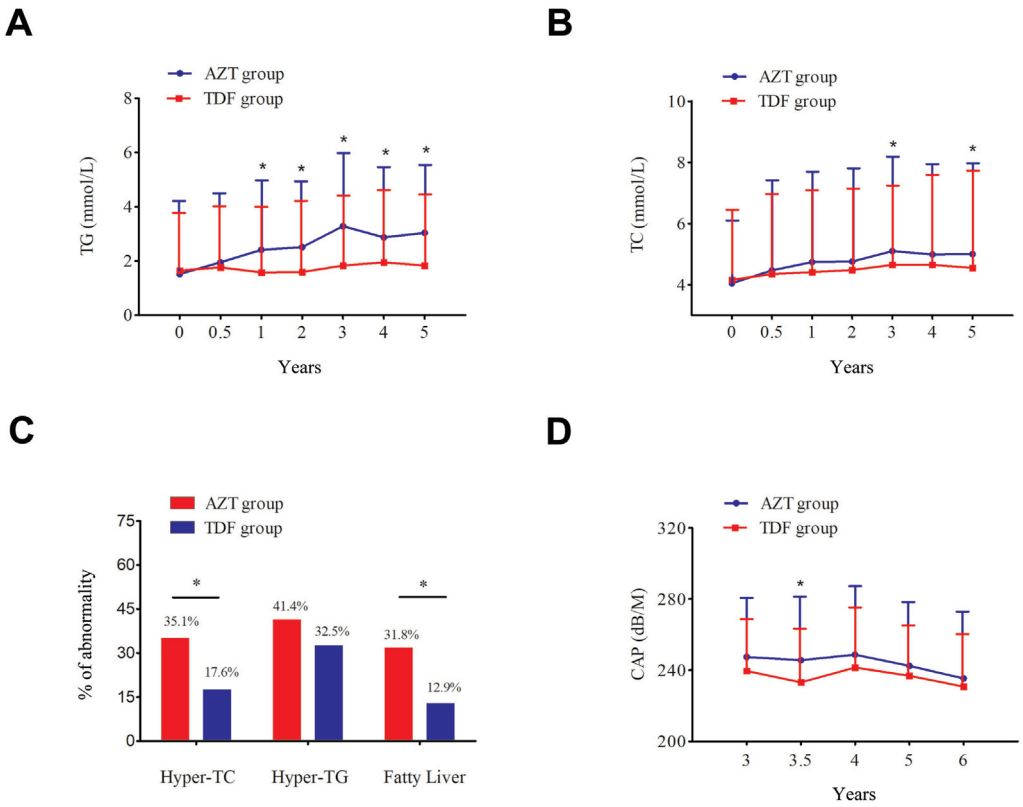

Figure 2. Changes in serum lipids and liver fat CAP. AZT, Zidovudine; TDF: Tenofovir Disoproxil Fumarate; TG: Triglycerides; TC: Total Cholesterol; Hyper-TG: Hypertriglyceridemia; Hyper-TC: Hypercholesterolemia. CAP: Controlled Attenuation Parameter. *P<0.05. TG (A) and TC (B) level changes over 5 years of ART in AZT and TDF groups. (C) New recurrence rate of hypertriglyceridemia, hypercholesteremia and fatty liver after 5 ART. (D) Mean CAP changes over last 3 years of ART in AZT and TDF groups.

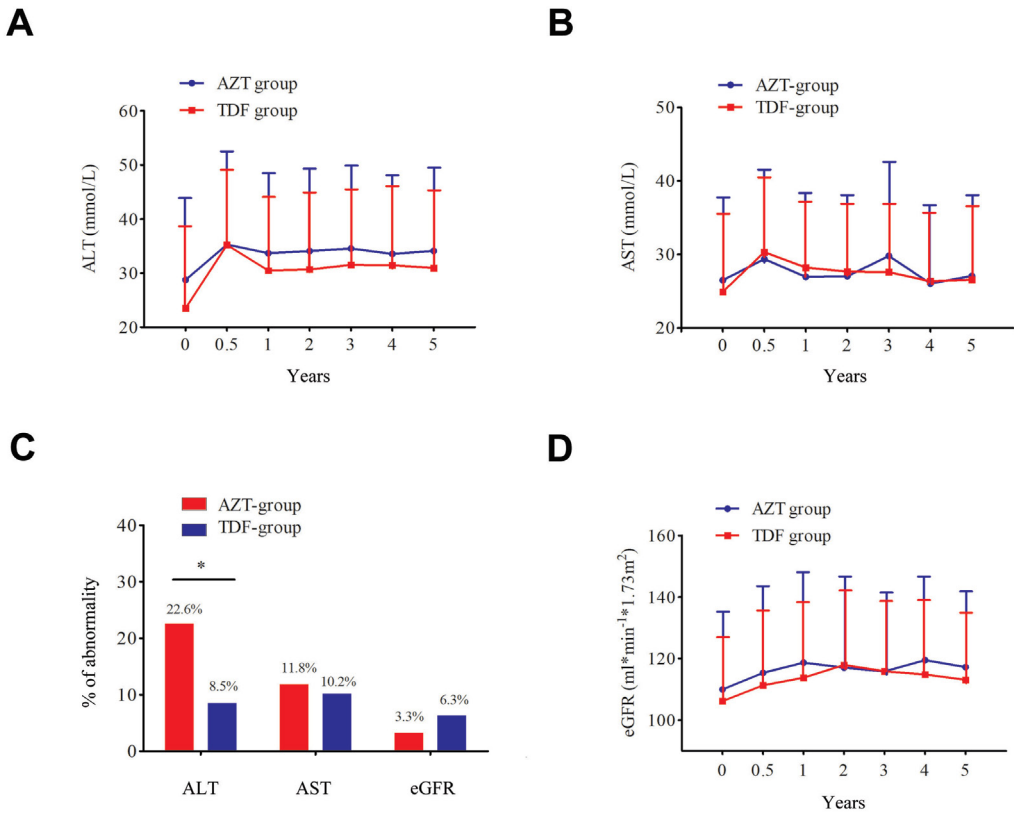

Figure 3. Changes in liver and renal functions. AZT, Zidovudine; TDF: Tenofovir Disoproxil Fumarate; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; eGFR: Estimated Glomerular Filtration Rate. *P<0.05. ALT (A) and AST (B) level changes over 5 years of ART in AZT and TDF groups. (C) New recurrence rate of abnormal ALT (>50 U/L), AST (>40 U/L) and eGFR (>90 ml*min^{-1}*1.73m^2) after 5 ART. (D) Mean CAP eGFR over 5 years of ART in AZT and TDF groups.

Variable	By variable	Correlation coefficient	P value
TG	Age	.010	.923
TG	Sex	-.109	.284
TG	Marriage	.043	.678
TG	Transmission route	.115	.259
TG	BMI	.285	.004
TG	Glucose	.048	.636
TG	CD4+ T cell count	.284	.021
TC	Age	.198	.051
TC	Sex	.053	.602
TC	Marriage	.055	.590
TC	Transmission route	.089	.383
TC	BMI	.139	.171
TC	Glucose	-.065	.527
TC	CD4+ T cell count	.270	.028
ALT	Age	.034	.738
ALT	Sex	-.273	.006
ALT	Marriage	-.152	.136
ALT	Transmission route	-.250	.013
ALT	BMI	.235	.020
ALT	Glucose	.262	.009
ALT	CD4+ T cell count	.019	.879
AST	Age	.173	.089
AST	Sex	-.162	.113
AST	Marriage	.020	.848
AST	Transmission route	-.011	.919
AST	BMI	.188	.066
AST	Glucose	.262	.009
AST	CD4+ T cell count	.263	.035
eGFR	Age	-.360	.000
eGFR	Sex	.155	.139
eGFR	Marriage	-.015	.890
eGFR	Transmission route	.083	.434
eGFR	BMI	-.018	.868
eGFR	Glucose	.015	.885
eGFR	CD4+ T cell count	.081	.528

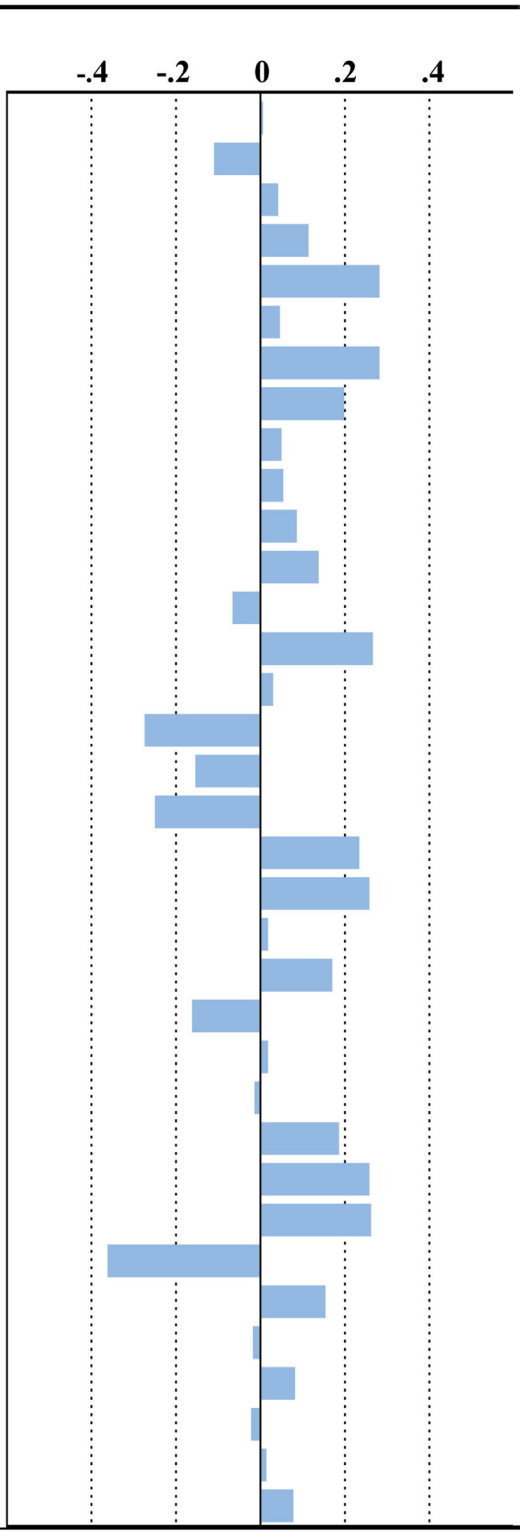

Figure 4. Correlation analyses of lipid, liver and renal profiles with general clinical data in TDF group. TG: Triglycerides; TC: Total Cholesterol; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; eGFR: Estimated Glomerular Filtration Rate; BMI: Body Mass Index. Red characters indicate statistical significances; blue characters indicate marginal significances.

Influences of TDF-related lipid changes on liver and renal functions

The above correlation analyses showed that ALT and TG had a co-associated factor BMI, and AST and TC had a co-associated factor CD4+ T cell count (Figure 4), but neither TG nor TC and eGFR had any co-associated factors. These results suggest that the TDF-related lipid changes may influence the liver rather than the renal functions. To confirm this possibility, we conducted correlation analyses of TG and TC levels with the liver and renal function profiles in TDF group of patients. Both ALT and AST levels were not correlated with TG level (Figures 5A and 5B), but significantly positively correlated with TC level (Figures 5C and 5D). The eGFR level was correlated with neither TG nor TC levels (Figures 5E and 5F).

Discussion

Current ART are less toxic and more effective than those regimens used in

the early years. Lipodistrophy and dyslipidemia are the main causes of long-term toxicities [7]. Worse, the impact of NAFLD is significant with a prevalence of up to 50% in HIV-infected patients [10]. Fortunately, the commonest ART agent, TDF, has been confirmed to be favorable for lipid metabolism. In this study, no increase in TG and moderate increase in TC were found in TDF group. The increments and level changes over time were much less serious than those in AZT group during 5 years of ART. The advantage of TDF in lipid metabolism was accompanied by lower new occurrence rates of hypercholesterolemia, fatty liver and abnormality of ALT. The correlation analyses further showed that there were close correlations between TG and BMI, BMI and ALT, TC and ALT, and TC and AST, but no correlations between eGFR and TG or TC in patients treated with TDF-based regimen. These results imply that the TDF-related lipid-lowering effects that are unrelated with its intrinsic renal toxicity have protective effects on liver functions. Together with its potential protective effects on CVDs [7-9], this study suggests that TDF-containing regimens have some advantages in avoidance of dyslipidemia as long as few victims of renal toxicity are screened out.

Dyslipidemia is prevalent in HIV-infected patients. It can be caused by either ART or HIV infection itself [7,10,18,35], perhaps via insulin resistance and mitochondrial dysfunction. HIV-related immune activation is associated with insulin resistance. The early-generation nucleoside reverse transcriptase inhibitors and protease inhibitors often cause insulin resistance and mitochondrial dysfunction [7,10]. Integrase inhibitors are thought to have a minimal impact on lipids profile, but switching from TDF-based regimen to DTG regimen (TDF-free) results in weight gain [36]. Among current ARTs including another prodrug of tenofovir (TAF), TDF is the only drug that has the characteristics of lowering lipid. In this study, no increase in TG, smaller increase in TC, and lower new occurrence rates of hypercholesterolemia and fatty liver were found in TDF group when compared with those in AZT-based regimen during 5 years of ART. The results further confirmed the lipid-lowering effect of TDF. However, TDF-based regimen could not completely offset hyperlipidemia, especially the increase in TC, caused by HIV infection and other antiretroviral drugs as reported [18]. Though it was the new occurrence rate of hypercholesterolemia rather than hypertriglyceridemia was significantly lower in TDF group, TDF lowered TG much better than TC by the rest means in this study. Such unbalanced effects of TDF may result from its HIV replication inhibition or the effect of boosters since HIV infection increases TG and decreases TC, and other ARTs prefer to increase TC [37]. The TC increase preference of AZT and its boosters, together with limited case sizes, may also explain the contradictory results about the new occurrence rates of hypercholesterolemia and hypertriglyceridemia in TDF group. Therefore, HIV-infected patients still need to monitor or intervene in lipid metabolism after the onset of ART including TDF-containing regimens.

Many experts warn that dyslipidemia is a risk factor of CVDs in HIV-infected patients [7-9]. Fortunately, there were no CVD events in this study,

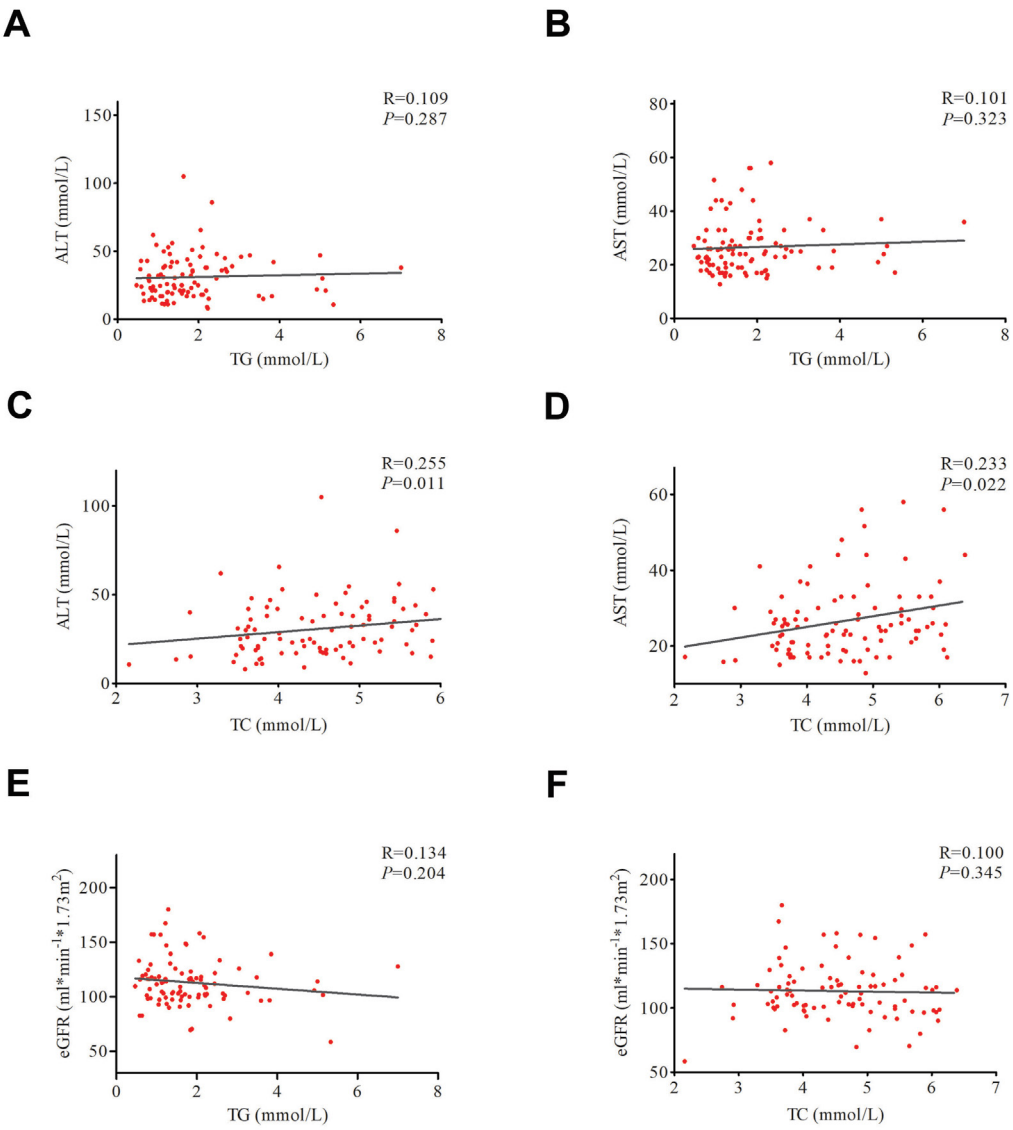

Figure 5. Influences of TDF-related lipid changes on liver and renal functions in TDF group. ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; TG: Triglycerides; TC: Total Cholesterol; eGFR: Estimated Glomerular Filtration Rate. Each red point represents one patient. TG was not correlated with ALT (A) and AST (B), but TC was significantly correlated with ALT (C) and AST (D). The eGFR was correlated with neither TG nor TC.

perhaps due to the valid patients with ages from 18 to 45 years old. NAFLD is prevalent and dyslipidemia is associated NASH and liver fibrosis in HIV-infected patients [6,10-12]. However, rare studies are involved in the influences of lipid-lowering effect of TDF on liver function or fatty liver. In this study, TDF-based regimen had lower abnormality rate of ALT than AZT-based regimen after long-term ART, suggesting a liver function-protective role. Unfortunately, there were an increase tread in ALT in both groups and no significant difference in levels of ALT and AST. The possible explanation is the limited case sizes, especially in AZT group. Nonetheless, the liver function-protective role of TDF-related lipid-lowering effect was believable, which was further strengthened by the prevalence of fatty liver and CAP levels (only in some observation time point) that were both lower and the close correlations among TG, BMI and ALT in TDF group. However, our results suggest that the lipid-lowering effect of TDF only moderately reduce the risk of fatty liver and protect the liver functions, which was in concordance with relative higher rate of impaired liver function in patients treated with TDF-containing regimen [5]. The further correlation analyses showed that it was TC, but TG, that was closely correlated with the levels of ALT and AST in patients treated with TDF-based regimen. These results suggest that lower rate of abnormal ALT in TDF group is correlated with the TG-lowering preference of TDF, perhaps by reducing liver fat. In contrast, TC due to limited lowering effect of TDF is the major cause of abnormal ALT and AST, and statins may be helpful for those treated patients. In addition, both ALT and AST were found to be positively correlated with blood glucose, suggesting that it is worth to notice that insulin resistance or diabetes takes a part in the liver damage of HIV-infected patients.

TDF, as first-line drug, has been included in most recommended regimens from 2002. It has been confirmed to be of high efficacy and generally good tolerance, as demonstrated in clinical trials and real-life studies [38,39]. Unfortunately, it has unpleasant side-effects on renal function and bone metabolism [29]. In our retrospective study, the HIV RNA level in 96.7% of patients was below the lower limit of detection after 5 years of ART. Four patients (1.3%) switched to other regimen due to the renal dysfunction defined by eGFR below 60 ml × min^{-1} × 1.73 m^2 in 153 patients initially treated with TDF-based regimen. Among those 115 patients who finished the follow up of 5 years, eGFR was similar to that of AZT group, and did not significantly decrease over time as reported [18,40,41]. Therefore, the renal toxicity of TDF in those patients was relatively limited perhaps due to their ages of younger than 45 years old. Indeed, the eGFR was only correlated with age in those patients. The further correlation analyses showed that eGFR was not correlated with TC and TG levels in patients treated with TDF-based regimen, suggesting that the lipid-lowering effects of TDF is independent on its renal toxicity. However, many researchers believe that higher circulating plasma levels of tenofovir diphosphate, the final active moiety of TDF, are involved in mitochondrial, renal and bone toxicities [42,43]. The mitochondrial toxicity of reduction in mRNA expression of squalene epoxidase is then related to the changes in lipid profiles [44]. So, the lipid-lowering effects and the renal toxicity of TDF are pathogenically similar, which are in concordance with that lower body mass is the risk for renal toxicity [29,44]. Therefore, more attentions would be paid during the exploration of lipid-lowering effects of TDF though it was safe in patients with age of younger than 45 years old as long as few victims were screened out in time.

Conclusion

The lipid-lowering effects of TDF was confirmed to prefer TG over TC in HIV-infected patients with long-term ART, which moderately protected the liver by reducing liver fat, but could not abolish the abnormalities in ALT and AST due to the limited lowering effect on TC. The renal toxicity of TDF in HIV-infected patients with age younger than 45 years old was controllable and the lipid-lowering effects of TDF were independent on renal toxicity. Therefore, in the era of TAF and integrase inhibitors, TDF-based regimens may remain to be the first choice for young HIV-infection patients with dyslipidemia, fatty liver and obesity.

Limitations & Recommendations for Future Studies

Our study had several limitations. Firstly, only 153 patients were enrolled in the study. Secondarily, both TDF- and AZT-based regimens consist of at least three drugs. The influences of the boosters should take into account in the future. Finally, the enrollment of patients younger than 45 years old was favorable for evaluation of TDF lipid-lowering effects, but unfavorable for evaluations of renal toxicity, CVDs and risk factor analyses. For these reasons, prospective studies with larger sample size and without age limitation should be conducted in order to clarify the total possible benefits of lipid-lowering effects of TDF in the future.

Conflict of Interest

There is no conflict of interest to disclose.

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