Virology Journal

RESEARCH

Open Access

Effects of tenofovir alafenamide fumarate on serum lipid profiles in patients with chronic hepatitis B

Fei Cao[1†], Tao Fan[1†], Xue Jiang[2†], Jian Wang[3,4†], Yilin Liu[1], Li Zhu[5], Ye Xiong[1], Shaoqiu Zhang[3], Zhiyi Zhang[1], Yifan Pan[6], Yuanyuan Li[6], Chao Jiang[7], Juan Xia[3], Xiaomin Yan[3], Jie Li[1,3,4], Xingxiang Liu[2], Chuanwu Zhu[5*], Rui Huang[1,3,4,6,7*] and Chao Wu[1,3,4,6*]

Abstract

Background Concerns have been raised regarding changes in lipid profiles among patients with chronic hepatitis B (CHB) during tenofovir alafenamide fumarate (TAF) treatment. We aimed to evaluate the effect of TAF treatment on the lipid profiles of patients with CHB.

Methods A total of 430 patients with CHB from three hospitals were retrospectively included, including 158 patients treated with TAF and 272 patients treated with tenofovir disoproxil fumarate (TDF).

Results In this multicenter cohort, the cumulative incidence of dyslipidemia was notably higher in the TAF group than in the TDF group ($P<0.001$). After TAF treatment, a significant elevation was observed in triglyceride (TG) levels (from 0.83 mmol/L to 1.02 mmol/L, $P<0.001$) and total cholesterol (TC) levels (from 4.16 mmol/L to 4.32 mmol/L, $P<0.001$). Similar changes in TG and TC levels were observed in the TAF group after propensity score matching (PSM). The TG levels (from 0.83 mmol/L to 1.04 mmol/L, $P<0.001$) and TC levels (from 4.16 mmol/L to 4.38 mmol/L, $P<0.001$) were both increased significantly compared to the baseline levels in the PSM cohort of patients treated with TAF. TAF treatment was independently associated with elevated TG levels (HR = 2.800, 95% CI: 1.334–5.876, $P=0.006$) and TC levels (HR = 9.045, 95% CI: 3.836–21.328, $P<0.001$).

Conclusions Compared with TDF treatment, TAF treatment was associated with dyslipidemia in patients with CHB. Close monitoring of lipid profiles is needed in patients with CHB who received TAF treatment.

Keywords Tenofovir alafenamide fumarate, Triglyceride, Total cholesterol, Chronic hepatitis B

†Fei Cao, Tao Fan, Xue Jiang and Jian Wang contributed equally to this work.

*Correspondence:
Chuanwu Zhu
zhuchw@126.com
Rui Huang
doctor_hr@126.com
Chao Wu
dr.wu@nju.edu.cn

Full list of author information is available at the end of the article

Introduction

Chronic hepatitis B virus (HBV) infection is one of the leading risk factors for cirrhosis and hepatocellular carcinoma (HCC) [1, 2]. In 2019, WHO estimated that 296 million people were chronically infected and living with hepatitis B, and the global prevalence of HBV infection was approximately 3.5% [3]. Nucleos(t)ide analogs (NAs) have potent viral inhibition ability to suppress HBV replication and are widely used for antiviral treatment in patients with chronic hepatitis B (CHB). However, they rarely induce functional cure and patients with NAs treatment generally require long-term treatment to maintain viral suppression to prevent relapse and avoid severe complications [4–6]. Entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF) are potent NAs with a high barrier to resistance and are recommended as first-line drugs for the treatment of CHB [4–6].

However, long-term TDF treatment is associated with nephrotoxicity and decreased bone mineral density [7–9]. Compared to TDF, TAF has higher plasma stability, with less impact on renal and skeletal safety [10–12]. It has recently been reported that treatment with TDF decreases serum lipid levels in patients with HBV and/or human immunodeficiency virus infection [13–15]. In contrast, several studies have suggested that TAF may be associated with elevated triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) compared to TDF [16–18]. Currently, few studies have reported serum lipid changes in CHB patients treated with TAF in real-world settings. Therefore, this study aimed to evaluate the dynamic changes in serum lipid profiles in CHB patients with TAF and to compare the impact of lipid profiles between TAF and TDF in a multicenter Asian cohort of patients with CHB.

Methods

Study population

This was a retrospective multicenter cohort study. We included treatment-naïve patients with CHB who were initially treated with TAF or TDF in three hospitals in Jiangsu Province, including Nanjing Drum Tower Hospital (Nanjing, China), Huai'an No. 4 People's Hospital (Huai'an, China), and the Affiliated Infectious Diseases Hospital of Soochow University (Suzhou, China) between 2016 and 2023. The inclusion criteria were as follows: (1) age ≥ 18 years old; (2) TAF or TDF therapy for at least 3 months; (3) triglyceride and total cholesterol levels within the normal range before treatment initiation. The exclusion criteria were as follows: (1) concurrent HCC or other malignancies; (2) co-infected with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus; (3) coexisting other liver diseases such as alcoholic liver disease, fatty liver (diagnosed by ultrasonography) and autoimmune liver diseases; (4) pregnant at enrollment; (5) patients treated with lipid-lowering drugs, hormones or immunosuppressive drugs.

This study followed the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of local hospitals.

Data collection and follow-up

Demographic and clinical information such as age, sex, laboratory data, and comorbidities were retrospectively collected from the electronic medical record system.

Patients were generally followed longitudinally at intervals of 6 months or less and laboratory data including fasting metabolic parameters were collected. Baseline laboratory measurements were determined before the initiation of the TAF or TDF treatment. Patients were followed from baseline until the presence of dyslipidemia, change of antiviral agents, or last time of follow-up, whichever came first.

Clinical outcomes and definitions

The primary endpoint of this study was the incidence of dyslipidemia. According to the diagnostic criteria in the relevant guidelines [19], the normal ranges of lipid indices in the adult population are TG < 1.7 mmol/L (150 mg/dL) and TC < 5.2 mmol/L (200 mg/dL). In this study, the presence of TG ≥ 1.7 mmol/L and/or TC ≥ 5.2 mmol/L were defined as dyslipidemia [20].

Statistical analysis

Continuous variables were presented as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test as appropriate. The paired t-test was used to assess the differences in serum lipid levels between the baseline and the end of follow-up. To reduce the impact of potential confounders, propensity score matching (PSM) with 1:1 was used to balance the baseline characteristics between the TAF and TDF groups, including age, sex, body Mass Index (BMI), TG, TC, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose (Glu), hepatitis B e antibody (HBeAg), hepatitis B surface antigen (HBsAg), platelet (PLT), albumin (ALB), fibrosis index based on 4 factors (FIB-4) score and HBV DNA at baseline. The Kaplan-Meier method was used to compare the cumulative incidence of dyslipidemia, and a log-rank test was used to compare the differences between groups. Cox regression analysis was conducted to identify the factors related to dyslipidemia. Statistical analyses were conducted using the SPSS software (version 26.0; IBM Corporation, Armonk, NY, USA) and R software (version

4.3.0; R Foundation, Vienna, Austria). All *P* values were two-tailed, and the level of significance was set at $P<0.05$.

Results

Baseline characteristics of the study population

This study included 430 treatment-naïve CHB patients who received antiviral treatment, including 158 patients treated with TAF and 272 patients treated with TDF. Table 1 presents the baseline clinical characteristics of the study population. Compared with the TDF group, the TAF group had a lower proportion of HBeAg-positive patients (44.4% vs. 57.0%, $P=0.019$). The baseline TC levels of patients with TAF treatment were significantly higher than those treated with TDF (4.2 mmol/L vs. 4.0 mmol/L, $P=0.022$). The levels of ALT (44.1 U/L vs. 76.2 U/L, $P<0.001$) and AST (31.8 U/L vs. 43.1 U/L, $P=0.001$) in the TAF group were lower than those in the TDF group. However, no significant differences were observed in other baseline characteristics between the two groups, including age, sex, BMI values, levels of TG, PLT, ALB and Glu, FIB-4 scores, proportion of patients with diabetes mellitus, as well as the serum HBsAg and HBV DNA levels.

Incidence of dyslipidemia in the unmatched cohort

The follow-up duration of the TDF group was significantly longer than that of the TAF group (18.0 months vs. 16.0 months, $P=0.001$). After treated with TAF, 42 patients developed dyslipidemia. A total of 21 participants had elevated TG levels, with an incidence rate of 12.3 per 100 person-years. Twenty-seven patients had elevated TC levels, with an incidence rate of 15.8 per 100 person-years. Among the patients in the TDF group, 29 developed dyslipidemia, the incidence rates per 100 person-years of elevated TG and TC levels were 4.9 and 2.2, respectively (Table S2). In the Kaplan-Meier analysis, the cumulative incidences of dyslipidemia, elevated TG, and TC were significantly higher in the TAF group than in the TDF group ($P<0.001$, $P=0.001$, and $P<0.001$, Fig. 1A and B, and 1C).

Comparison of TG and TC changes in the unmatched cohort

We further compared the changes in fasting TG and TC levels from baseline to the end of follow-up in the TAF and TDF groups. At the end of follow-up, there was a significant increase in both TG (from 0.83 mmol/L to 1.02 mmol/L, $P<0.001$) and TC levels (from 4.16 mmol/L to 4.32 mmol/L, $P<0.001$) compared to baseline in the TAF group. Conversely, TC levels were significantly decreased at the end of follow-up (from 4.05 mmol/L to 3.78 mmol/L, $P<0.001$), while TG levels remained stable in the TDF group (0.82 mmol/L vs. 0.77 mmol/L, $P=0.631$, Fig. 2A and B). We compared the changes in lipid profiles at different time points after treatment between TAF and TDF groups. We found that TG and TC levels in the TAF group were significantly higher than those in the TDF group after 6, 12, 18, and 24 months of treatment (all $P<0.05$, Fig. 3).

Incidence of dyslipidemia in the matched cohort

PSM was conducted between the TDF and TAF groups at a 1:1 ratio, and 149 pairs were obtained. The clinical features and follow-up time were comparable between the TAF and TDF groups after PSM (Table S1). The median follow-up time of the TAF and TDF groups were 16.0

Table 1 Comparison of clinical features between CHB patients treated with TDF and TAF

Variables	All patients ($n=430$)	TDF ($n=272$)	TAF ($n=158$)	*P* value
Age (yr)	38.0 (33.0, 45.0)	38.0 (33.0, 46.0)	38.0 (33.0, 45.0)	0.718
Male (%)	280 (65.1)	171 (62.9)	109 (69.0)	0.239
HBeAg positive (%)	210 (52.2)	143 (57.0)	67 (44.4)	0.019
BMI (kg/m^2)	22.9 (20.7, 24.8)	22.9 (20.6, 25.0)	22.9 (20.8, 24.8)	0.904
ALT (U/L)	58.0 (29.0, 128.0)	76.2 (33.2, 155.6)	44.1 (24.5, 103.0)	< 0.001
AST (U/L)	38.2 (24.2, 76.1)	43.1 (25.8, 90.5)	31.8 (22.8, 54.8)	0.001
Glu (mmol/L)	4.7 (4.4, 5.1)	4.7 (4.3, 5.0)	4.7 (4.4, 5.1)	0.501
TG (mmol/L)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.6, 1.0)	0.724
TC (mmol/L)	4.1 (3.7, 4.5)	4.0 (3.6, 4.5)	4.2 (3.8, 4.6)	0.022
HBsAg ($\log_{10}$ IU/ml)	3.6 (3.0, 4.2)	3.6 (3.1, 4.2)	3.4 (2.9, 4.0)	0.060
HBV DNA ($\log_{10}$ IU/ml)	5.8 (3.7, 7.3)	6.1 (3.9, 7.4)	5.2 (3.3, 7.3)	0.064
PLT ($\times 10^9$/L) ($n=414$)	183.5 (146.0, 218.0)	182.0 (140.0, 214.5)	185.0 (150.5, 221.5)	0.189
ALB (g/L)	44.1 (41.9, 45.9)	44.1 (41.8, 45.9)	44.2 (42.4, 45.9)	0.634
FIB-4 score ($n=413$)	1.1 (0.8, 1.8)	1.1 (0.8, 2.0)	1.1 (0.8, 1.7)	0.145
Diabetes mellitus (%)	19 (4.4)	11 (4.0)	8 (5.1)	0.801
Follow-up time (months)	17.0 (9.0, 26.0)	18.0 (11.0, 28.0)	16.0 (9.0, 20.0)	0.001

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antibody; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; TG, triglyceride; TC, total cholesterol; Glu, glucose; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ALB, albumin; PLT, platelet; FIB-4, fibrosis index based on 4 factors

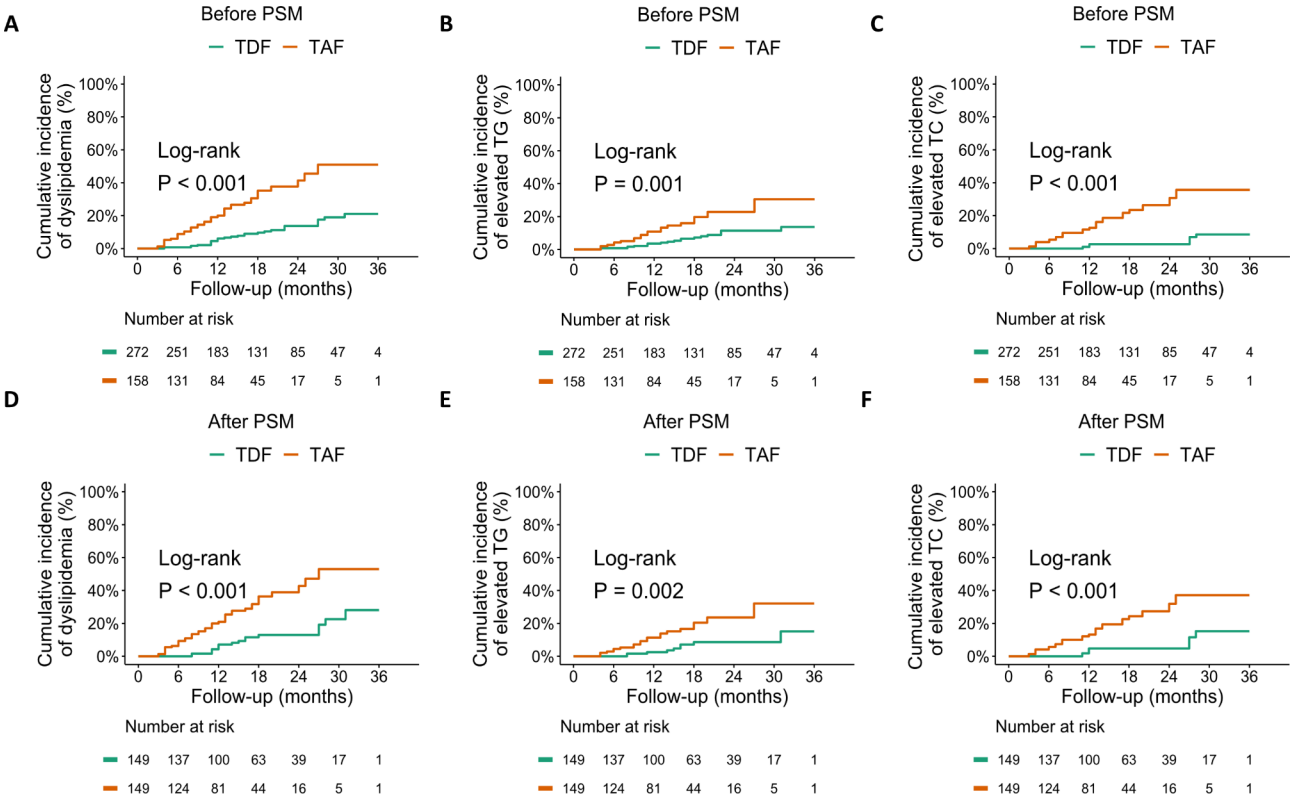

Fig. 1 Cumulative incidence of dyslipidemia, elevated TG and TC in different treatment groups before (**A**, **B**, **C**) and after (**D**, **E**, **F**) propensity score matching

months and 17.0 months, respectively. During the follow-up period, 42 (25.7%), 21 (12.8%), and 27 (16.5%) participants had dyslipidemia, elevated TG, and TC levels in the TAF group, respectively. In comparison, only 17 (8.1%), 9 (4.3%), and 8 (3.8%) patients had dyslipidemia, elevated TG, and TC levels in the TDF group, respectively (Table 2). In the Kaplan-Meier analysis, the cumulative incidences of dyslipidemia, elevated TG, and TC were significantly higher in the TAF group ($P<0.001$, $P=0.002$, and $P<0.001$, Fig. 1D and E, and 1F), consistent with the findings in the unmatched cohort.

Comparison of TG and TC changes in the matched cohort

In the matched cohort, there was still a significant increase in both TG (from 0.83 mmol/L to 1.04 mmol/L, $P<0.001$) and TC (from 4.16 mmol/L to 4.38 mmol/L, $P<0.001$) levels in the TAF group. For the TDF group, we observed a significant decrease of TC levels (from 4.22 mmol/L to 3.95 mmol/L, $P<0.001$) and no significant change of TG levels (from 0.85 mmol/L to 0.80 mmol/L, $P=0.426$) from the baseline (Fig. 2C and D).

Subgroup analysis of cumulative incidence of dyslipidemia after treated with TAF or TDF

We compared the lipid profiles of patients in different subgroups based on HBeAg status, BMI level, sex, and age. Regardless of HBeAg status, the cumulative incidences of dyslipidemia, elevated TG, and TC levels in the TAF group were significantly higher than those in the TDF group (Figure S2). Similar results were found in patients with BMI≥23 kg/m^2. However, for patients with BMI<23 kg/m^2, the cumulative incidences of dyslipidemia and elevated TC were higher in the TAF group, while the elevated TG was comparable with the TDF group. (Figure S3).

Among the male patients, a higher proportion of patients in the TAF group developed dyslipidemia, elevated TG, and TC levels at the end of follow-up before and after PSM. In female patients, the cumulative incidence of elevated TC levels was higher than that in the TDF group before and after PSM (Figure S4).

After stratifying patients by age, we observed that patients aged≥35 years in the TAF group had a higher cumulative incidence of dyslipidemia, elevated TG, and TC levels before and after PSM. Among patients aged<35 years, the incidence rates of dyslipidemia, elevated TG, and TC levels were similar between the TAF and TDF groups in the matched cohort (Figure S5).

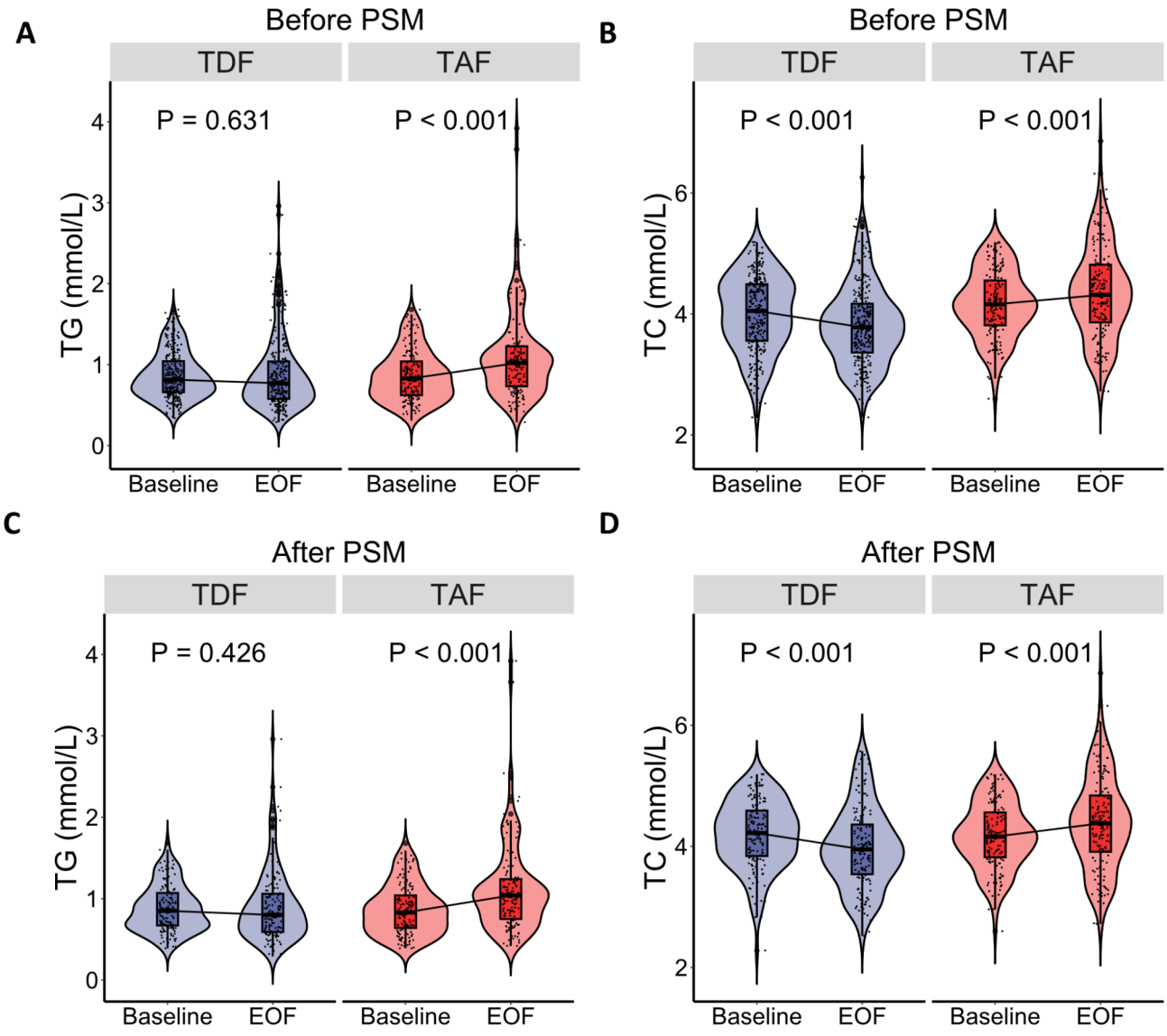

Fig. 2 Comparison of TG and TC changes between baseline and the end of follow-up in different treatment groups before (**A**, **B**) and after (**C**, **D**) propensity score matching

Subgroup analysis of TG and TC changes after treated with TAF or TDF

Generally, the serum TG levels did not change significantly in patients with different HBeAg status (Figure S6), BMI (Figure S7), sex (Figure S8), and age (Figure S9) both in the unmatched and matched TDF cohorts, whereas the TC levels decreased in different subgroups. In patients with different HBeAg status (Figure S6), BMI (Figure S7), sex (Figure S8) as well as patients aged ≥ 35 years (Figure S9), both TG and TC levels were significantly elevated in the matched TAF cohorts. However, TC levels did not change significantly in patients aged < 35 years in the matched and unmatched TAF cohorts (Figure S9).

Factors associated with dyslipidemia

To further identify the factors associated with dyslipidemia during treatment, a Cox regression analysis was performed. The TAF treatment (HR = 3.950, 95% CI: 2.157–7.232, $P < 0.001$), baseline TG level (HR = 4.030, 95% CI: 1.755–9.258, $P = 0.001$), baseline TC level (HR = 2.878, 95% CI: 1.624–5.098, $P < 0.001$) and PLT (HR = 1.004, 95% CI: 1.000-1.008, $P = 0.028$) were independently associated with dyslipidemia (Table S3). In addition, TAF treatment (HR = 2.800, 95%CI: 1.334–5.876, $P = 0.006$), baseline TG level (HR = 7.431, 95% CI: 2.439–22.640, $P < 0.001$) and PLT (HR = 1.007, 95% CI: 1.002–1.011, $P = 0.004$) were independent factors associated with elevated TG levels. TAF treatment (HR = 9.045, 95% CI: 3.836–21.328, $P < 0.001$) and baseline TC level

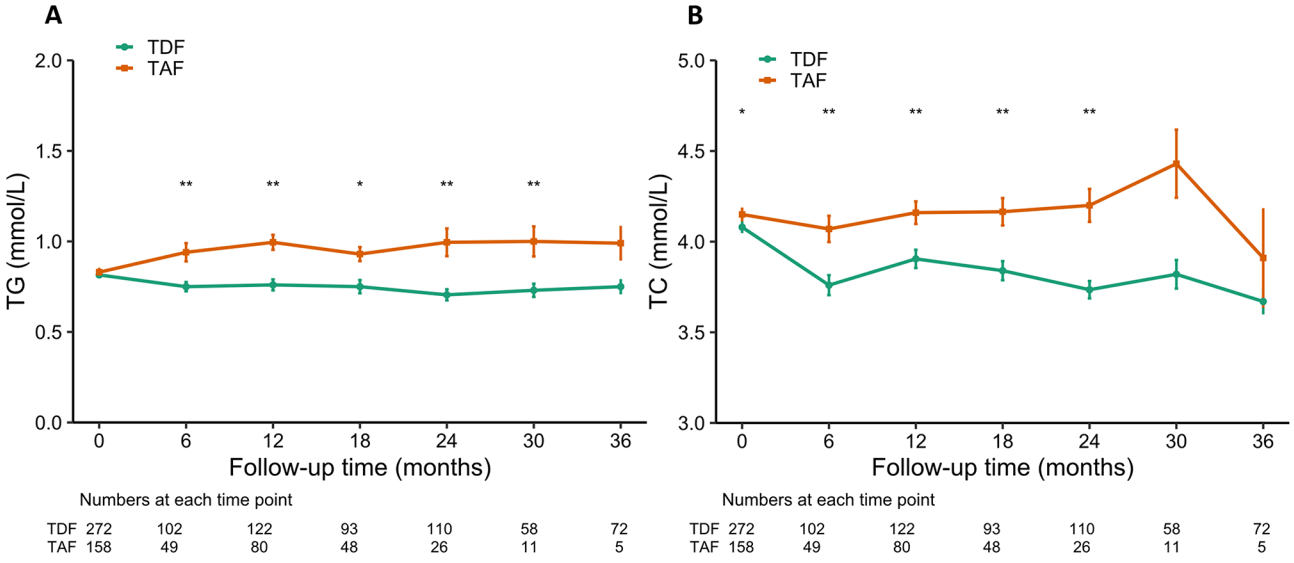

Fig. 3 Changes of TG and TC levels over time after antiviral treatment. *$P<0.05$, **$P<0.01$

Table 2 Incidence rates of dyslipidemia, elevated TG and TC between CHB patients treated with TDF and TAF in the matched cohort

	NAs	*N*	Events	Follow-up (person-years)	Incidence rate (100PYs) 95% CI
Dyslipidemia	TDF	149	17	210.25	8.1 (4.9,12.8)
	TAF	149	42	163.42	25.7 (19.3, 33.2)
Elevated TG	TDF	149	9	210.25	4.3 (2.1, 8.2)
	TAF	149	21	163.42	12.8 (8.3, 19.2)
Elevated TC	TDF	149	8	210.25	3.8 (1.8, 7.6)
	TAF	149	27	163.42	16.5 (11.4, 23.3)

NAs, nucleos(t)ide analogues; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

(HR=13.401, 95% CI: 5.520-32.534, $P<0.001$) were independent factors of elevated TC levels (Table 3). Similar results were found in the matched cohort (Table 4).

Disscussion

In this multicenter real-world retrospective cohort study involving 430 treatment-naïve CHB patients, we analyzed the serum lipid profiles before and after treatment with TAF or TDF. Our results indicated that patients treated with TAF were more likely to have elevated TG and TC levels. In contrast, during TDF treatment, no significant impact was observed on TG levels, while TC levels showed a decreasing trend.

Antiviral treatment is the primary therapeutic strategy to prevent disease progression and improve long-term prognosis for patients with CHB [21]. TDF and TAF, as potent NAs with a high resistance barrier, are recommended as first-line agents for the treatment of chronic HBV infection [22]. TAF presents a comparable antiviral efficacy with TDF, while TAF has a better safety profile for bone and kidney than TDF [23]. Numerous studies have demonstrated that TDF therapy may have a lipid-lowering effect during long-term treatment of HBV-infected and HIV-infected patients [24–26]. However, few studies have investigated the effects of TAF treatment on lipid metabolism in CHB patients. Recently, Cheng et al. found that the switch from TDF to TAF significantly increased serum triglyceride, total cholesterol, HDL and LDL [27]. Several randomized, double-blind, phase 3 clinical trials revealed that CHB patients treated with TAF had relatively higher fasting TC levels at 48 and 96 weeks compared with those treated with TDF [14–16]. Similarly, another study showed that after 1-year of TAF treatment, the TG and TC levels were elevated compared to the pre-treatment levels [28]. However, a study from Korea reported that after 48 weeks of treatment, TAF did not appear to have a significant effect on TC levels in patients with CHB, whereas TDF treatment was associated with a decrease in TG and TC levels [29]. Fung et al. found that over the 96-week double-blind TAF treatment period, fasting TG levels significantly increased, while fasting TC levels were unaffected. In contrast, the 96-week double-blind period of TDF treatment was associated with a significant reduction in both fasting TC and TG levels [30]. According to our study, CHB patients in the TAF group exhibited a significant increasing trend in both TG and TC levels, which was consistent with previous studies [27, 28]. After adjusting for the confounding factors such as age, BMI, similar results were also found. In a study from Canada, patients showed a significant decrease in TC levels after treated with TDF for at least a year, while TG levels remained the same [31]. Similar

Table 3 Cox regression analysis of factors associated with elevated TG and TC

Variables	Elevated TG				Elevated TC			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (yr)	0.995 (0.964, 1.028)	0.781			1.010 (0.978, 1.042)	0.545		
Sex								
Female	Reference		Reference		Reference			
Male	1.846 (0.881, 3.870)	0.104			1.197 (0.589, 2.434)	0.619		
ALT (U/L)	1.000 (0.998, 1.002)	0.829			1.000 (0.998, 1.002)	0.970		
AST (U/L)	0.999 (0.996, 1.003)	0.689			0.999 (0.996, 1.003)	0.730		
Baseline Glu (mmol/L)	1.395 (1.104, 1.763)	0.005	1.278 (0.999, 1.635)	0.051	0.666 (0.349, 1.272)	0.218		
Baseline TG (mmol/L)	6.660 (2.660, 16.673)	< 0.001	7.431 (2.439, 22.640)	< 0.001	3.589 (1.319, 9.765)	0.012	1.824 (0.583, 5.706)	0.302
Baseline TC (mmol/L)	1.504 (0.889, 2.545)	0.129			12.656 (5.536, 28.932)	< 0.001	13.401 (5.520, 32.534)	< 0.001
HBsAg (log_{10} IU/ml)	0.752 (0.581, 0.972)	0.029	0.941 (0.707, 1.253)	0.677	0.932 (0.675, 1.287)	0.669		
HBV DNA (log_{10} IU/ml)	0.922 (0.784, 1.084)	0.325			1.009 (0.844, 1.206)	0.920		
PLT ($\times 10^9$/L)	1.006 (1.002, 1.010)	0.006	1.007 (1.002, 1.011)	0.004	1.005 (1.000, 1.010)	0.037	1.002 (0.996, 1.007)	0.558
ALB (g/L)	1.025 (0.932, 1.128)	0.613			0.967 (0.881, 1.062)	0.483		
FIB-4 score	0.876 (0.681, 1.126)	0.301			0.830 (0.609, 1.131)	0.237		
Diabetes mellitus	1.760 (0.543, 5.704)	0.346			1.968 (0.603, 6.420)	0.262		
BMI level								
< 23 (kg/m^2)	Reference		Reference		Reference			
≥ 23 (kg/m^2)	2.206 (1.143, 4.260)	0.018	1.324 (0.610, 2.875)	0.477	1.152 (0.599, 2.216)	0.672		
HBeAg status								
Negative	Reference				Reference			
Positive	0.691 (0.368, 1.300)	0.252			0.846 (0.434, 1.646)	0.622		
Antiviral drug								
TDF	Reference		Reference		Reference			
TAF	2.721 (1.459, 5.074)	0.002	2.800 (1.334, 5.876)	0.006	8.247 (3.806, 17.868)	< 0.001	9.045 (3.836, 21.328)	< 0.001

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antibody; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; TG, triglyceride; TC, total cholesterol; Glu, glucose; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ALB, albumin; PLT, platelet; FIB-4, fibrosis index based on 4 factors

results were also found in our study. Hong et al. investigated changes in lipid profiles from baseline after 1, 2, 3, and 4 years of treatment. They found that patients treated with TDF exhibited a significantly greater decline in median changes in TC and TG levels than those treated with TAF [32]. Our results also indicated that TG and TC levels in the TAF group were significantly higher than those in the TDF group at 6, 12, 18, and 24 months of treatment. However, the differences were not significant at 30 and 36 months of treatment due to the small sample size.

Few studies have investigated the cumulative incidence of dyslipidemia after treated with TDF or TAF in real-world cohorts. Our study found that a significantly higher proportion of patients treated with TAF had dyslipidemia. Suzuki et al. evaluated the effects of switching from TDF to TAF on lipid profiles of patients with CHB. Their results showed that after 6–12 months of TDF treatment, the rate of abnormal TC decreased from 33.3 to 9.1%, whereas in the TAF-treated group, the rate of abnormal TC increased from 21.2 to 42.4% [33]. This is also consistent with the results of our study, although the baseline TG and TC levels of the patients included in our study were both normal. Furthermore, our study investigated the effect of TAF on lipid profiles in patients across different subgroups. The results suggested that the effect of TAF on serum lipids might be slight in patients younger than 35. However, due to the relatively small sample sizes of the subgroups, the actual effect and mechanism of TAF treatment on lipids needs to be validated in future studies.

TAF and TDF are two different precursors of TFV, both of which are hydrolyzed into TFV, and after intracellular phosphorylation to tenofovir diphosphate (TFV-DP), they are incorporated into the viral DNA chain to block viral replication and exert antiviral effects [34]. However, TAF and TDF have different metabolic pathways due to their different chemical structures [34, 35]. TDF

Table 4 Cox regression analysis of factors associated with elevated TG and TC in the matched cohort

Variables	Elevated TG				Elevated TC			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (yr)	0.979 (0.941, 1.019)	0.299			1.000 (0.969, 1.032)	0.997		
Sex								
Female	Reference		Reference		Reference			
Male	3.025 (1.055, 8.670)	0.039	2.411 (0.695, 8.362)	0.166	1.143 (0.549, 2.381)	0.722		
ALT (U/L)	0.999 (0.996, 1.002)	0.505			1.000 (0.999, 1.002)	0.516		
AST (U/L)	0.997 (0.990, 1.004)	0.403			1.001 (0.997, 1.004)	0.647		
Baseline Glu (mmol/L)	1.372 (1.089, 1.729)	0.007	1.271 (0.999, 1.617)	0.051	0.597 (0.297, 1.197)	0.146		
Baseline TG (mmol/L)	8.365 (2.850, 24.556)	< 0.001	7.254 (2.022, 26.024)	0.002	3.183 (1.151, 8.798)	0.026	1.834 (0.618, 5.443)	0.275
Baseline TC (mmol/L)	1.537 (0.772, 3.059)	0.221			8.907 (3.903, 20.328)	< 0.001	10.814 (4.625, 25.289)	< 0.001
HBsAg (log_{10} IU/ml)	0.842 (0.630, 1.125)	0.244			0.975 (0.719, 1.321)	0.869		
HBV DNA (log_{10} IU/ml)	0.874 (0.724, 1.055)	0.162			1.033 (0.869, 1.228)	0.714		
PLT ($\times 10^9$/L)	1.006 (1.002, 1.011)	0.004	1.006 (1.002, 1.011)	0.007	1.004 (1.000, 1.009)	0.075		
ALB (g/L)	1.044 (0.929, 1.173)	0.470			0.946 (0.861, 1.040)	0.251		
FIB-4 score	0.587 (0.331, 1.041)	0.068			0.871 (0.640, 1.185)	0.380		
Diabetes mellitus	1.526 (0.362, 6.437)	0.565			1.922 (0.585, 6.314)	0.281		
BMI level								
< 23 (kg/m^2)	Reference		Reference		Reference			
≥ 23 (kg/m^2)	2.269 (1.039, 4.955)	0.040	1.068 (0.442, 2.578)	0.884	1.170 (0.602, 2.276)	0.643		
HBeAg status								
Negative	Reference				Reference			
Positive	0.762 (0.366, 1.585)	0.466			1.165 (0.599, 2.267)	0.653		
Antiviral drug								
TDF	Reference		Reference		Reference			
TAF	3.155 (1.436, 6.931)	0.004	2.773 (1.186, 6.482)	0.019	4.848 (2.178, 10.790)	< 0.001	7.617 (3.182, 18.235)	< 0.001

HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antibody; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; TG, triglyceride; TC, total cholesterol; Glu, glucose; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ALB, albumin; PLT, platelet; FIB-4, fibrosis index based on 4 factors

is hydrolyzed to TFV in the gastrointestinal tract and blood circulation, while TAF exists in the blood circulation as a prototype and is hydrolyzed to TFV in hepatocytes [35]. Murata et al. reported that TDF promotes gastrointestinal cells to release interferon-lambda 3, which could affect serum HBsAg levels [36]. Regarding the mechanism of lowering serum lipids, previous studies reported that TDF could reduce the serum cholesterol level through the upregulation of the CD36/PPAR-α axis [37]. Although studies have shown the effect of TAF on lipid profile, the mechanism is not yet clear. A possible explanation might be the different pharmacokinetics of TAF, which enables high intracellular transfer compared with TDF and lowers plasma TFV concentration [29]. However, the exact mechanism by which TAF affects blood lipids remains to be explored.

This study had several limitations. First, the sample size of our study was relatively small, and the results need to be validated in future studies. Second, this study is limited by its retrospective nature, which may have been influenced by selection bias and other confounding factors. Third, this study only analyzed the effects of TDF and TAF on TG and TC levels. The impact of TAF on HDL-C, LDL-C levels, and body weight was not analyzed due to insufficient data. Fourth, the patients in this study were from an Asian population, and the effect of TAF on patients of other ethnicities still needs further investigation.

In conclusion, TAF was associated with increased TG and TC levels in CHB patients. Close monitoring of lipid profiles is needed in CHB patients with TAF treatment. However, although TAF was associated with increased dyslipidemia in patients with CHB, no significant difference in the long-term risk of cardiovascular events was reported between patients treated with TAF and TDF in a recent study [32]. Thus, more efforts are needed to validate our findings and explore the long-term impact of TAF on lipid profiles and cardiovascular risk in patients with CHB.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-024-02515-7.

Supplementary Material 1

Author contributions
All authors contributed to this study at different levels. Study concept and design (C W, R H, Cw Z, F C); acquisition of data (T F, J W, Yl L, L Z, Y X, Sq Z, Zy Z, Yf P, Yy L, C J, J X, Xm Y, J L, Xx L); statistical analysis and interpretation of data (F C); drafting of the manuscript (F C, X J, R H); critical revision of the manuscript for important intellectual content (C W, R H).

Funding
Dr. Rui Huang wishes to acknowledge the support from Nanjing Medical Science and Technique Development Foundation (JQX21002 and QRX17121), Natural Science Foundation of Jiangsu Province (BK20211004), and the Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University (2022-LCYJ-MS-07). Dr. Jian Wang wishes to acknowledge the support from the National Natural Science Fund (82300719), Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University (2021-LCYJ-PY-43), and Nanjing Medical Science and Technique Development Foundation (YKK21067).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Review Board of Nanjing Drum Tower Hospital (IRB number: 2008022) and was performed according to the ethical guidelines of the Declaration of Helsinki. A waiver of informed consent was approved by the ethics committee due to a retrospective design and deidentified data. This study has been registered under ClinicalTrials.gov (NCT03097952).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Infectious Diseases, Nanjing Drum Tower Hospital Clinical College of Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, No. 321 Zhongshan Road, Nanjing, Jiangsu 210008, China
[2]Department of Clinical Laboratory, Huai'an No. 4 People's Hospital, Huai'an, Jiangsu, China
[3]Department of Infectious Diseases, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China
[4]Institute of Viruses and Infectious Diseases, Nanjing University, Nanjing, Jiangsu, China
[5]Department of Infectious Diseases, The Affiliated Infectious Diseases Hospital of Soochow University, Suzhou, Jiangsu, China
[6]Department of Infectious Diseases, Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing, Jiangsu, China
[7]Department of Infectious Diseases, Nanjing Drum Tower Hospital Clinical College of Jiangsu University, Nanjing, Jiangsu, China

Received: 20 June 2024 / Accepted: 22 September 2024
Published online: 28 September 2024

References

1. Global regional. National age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the global burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.
2. Lee WM. Hepatitis B virus infection. N Engl J Med. 1997;337(24):1733–45.
3. WHO. Guidelines for the diagnosis, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization. 2024. https://www.who.int/publications/i/item/9789240090903 (accessed April 16, 2024).
4. Jeng WJ, Papatheodoridis GV, Lok ASF, Hepatitis B. Lancet. 2023;401(10381):1039–52.
5. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370–98.
6. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560–99.
7. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. Am J Kidney Dis. 2011;57(5):773–80.
8. Mateo L, Holgado S, Mariñoso ML, et al. Hypophosphatemic osteomalacia induced by tenofovir in HIV-infected patients. Clin Rheumatol. 2016;35(5):1271–9.
9. Lampertico P, Chan HLY, Janssen HLA, Strasser SI, Schindler R, Berg T. Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. Aliment Pharmacol Ther. 2016;44(1):16–34.
10. Ogawa E, Nakamuta M, Koyanagi T, et al. Switching to tenofovir alafenamide for nucleos(t)ide analogue-experienced patients with chronic hepatitis B: week 144 results from a real-world, multi-centre cohort study. Aliment Pharmacol Ther. 2022;56(4):713–22.
11. Byun KS, Choi J, Kim JH, et al. Tenofovir Alafenamide for Drug-Resistant Hepatitis B: a Randomized Trial for switching from Tenofovir Disoproxil Fumarate. Clin Gastroenterol Hepatol. 2022;20(2):427–e4375.
12. Chan HLY, Buti M, Lim YS, et al. Long-term treatment with Tenofovir Alafenamide for Chronic Hepatitis B results in high rates of viral suppression and favorable renal and bone safety. Am J Gastroenterol. 2024;119(3):486–96.
13. Fabbiani M, Bracciale L, Doino M, et al. Lipid-lowering effect of tenofovir in HIV-infected patients. J Antimicrob Chemother. 2011;66(3):682–3.
14. Chan HLY, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1(3):185–95.
15. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1(3):196–206.
16. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018;68(4):672–81.
17. Squillace N, Ricci E, Menzaghi B, et al. The Effect of switching from Tenofovir Disoproxil Fumarate (TDF) to Tenofovir Alafenamide (TAF) on liver enzymes, glucose, and lipid Profile. Drug Des Devel Ther. 2020;14:5515–20.
18. Mallon PWG, Brunet L, Fusco JS, et al. Lipid changes after switch from TDF to TAF in the OPERA cohort: LDL Cholesterol and triglycerides. Open Forum Infect Dis. 2022;9(1):ofab621.
19. Expert Panel on Detection. Evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486–97.
20. Pengpid S, Peltzer K. National high prevalence, and low awareness, treatment and control of dyslipidaemia among people aged 15–69 years in Mongolia in 2019. Sci Rep. 2022;12(1):10478.
21. Martin P, Nguyen MH, Dieterich DT, et al. Treatment algorithm for managing chronic Hepatitis B Virus infection in the United States: 2021 update. Clin Gastroenterol Hepatol. 2022;20(8):1766–75.
22. Pan CQ, Afdhal NH, Ankoma-Sey V, et al. First-line therapies for hepatitis B in the United States: a 3-year prospective and multicenter real-world study after approval of tenofovir alefenamide. Hepatol Commun. 2022;6(8):1881–94.
23. Roade L, Riveiro-Barciela M, Esteban R, Buti M. Long-term efficacy and safety of nucleos(t)ides analogues in patients with chronic hepatitis B. Ther Adv Infect Dis. 2021;8:2049936120985954.
24. Tungsiripat M, Kitch D, Glesby MJ, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. AIDS. 2010;24(11):1781–4.
25. Zhang Q, Liang J, Yin J, et al. Real-life impact of tenofovir disoproxil fumarate and entecavir therapy on lipid profile, glucose, and uric acid in chronic hepatitis B patients. J Med Virol. 2022;94(11):5465–74.
26. Santos JR, Saumoy M, Curran A, et al. The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. Clin Infect Dis. 2015;61(3):403–8.

27. Cheng PN, Feng IC, Chen JJ, et al. Body weight increase and metabolic derangements after tenofovir disoproxil fumarate switch to tenofovir alafenamide in patients with chronic hepatitis B. Aliment Pharmacol Ther. 2024;59(2):230–8.
28. Lai RM, Lin S, Wang MM, et al. Tenofovir alafenamide significantly increased serum lipid levels compared with entecavir therapy in chronic hepatitis B virus patients. World J Hepatol. 2023;15(8):964–72.
29. Jeong J, Shin JW, Jung SW, Park EJ, Park NH. Tenofovir alafenamide treatment may not worsen the lipid profile of chronic hepatitis B patients: a propensity score-matched analysis. Clin Mol Hepatol. 2022;28(2):254–64.
30. Fung SK, Pan CQ, Wong GLH, et al. Atherosclerotic cardiovascular disease risk profile of patients with chronic hepatitis B treated with tenofovir alafenamide or tenofovir disoproxil fumarate for 96 weeks. Aliment Pharmacol Ther. 2024;59(2):217–29.
31. Shaheen AA, AlMattooq M, Yazdanfar S, et al. Tenofovir disoproxil fumarate significantly decreases serum lipoprotein levels compared with entecavir nucleos(t)ide analogue therapy in chronic hepatitis B carriers. Aliment Pharmacol Ther. 2017;46(6):599–604.
32. Hong H, Choi WM, Lee D, et al. Cardiovascular risk in chronic hepatitis B patients treated with tenofovir disoproxil fumarate or tenofovir alafenamide. Clin Mol Hepatol. 2024;30(1):49–63.
33. Suzuki K, Suda G, Yamamoto Y, et al. Effect of switching from tenofovir disoproxil fumarate to tenofovir alafenamide on lipid profiles in patients with hepatitis B. PLoS ONE. 2022;17(1):e0261760.
34. Ray AS, Fordyce MW, Hitchcock MJ. Tenofovir alafenamide: a novel prodrug of tenofovir for the treatment of human immunodeficiency virus. Antiviral Res. 2016;125:63–70.
35. Kearney BP, Flaherty JF, Shah J. Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. Clin Pharmacokinet. 2004;43(9):595–612.
36. Murata K, Asano M, Matsumoto A, et al. Induction of IFN-λ3 as an additional effect of nucleotide, not nucleoside, analogues: a new potential target for HBV infection. Gut. 2018;67(2):362–71.
37. Suzuki K, Suda G, Yamamoto Y, et al. Tenofovir-disoproxil-fumarate modulates lipid metabolism via hepatic CD36/PPAR-alpha activation in hepatitis B virus infection. J Gastroenterol. 2021;56(2):168–80.

Publisher's note