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Effect of nucleos(t)ide analogues on blood lipid profiles in patients with chronic hepatitis B

A cross-sectional survey

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Abstract

This study aimed to explore the effects of the 3 nucleos(t)ide analogues (NAs) on lipid levels. We retrospectively included patients treated with NAs at 2 centers and collected their clinical data at their visiting points. Differences in blood lipid levels were analyzed by statistical methods, and factors related to hyperlipidemia were discussed. In these 2 centers, the prevalence rates of hypercholesterolemia were 12/181 (6.6%) for tenofovir alafenamide fumarate (TAF)-, 0/158 (0%) for tenofovir disoproxil fumarate (TDF)-, and 13/182 (7.1%) for entecavir (ETV)-treated individuals ($P = .003$). The prevalence rates of hypertriglyceridemia were 30/181 (16.6%) for TAF-, 11/158 (7.0%) for TDF-, and 26/182 (14.3%) for ETV-treated individuals ($P = .025$). In TAF (n = 181, 10 [6, 15] months), TDF (n = 158, 18 [7.5, 45] months), and ETV (n = 182, 24 [10, 60] months) groups, total cholesterol (TC) levels were 4.63 ± 0.91 mmol/L, 3.86 ± 0.61 mmol/L, and 4.53 ± 0.87 mmol/L, respectively; triglyceride (TG) levels were 1.27 ± 0.76 mmol/L, 0.87 ± 0.51 mmol/L, and 1.14 ± 0.67 mmol/L, respectively ($P < .001$). In multivariate regression analysis, factors associated with hypercholesterolemia were age (adjusted hazard risk [HR] = 1.055 [1.018–1.094]; $P = .003$) and body mass index (BMI) (adjusted HR = 0.817 [0.669–0.998]; $P = .048$). Factors associated with hypertriglyceridemia were TAF group (vs. TDF group) (adjusted HR = 0.405 [0.167–0.980]; $P = .045$), age (adjusted HR = 1.028 [1.002–1.055]; $P = .038$), and sex (adjusted HR = 0.190 [0.079–0.456]; $P < .001$). Among the patients treated with TAF (10 [6, 15] months), TDF (18 [7.5, 45] months), and ETV (24 [10, 60] months), the blood lipid levels in the TDF group were lower than those in the TAF group and ETV group, and the occurrence of hyperlipidemia was associated with age, sex, BMI, and different treatment.

Abbreviations: BMI = body mass index, CHB = chronic hepatitis B, DNA = deoxyribonucleic acid, ETV = entecavir, FLD = fatty liver disease, HBeAg = hepatitis B envelope antigen, HBV = hepatitis B virus, HDL-C = high-density lipoprotein cholesterol, HR = hazard risk, LDL-C = low-density lipoprotein cholesterol, Mets = metabolic syndrome, NAs = nucleos(t)ide analogues, PEG-IFN = peg-interferon, TAF = tenofovir alafenamide fumarate, TC = total cholesterol, TDF = tenofovir disoproxil fumarate, TG = triglyceride, TMF = tenofovir amibufenamide, VLDL-C = very low-density lipoprotein cholesterol.

Keywords: hepatitis B virus, hyperlipidemia, lipid metabolism, nucleos(t)ide analogues

1. Introduction

Chronic hepatitis B (CHB) is a global health problem. According to the World Health Organization,[1] in 2015, about 257 million people worldwide were infected with the hepatitis B virus (HBV), and 887,000 of them died due to late complications of CHB, such as liver cirrhosis and liver cancer.[2] At present, 2 ways to treat CHB patients include oral nucleos(t)ide analogues (NAs) and peg-interferon (PEG-IFN) immunotherapy.[3,4] There are 3 first-line NAs, namely, entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF). ETV and TDF have been on the market for >10 years, and most adverse reactions of patients have been observed. In patients with previous drug-resistance history of adefovir dipivoxil (ADV) and lamivudine, ETV increases the probability of drug resistance.[5] TDF has definite nephrotoxicity and can affect calcium and phosphorus metabolism, resulting in abnormal bone mineral density.[6–9] However, it has good safety in hepatitis B envelope antigen (HBeAg)-positive pregnant women and lactating women, and blocks mother-to-child transmission.[10] TAF has been modified on the basis of TDF to enhance its entrance to the liver.[11,12] Moreover, the dose has

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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been reduced from 300 mg of TDF to 25 mg of TAF, which has greatly reduced the occurrence of toxic reactions.[13] TAF, which was listed on the market at the end of 2018 in China, is relatively expensive; thus, the number of patients who receive it is not high, and it is difficult to obtain large-scale adverse reaction monitoring data.

The liver is one of the important metabolic organs of the human body. It is involved not only in fat synthesis, but also in the processes of fat digestion and absorption. The liver has the strongest ability to synthesize fat, mainly triglycerides (TGs).[14] After synthesis, TG combines with apolipoprotein and cholesterol to form very low-density lipoprotein cholesterol (VLDL-C), which is transported by blood to extrahepatic tissues for storage or utilization. The target organ of HBV is the liver, that is, the virus damages the liver. In CHB patients, if the liver function is affected, the synthesis and metabolism of fat are altered, which results in dyslipidemia.

Clinically, TAF has to be taken with meals to facilitate its absorption. This is based on the results of the pharmacokinetic analysis of phase 3 overseas CHB subjects, which showed that compared with fasting conditions, giving a single dose of TAF with high-fat meals increased the exposure of TAF by 65%.[15] A question arises as to whether fat metabolism in the human body will be affected and whether the blood lipid content will be abnormal in individuals taking TAF with a high-fat meal if their liver is damaged by the virus. In the TAF manual, 4 comparison tables of blood lipids after taking TAF and TDF are listed: the average absolute values of low-density lipoprotein cholesterol (LDL-C) and TG in TAF patients increased by 6 and 11, respectively, while those of TDF patients decreased by 11 and 10, respectively. It has been shown in some HIV treatment studies[16] that the cholesterol level in individuals who switch from TDF to TAF continues to rise, and the total cholesterol (TC) level triples, from 5.2% to 15.5%. The former "four-in-one" [stribild (including TDF)] and the current "four-in-one" [genvoya (including TAF)] clinical tests analyzed similarities and differences in serum lipids from 48 to 96 to 144 weeks. It was found that genvoya (including TAF) increased blood lipids more than stribild (including TDF) did.[17] Suzuki et al[18] analyzed blood lipid changes in newly treated patients after taking ETV and TDF for 6 to 12 months, and they found that TDF reduced the levels of TC and high-density lipoprotein cholesterol (HDL-C), which was confirmed by in vitro experiments. Based on the above, we assessed the effects of first-line antiviral drugs on blood lipids in CHB patients so as to avoid potential cardiovascular risk in such patients.

2. Materials and methods

2.1. Patients

This study was a cross-sectional study. Clinical data of 405 patients in the hepatitis clinic of Huashan Hospital affiliated to Fudan University and 116 patients in the Public Health Clinical Center affiliated to Fudan University from 2021 to 2022 were retrospectively collected. In Huashan Hospital, 135 patients took TAF; 129 took TDF; and 141 took ETV. In the Public Health Clinical Center, 46 took TAF; 29 took TDF; and 41 took ETV. Blood lipid data at a visiting point after taking the medicine were available for these patients. The inclusion criteria were as follows: monotherapy with NAs; patients treated with 1 of 3 NAs; and available clinical information. The exclusion criteria were as follows: untreated patients; multitherapy with NAs or combination therapy with PEG-IFN; coexistence of other infectious diseases, such as acquired immunodeficiency syndrome (AIDS) and chronic hepatitis C (CHC); presence of severe fatty liver disease (FLD), hyperlipidemia, and uncontrollable cardiovascular diseases; use of other drugs; incomplete clinical information; or loss to follow-up.

The study was conducted in compliance with the Helsinki Declaration and approved by the Medical Ethics Committee of Huashan Hospital affiliated to Fudan University and Public Health Clinical Center affiliated to Fudan University. All of the enrolled patients provided written informed consent.

2.2. Statistical analysis

All of the variables were analyzed by IBM SPSS statistics 20 (IBM Inc., Armonk, NY). Continuous variables adhering to normal distribution are expressed as mean ± standard deviation, and continuous variables without normal distribution are expressed as median (lower quartile, upper quartile). The Kruskal–Wallis single-factor test was used to analyze differences among the 3 groups of independent samples, and the classified variables were tested by the chi-square test. All of the *P*-values were 2-sided, and $P < .05$ was set as the statistically significant threshold. GraphPad Prism 9.0 (GraphPad Software Inc., San Diego, CA) was used to make a histogram and analyze the data.

3. Results

3.1. Patients' characteristics

Figure 1 shows the screening and selection processes. Table 1 shows the main characteristics of 521 patients in these 2 centers. Among the 3 groups, the patients taking ETV were older and their duration of treatment was longer. The proportion of men taking TDF was lower (87/158, 55.06%) than those taking TAF (112/181, 61.88%) and ETV (114/182, 62.64%), and the duration of treatment in the TAF group was shorter than that in the TDF and ETV groups. At the follow-up point, the mean alanine transaminase (ALT), aspartate aminotransferase (AST), albumin (ALB), alpha fetoprotein (AFP), serum creatinine (SCr), and estimated glomerular filtration rate (eGFR) levels of the 3 groups were normal. The mean HBV deoxyribonucleic acid (DNA) level was lower than the lower limit of detection (2 log copies/mL), which suggests that they might have been treated with NAs or PEG-IFN. Given that the mean aspartate aminotransferase/platelet count ratio index (APRI) score in the 3 groups was normal, there were few cases of liver cirrhosis. There were no significant differences in mean age, proportion of elderly patients (>70 years), sex, body mass index (BMI), and hepatitis B surface antigen (HBsAg) levels among the 3 groups. The median treatment time (interquartile interval) was 10 (6, 15) months in the TAF group, 18 (7.5, 45) months in the TDF group, and 24 (10, 60) months in the ETV group ($P < .001$).

3.2. Serum lipids

Among the 521 patients, the prevalence rates of hypercholesterolemia in the TAF, TDF, and ETV groups were 12/181 (6.6%), 0/158 (0), and 13/182 (7.1%), respectively ($P = .003$). The prevalence rates of hypertriglyceridemia in the TAF, TDF, and ETV groups were 30/181 (16.6%), 11/158 (7.0%), and 26/182 (14.3%) ($P = .025$). Moreover, the blood lipid levels at the visiting point were significantly different among the 3 different treatment groups. The level of each index (including TC, TG, HDL-C, LDL-C, and VLDL-C) in the whole set of blood lipids in the TDF group was lower than that in the TAF group and that in the ETV group, in terms of the average level. For example, TC (TDF vs. TAF, −0.77; TDF vs. ETV, −0.67; $P < .001$), TG (TDF vs. TAF, −0.4; TDF vs. ETV, −0.27; $P < .001$), HDL-C (TDF vs. TAF, −0.19; TDF vs. ETV, −0.14; $P < .001$), LDL-C (TDF vs. TAF, −0.4; TDF vs. ETV, −0.39; $P < .001$), VLDL-C (TDF vs. TAF, −0.18; TDF vs. ETV, −0.13; $P < .001$), apolipoprotein A1 (APoA1) (TDF vs. TAF, −0.12; TDF vs. ETV, −0.09; $P < .001$), and apolipoprotein B (APoB) (TDF vs. TAF, −0.08; TDF vs. ETV, −0.1; $P < .001$) (Table 2).

Although the blood lipid levels of the 3 groups were different, due to the existence of many confounding factors, we also

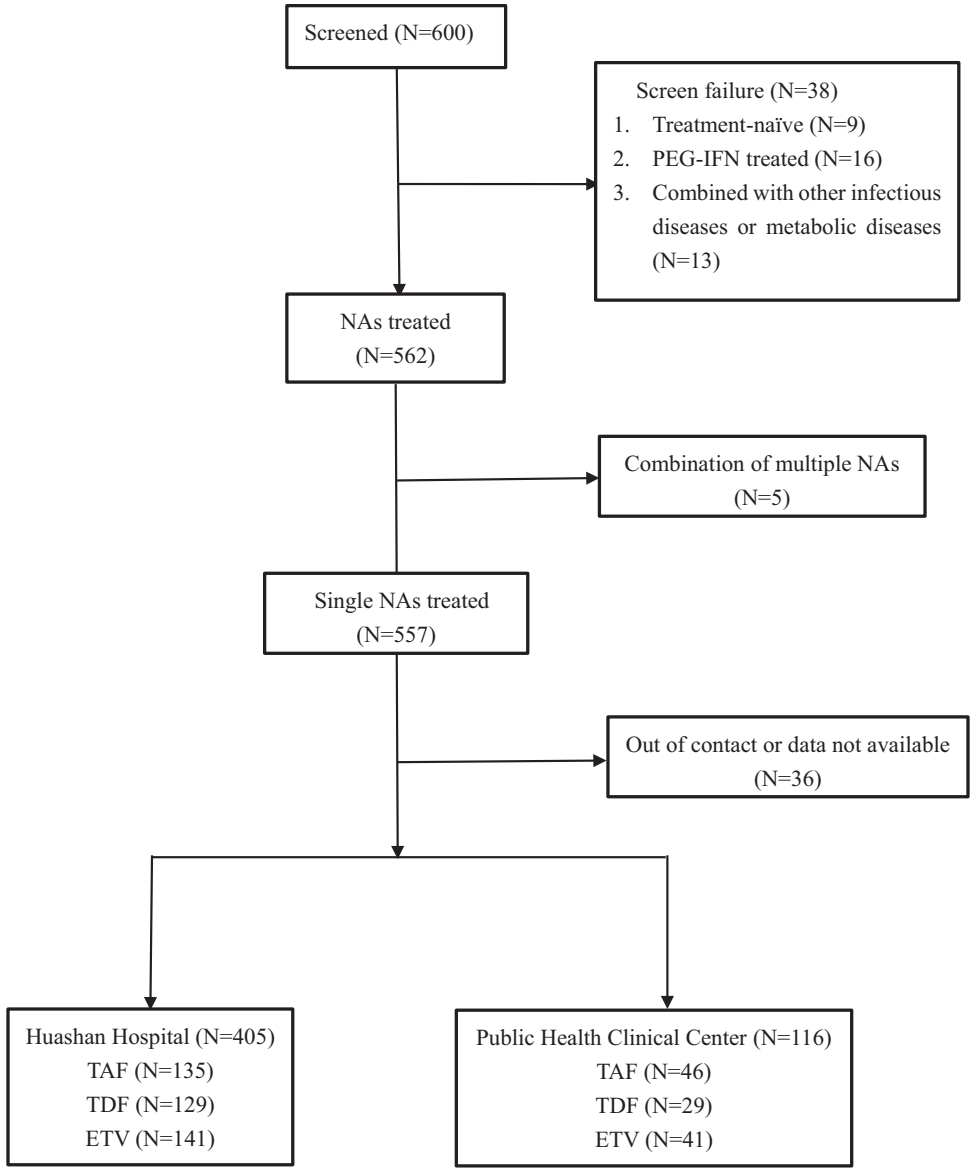

Figure 1. Screening process for enrolled patients in the 2 centers. Screening, enrollment and flowchart of patients with HBV who went to Huashan Hospital and the Public Health Clinical Center during 1 year from 2021 to 2022. 16 patients were treated with only PEG-IFN or NAs plus PEG-IFN. 13 patients were combined with CHC, ALD or FLD. 5 patients were treated with 2 different NAs, such as ETV plus TDF. ALD = atutoimmune liver diseases, CHC = chronic hepatitis C, ETV = entecavir, FLD = fatty liver diseases, HBV = hepatitis B virus, NAs = nucleos(t)ide analogues, PEG-IFN = pegylated interferon, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate.

compared the blood lipid levels after the stratification of the confounding factors, namely, in patients <50 years, the blood lipid levels after TDF treatment were lower than those in TAF and ETV groups, and there were significant differences ($P < .001$). In patients >50 years, similar differences were observed in TC ($P < .05$), HDL-C ($P < .001$). In group "≤50," TC levels were TAF (4.53 ± 0.79 mmol/L, N = 134), TDF (3.84 ± 0.66 mmol/L, N = 128) and ETV (4.38 ± 0.95 mmol/L, N = 130); HDL-C levels were TAF (1.29 ± 0.31 mmol/L, N = 128), TDF (1.11 ± 0.28 mmol/L, N = 127) and ETV (1.26 ± 0.33 mmol/L, N = 129); LDL-C levels were TAF (2.74 ± 0.71 mmol/L, N = 128), TDF (2.31 ± 0.57 mmol/L, N = 127) and ETV (2.64 ± 0.73 mmol/L, N = 129) (Fig. 2A). In group ">50," TC levels were TAF (4.67 ± 1.00 mmol/L, N = 47), TDF (4.18 ± 0.79 mmol/L, N = 29) and ETV (4.66 ± 0.95 mmol/L, N = 52); HDL-C levels were TAF (1.32 ± 0.38 mmol/L, N = 44), TDF (1.10 ± 0.31 mmol/L, N = 28) and ETV (1.38 ± 0.37 mmol/L, N = 52); LDL-C levels were TAF (2.71 ± 0.81 mmol/L, N = 44), TDF (2.57 ± 0.61 mmol/L, N = 28) and ETV (2.76 ± 0.74 mmol/L, N = 52) (Fig. 2A).

We also stratified the patients according to sex. Blood lipid levels were lower in patients treated with TDF compared to those in the other 2 groups. In male patients, differences were observed in TC ($P < .001$), HDL-C ($P < .001$), LDL-C ($P < .05$). Among female patients, the differences were observed in TC ($P < .001$), HDL-C ($P < .001$), LDL-C ($P < .05$). In group "male," TC levels were TAF (4.44 ± 0.83 mmol/L, N = 112), TDF (3.82 ± 0.72 mmol/L, N = 86) and ETV (4.29 ± 0.84 mmol/L, N = 114); HDL-C levels were TAF (1.17 ± 0.27 mmol/L, N = 109), TDF (0.98 ± 0.21 mmol/L, N = 86) and ETV (1.18 ± 0.29 mmol/L, N = 113); LDL-C levels were TAF (2.76 ± 0.74 mmol/L, N = 109), TDF (2.35 ± 0.64 mmol/L, N = 86) and ETV (2.63 ± 0.70 mmol/L, N = 113) (Fig. 2B). In group "female," TC levels were TAF (4.76 ± 0.84 mmol/L, N = 69), TDF (4.00 ± 0.66 mmol/L, N = 71) and ETV (4.74 ± 1.06 mmol/L, N = 68); HDL-C levels were TAF

Table 1

General characteristics of the participating patients according to treatment.

	TAF	TDF	ETV	*P*-value
Total number, n (%)	181 (34.7)	158 (30.3)	182 (34.9)	-
Age (yrs)	43 ± 13	40 ± 10	46 ± 13	.082
Age (yrs) >70, n (%)	4 (2.2)	2 (1.3)	1 (0.5)	.387
Sex (male/female)	112/69	87/71	114/68	.301
BMI (kg/m^2)	22.60 ± 3.23	22.60 ± 3.01	23.21 ± 3.48	.194
Duration of treatment (mo)	10 (6,15)	18 (7.5,45)	24 (10,60)	<.001
APRI score	0.40 ± 0.34	0.34 ± 0.21	0.40 ± 0.30	.407
ALT level (U/L)	35 ± 41	34 ± 36	28 ± 31	.061
AST level (U/L)	27 ± 21	27 ± 16	25 ± 16	.070
ALB (g/L)	46 ± 3	46 ± 2	45 ± 3	.001
AFP (ng/mL)	3.25 ± 2.19	3.63 ± 5.84	2.88 ± 2.73	.280
SCr (μmol/L)	66 ± 15	64 ± 14	63 ± 14	.011
eGFR (mL/min)	109 ± 16	113 ± 13	109 ± 14	<.001
HBsAg (Log IU/mL)	3.22 ± 1.06	3.06 ± 1.14	3.07 ± 0.85	.650
HBeAg (positive/negative)	106/64	73/85	78/103	.001
HBV DNA (Log copies/mL)	1.89 ± 0.53	1.84 ± 0.69	1.90 ± 0.63	.769

AFP = alpha fetoprotein, ALB = albumin, ALT = alanine transaminase, APRI = aspartate aminotransferase/platelet count ratio index, AST = aspartate aminotransferase, BMI = body mass index, eGFR = estimated glomerular filtration rate, ETV = entecavir, HBeAg = hepatitis B envelope antigen, HBsAg = hepatitis B surface antigen, HBV DNA = hepatitis B virus-deoxyribonucleic acid, SCr = serum creatinine, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate.

Table 2

General characteristics of serum lipids at the moments of follow-up.

	TAF	TDF	ETV	*P*-value
Hypercholesterolemia, n (%)	12 (6.6)	0 (0)	13 (7.1)	.003
Hypertriglyceridemia, n (%)	30 (16.6)	11 (7.0)	26 (14.3)	.025
TC (mmol/L)	4.63 ± 0.91	3.86 ± 0.61	4.53 ± 0.87	<.001
TG (mmol/L)	1.27 ± 0.76	0.87 ± 0.51	1.14 ± 0.67	.004
HDL-C (mmol/L)	1.32 ± 0.34	1.13 ± 0.26	1.27 ± 0.33	<.001
LDL-C (mmol/L)	2.72 ± 0.71	2.32 ± 0.53	2.71 ± 0.73	<.001
VLDL-C (mmol/L)	0.59 ± 0.40	0.41 ± 0.19	0.54 ± 0.25	<.001
APoA1 (mmol/L)	1.02 ± 0.15	0.90 ± 0.13	0.99 ± 0.14	<.001
APoB (mmol/L)	0.55 ± 0.13	0.47 ± 0.11	0.57 ± 0.23	<.001

APoA1 = apolipoprotein A1, APoB = apolipoprotein B, ETV = entecavir, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TAF = tenofovir alafenamide fumarate, TC = total cholesterol, TDF = tenofovir disoproxil fumarate, TG = triglyceride, VLDL-C = very low-density lipoprotein cholesterol.

(1.50 ± 0.32 mmol/L, N = 63), TDF (1.28 ± 0.28 mmol/L, N = 69) and ETV (1.48 ± 0.35 mmol/L, N = 68); LDL-C levels were TAF (2.68 ± 0.72 mmol/L, N = 63), TDF (2.37 ± 0.52 mmol/L, N = 69) and ETV (2.75 ± 0.77 mmol/L, N = 68) (Fig. 2B).

After HBeAg status stratification, the blood lipid levels in TDF group were still lower than those in TAF group and ETV group. Among HBeAg-positive patients, the specific differences were observed in TC ($P < .05$), HDL-C ($P < .05$), LDL-C ($P < .05$). In HBeAg-negative patients, the specific differences were observed in TC ($P < .001$), HDL-C ($P < .05$), LDL-C ($P < .05$). In group "HBeAg (+)," TC levels were TAF (4.61 ± 0.81 mmol/L, N = 106), TDF (3.92 ± 0.62 mmol/L, N = 73) and ETV (4.38 ± 0.89 mmol/L, N = 78); HDL-C levels were TAF (1.32 ± 0.31 mmol/L, N = 106), TDF (1.14 ± 0.31 mmol/L, N = 71) and ETV (1.25 ± 0.30 mmol/L, N = 77); LDL-C levels were TAF (2.76 ± 0.67 mmol/L, N = 106), TDF (2.38 ± 0.50 mmol/L, N = 71) and ETV (2.64 ± 0.68 mmol/L, N = 77) (Fig. 2C). In group "HBeAg (–)," TC levels were TAF (4.49 ± 0.94 mmol/L, N = 64), TDF (3.88 ± 0.76 mmol/L, N = 84) and ETV (4.51 ± 1.00 mmol/L, N = 103); HDL-C levels were TAF (1.26 ± 0.36 mmol/L, N = 60), TDF (1.08 ± 0.27 mmol/L, N = 84) and ETV (1.32 ± 0.37 mmol/L, N = 103); LDL-C levels were TAF (2.66 ± 0.82 mmol/L, N = 60), TDF (2.34 ± 0.65 mmol/L, N = 84) and ETV (2.70 ± 0.77 mmol/L, N = 103) (Fig. 2C).

Using univariate and multivariate binary logistic regression analyses, we examined factors associated with hypercholesterolemia and hypertriglyceridemia. As for TC level, the univariate binary logistic regression analysis revealed that age ($P = .009$) and sex ($P = .041$) significantly correlated with the occurrence of hypercholesterolemia, while TAF treatment (vs. TDF, $P = .995$; vs. ETV, $P = .847$), duration of treatment ($P = .849$), and BMI ($P = .072$) did not significantly correlate. Then, these factors were evaluated by the multivariate binary logistic regression. The results showed that age (adjusted hazard risk [HR] = 1.055 [1.018–1.094]; $P = .003$) and BMI (adjusted HR = 0.817 [0.669–0.998]; $P = .048$) were independent risk factors for hypercholesterolemia (Table 3).

As for TG level, the univariate binary logistic regression revealed that TAF treatment (vs. TDF, $P = .009$), sex ($P < .001$), and BMI ($P = .007$), but not duration of treatment ($P = .367$) and age ($P = .171$), significantly correlated with the occurrence of hypertriglyceridemia. Adjusted by multivariate binary logistic regression, we found that TAF treatment (vs. TDF, adjusted HR = 0.405 [0.167–0.980]; $P = .045$), age (adjusted HR = 1.028 [1.002–1.055]; $P = .038$), and sex (adjusted HR = 0.190 [0.079–0.456]; $P < .001$) were independent risk factors for hypertriglyceridemia (Table 3).

For some of the patients in Huashan Hospital, we also followed up their blood lipid levels at different time points before and after treatment (6–12 months), including 39 patients in the TAF group, 21 patients in the TDF group, and 21 patients in the ETV group. There was no significant difference in the changes of blood lipid levels between the 3 groups after 6 to 12 months of treatment ($P > .05$) (Table 4). From a cross-sectional viewpoint,

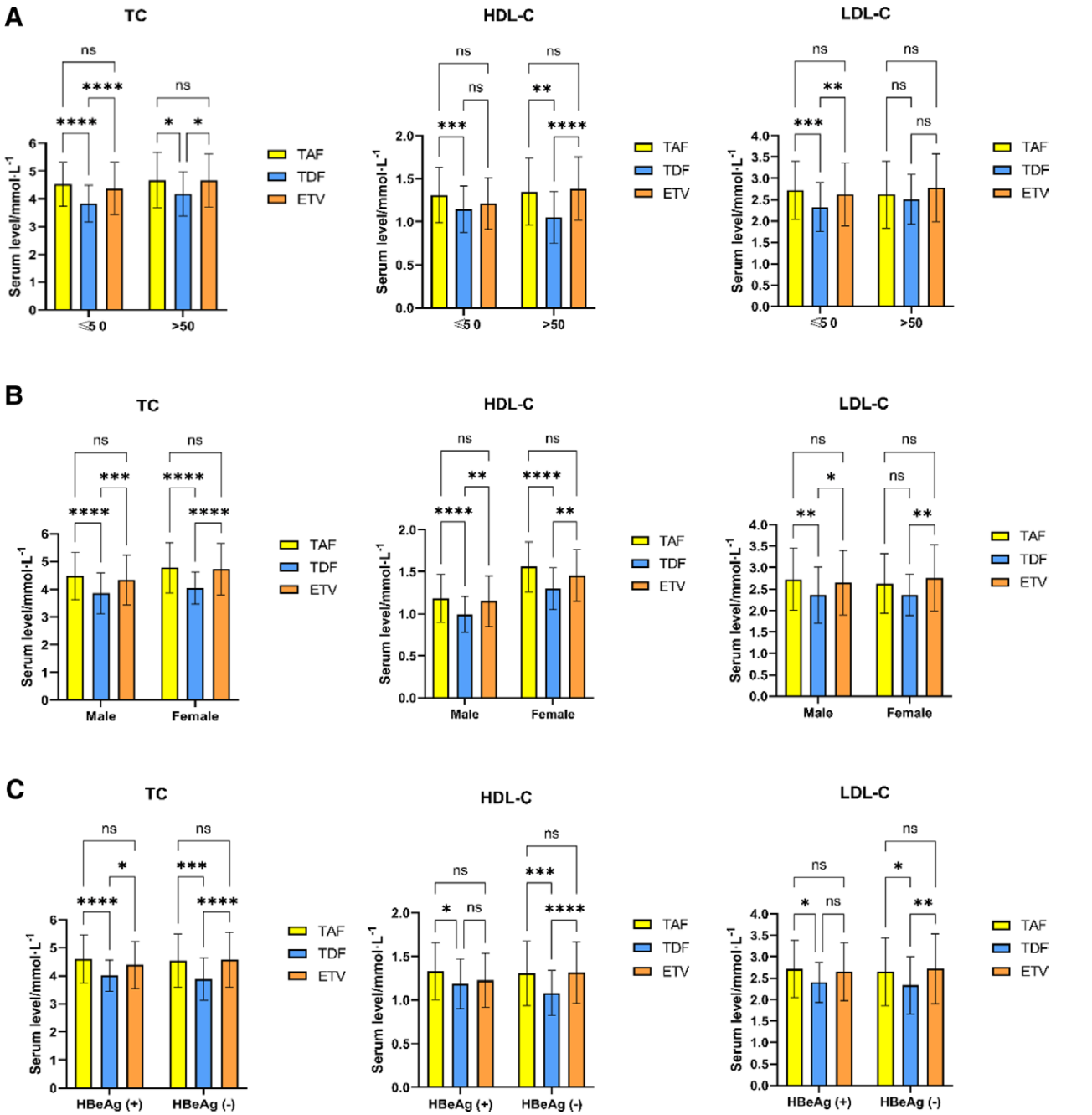

Figure 2. Serum lipid levels among the 3 groups after stratification. Data are shown as means ± standard deviation. ns: $P \geq .1$; *: $P < .05$; **: $P < .002$; ***: $P < .0002$; ****: $P < .0001$. (A) Serum lipid levels among the 3 groups after age stratification. TC levels. In group "≤50," the results of pairwise comparisons were <0.0001 (TAF vs. TDF), 0.320 (TAF vs. ETV) and <.0001 (TDF vs. ETV). In group ">50," the results of pairwise comparisons were .035 (TAF vs. TDF), .998 (TAF vs. ETV) and 0.036 (TDF vs. ETV). HDL-C levels. In group "≤50," the results of pairwise comparisons were <.0001 (TAF vs. TDF), .761 (TAF vs. ETV) and .001 (TDF vs. ETV). In group ">50," the results of pairwise comparisons were .016 (TAF vs. TDF), .577 (TAF vs. ETV) and .001 (TDF vs. ETV). LDL-C levels. In group "≤50," the results of pairwise comparisons were <.0001 (TAF vs. TDF), .476 (TAF vs. ETV) and <.001 (TDF vs. ETV). In group ">50," the results of pairwise comparisons were .674 (TAF vs. TDF), .933 (TAF vs. ETV) and .464 (TDF vs. ETV). (B) Serum lipid levels among the 3 groups after sex stratification. TC levels. In group "male," the results of pairwise comparisons were <.0001 (TAF vs. TDF), .348 (TAF vs. ETV) and <.001 (TDF vs. ETV). In group "female," the results of pairwise comparisons were <.0001 (TAF vs. TDF), .991 (TAF vs. ETV) and <.0001 (TDF vs. ETV). HDL-C levels. In group "male," the results of pairwise comparisons were <.0001 (TAF vs. TDF), 0.984 (TAF vs. ETV) and <.0001 (TDF vs. ETV). In group "female," the results of pairwise comparisons were <.0001 (TAF vs. TDF), 0.917 (TAF vs. ETV) and <.0001 (TDF vs. ETV). LDL-C levels. In group "male," the results of pairwise comparisons were <.0001 (TAF vs. TDF), .318 (TAF vs. ETV) and .012 (TDF vs. ETV). In group "female," the results of pairwise comparisons were .027 (TAF vs. TDF), .830 (TAF vs. ETV) and .004 (TDF vs. ETV). (C) Serum lipid levels among the 3 groups after HBeAg stratification. TC levels. In group "HBeAg (+)," the results of pairwise comparisons were <.0001 (TAF vs. TDF), .174 (TAF vs. ETV) and 0.003 (TDF vs. ETV). In group "HBeAg (–)," the results of pairwise comparisons were <.0001 (TAF vs. TDF), .984 (TAF vs. ETV) and <.0001 (TDF vs. ETV). HDL-C levels. In group "HBeAg (+)," the results of pairwise comparisons were .001 (TAF vs. TDF), .305 (TAF vs. ETV) and .124 (TDF vs. ETV). In group "HBeAg (–)," the results of pairwise comparisons were .004 (TAF vs. TDF), .404 (TAF vs. ETV) and <.0001 (TDF vs. ETV). LDL-C levels. In group "HBeAg (+)," the results of pairwise comparisons were .001 (TAF vs. TDF), .500 (TAF vs. ETV) and 0.054 (TDF vs. ETV). In group "HBeAg (–)," the results of pairwise comparisons were .015 (TAF vs. TDF), .951 (TAF vs. ETV) and .001 (TDF vs. ETV). ETV = entecavir, HBeAg = hepatitis B envelope antigen, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TAF = tenofovir alafenamide fumarate, TC = total cholesterol, TDF = tenofovir disoproxil fumarate.

the overall blood lipid level of the TDF group was lower than that of the TAF group and ETV group, especially the TC level, both before treatment (TDF vs. TAF, $P = .029$; TDF vs. ETV, $P = .044$) and after treatment (TDF vs. TAF, $P = .003$; TDF vs. ETV, $P = .065$) (Table 5).

4. Discussion

The rapid developments of modern society have substantially improved the quality of life of many people, including the quality of diet. However, because of nonstandard diet and lack of exercise, the onset of metabolic syndrome (Mets) (hyperlipidemia, hyperglycemia, and hypertension) has gradually shifted from the elderly to a younger age.[19,20] Hyperlipidemia refers to blood fat content, especially triglycerides, that exceeds the normal range. Given that the liver is an important organ of fat metabolism,[21,22] body fat metabolism is affected in people with organic or functional liver diseases. At present, if drug treatment is necessary, especially with drugs targeting the liver, it is impossible to predict an impact on liver function. This is true for individuals with CHB infection who need to take NAs. Therefore, we conducted this study to evaluate the effects of 3 antiviral drugs on blood lipids in patients with CHB, so as to exclude the risk of cardiovascular disease.

Over the past decade, many studies have explored the effect of HBV infection on human fat metabolism.[23–25] A large-scale community cohort study[26] found that the prevalence rates of hypercholesterolemia (9.1%) and hypertriglyceridemia (7.7%) in HBV-seropositive people were low, but the specific regulatory mechanism has not been clarified. The incidence rate of FLD of HBV infection and non-HBV infection in the general population was assessed by Wong et al[27] in Hong Kong, China. The results showed that HBV infection was associated with lower

Table 3

Risk factors for the development of hyperlipidemia.

Variables	Univariate analysis		Multivariate analysis	
	P-value	Adjusted HR	95% CI	*P*-value
Hypercholesterolemia				
TAF group (vs. TDF group)	.995			
TAF group (vs. ETV group)	.847			
Duration of treatment	.849			
Age	.009	1.055	1.018–1.094	.003
Sex	.041			
BMI	.072	0.817	0.669–0.998	.048
Hypertriglyceridemia				
TAF group (vs. TDF group)	.009	0.405	0.167–0.980	.045
TAF group (vs. ETV group)	.546			
Duration of treatment	.367			
Age	.171	1.028	1.002–1.055	.038
Sex	<.001	0.190	0.079–0.456	<.001
BMI	.007			

BMI = body mass index, CI = confidence interval, ETV = entecavir, HR = hazard risk, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate.

Table 4

Changes in lipid profile according to NAs treatment.

	Baseline	6 to 12 mo	*P*-value
TAF			
TC (mmol/L)	4.57 ± 1.09	4.60 ± 1.01	.297
TG (mmol/L)	0.92 ± 0.25	0.99 ± 0.46	.977
HDL-C (mmol/L)	1.47 ± 0.50	1.43 ± 0.39	1.000
LDL-C (mmol/L)	2.65 ± 0.87	2.68 ± 0.73	.306
VLDL-C (mmol/L)	0.46 ± 0.19	0.49 ± 0.20	.307
APoA1 (mmol/L)	1.07 ± 0.18	1.00 ± 0.16	.038
APoB (mmol/L)	0.55 ± 0.15	0.53 ± 0.13	.633
TDF			
TC (mmol/L)	3.87 ± 0.68	3.84 ± 0.69	.952
TG (mmol/L)	0.80 ± 0.71	0.76 ± 0.44	1.000
HDL-C (mmol/L)	1.20 ± 0.23	1.23 ± 0.21	1.000
LDL-C (mmol/L)	2.25 ± 0.48	2.23 ± 0.54	.841
VLDL-C (mmol/L)	0.42 ± 0.26	0.38 ± 0.16	.920
APoA1 (mmol/L)	0.96 ± 0.15	0.91 ± 0.10	.194
APoB (mmol/L)	0.46 ± 0.10	0.45 ± 0.12	.472
ETV			
TC (mmol/L)	4.47 ± 0.90	4.49 ± 0.90	.911
TG (mmol/L)	1.36 ± 0.85	1.09 ± 0.72	.998
HDL-C (mmol/L)	1.29 ± 0.32	1.34 ± 0.29	1.000
LDL-C (mmol/L)	2.58 ± 0.83	2.60 ± 0.89	.935
VLDL-C (mmol/L)	0.58 ± 0.23	0.54 ± 0.24	.425
APoA1 (mmol/L)	1.05 ± 0.13	0.98 ± 0.10	.159
APoB (mmol/L)	0.55 ± 0.16	0.53 ± 0.16	.699

APoA1 = apolipoprotein A1, APoB = apolipoprotein B, ETV = entecavir, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NAs = nucleos(t)ide analogues, TAF = tenofovir alafenamide fumarate, TC = total cholesterol, TDF = tenofovir disoproxil fumarate, TG = triglyceride, VLDL-C = very low-density lipoprotein cholesterol.

Table 5

Comparison in lipid profiles between patients treated with TAF, TDF and ETV before and after NAs treatment.

	TAF	TDF	ETV	TAF vs. TDF	TAF vs. ETV	TDF vs. ETV
Total number, n (%)	39 (48.14)	21 (25.93)	21 (25.93)	*P*-value		
Baseline lipid profile						
TC (mmol/L)	4.57 ± 1.09	3.87 ± 0.68	4.46 ± 0.90	.029	.910	.044
TG (mmol/L)	0.92 ± 0.25	0.80 ± 0.71	1.36 ± 0.85	1.000	.500	.351
HDL-C (mmol/L)	1.47 ± 0.50	1.20 ± 0.23	1.29 ± 0.32	.466	.999	.983
LDL-C (mmol/L)	2.65 ± 0.87	2.25 ± 0.48	2.58 ± 0.83	.211	.930	.298
VLDL-C (mmol/L)	0.46 ± 0.19	0.42 ± 0.26	0.58 ± 0.23	.469	.047	.019
APoA1 (mmol/L)	1.07 ± 0.18	0.96 ± 0.15	1.05 ± 0.13	.022	.564	.129
APoB (mmol/L)	0.55 ± 0.15	0.46 ± 0.10	0.55 ± 0.16	.153	.996	.209
Lipid profile after NA treatment						
TC (mmol/L)	4.60 ± 1.01	3.84 ± 0.69	4.49 ± 0.90	.003	.374	.065
TG (mmol/L)	0.99 ± 0.46	0.76 ± 0.44	1.09 ± 0.72	.771	1.000	.934
HDL-C (mmol/L)	1.43 ± 0.39	1.23 ± 0.21	1.34 ± 0.29	.451	1.000	.885
LDL-C (mmol/L)	2.68 ± 0.73	2.23 ± 0.54	2.60 ± 0.89	.017	.294	.234
VLDL-C (mmol/L)	0.49 ± 0.20	0.38 ± 0.16	0.54 ± 0.24	.128	.752	.107
APoA1 (mmol/L)	1.00 ± 0.16	0.91 ± 0.10	0.98 ± 0.10	.047	.712	.137
APoB (mmol/L)	0.53 ± 0.13	0.45 ± 0.12	0.53 ± 0.16	.068	.978	.101

APoA1 = apolipoprotein A1, APoB = apolipoprotein B, ETV = entecavir, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NAs = nucleos(t)ide analogues, TAF = tenofovir alafenamide fumarate, TC = total cholesterol, TDF = tenofovir disoproxil fumarate, TG = triglyceride, VLDL-C = very low-density lipoprotein cholesterol.

incidence rates of FLD (13.5% vs. 28.3%, $P = .003$), hypertriglyceridemia (1.3% vs. 2.1%, $P < .001$), and Mets (11% vs. 20.2%, $P = .034$) compared with the control group. It was also found that virus genotype, HBV DNA level, and HBeAg status were not associated with fatty liver, which may be related to the effect of virus replication on lipid metabolism. It was also reported that in HBeAg-negative CHB patients, both male and female, high HBV DNA load negatively correlated with hypertriglyceridemia.[28] Huang et al[29] constructed a structural equation model to show that HBV infection has a significant negative impact on dyslipidemia in men (B = –0.054) and women (B = –0.064), and this negative correlation may offer the net benefit for the blood lipid profile. A systematic review[30] searched the literature on HBV, HCV infection, Mets, FLD, and the components of lipid profiles in PubMed, and collected evidence from multiple studies that HBV infection may protect infected people from the development of Mets and hepatic steatosis.

The above-mentioned studies have pointed to the possibility that hyperlipidemia may rarely occur in CHB patients, but they did not evaluate the changes in blood lipid levels in patients after NA treatment or immunomodulator treatment. In fact, according to the guideline standards,[3,4] most of the existing CHB patients need treatment and are already in treatment. The oral drugs target the virus, but there have been not enough research reports on blood lipid levels in treated patients whose virus load was not detectable in peripheral blood.

Our cross-sectional study in 2 centers found that blood lipid levels of patients treated with TDF, including TC, TG, HDL-C, LDL-C, VLDL-C, apolipoprotein A1 (APoA1), and apolipoprotein B (APoB), were lower than those of patients treated with TAF and ETV. Although there were some confounding factors in the 3 groups, after stratified analysis to exclude the interference of age (50 years as the boundary), sex, and HBeAg status, the differences in blood lipid levels between the TDF group and the other 2 groups remained. This is consistent with the research by Suzuki et al.[18] A randomized controlled clinical trial[31] compared the efficacy and safety of 48 weeks of tenofovir amibufenamide (TMF) and TDF treatment in CHB patients. It was found that TG and LDL-C increased slightly in patients taking TMF, and the median changes were 0.11 (–0.21, 0.51) mmol/L and 0.05 (–0.2, 0.37) mmol/L, respectively. In patients taking TDF, the levels of TC, TG, and LDL-C decreased to varying degrees, and the median changes were –0.69 (–1.13, –0.26) mmol/L, –0.3 (–0.61, 0.03) mmol/L, and –0.09 (–0.32, 0.11) mmol/L, respectively. In addition, it was found that after 48 weeks of treatment, both body weight and BMI increased in the TMF group, while both parameters decreased in the TDF group.

When analyzing the factors related to hyperlipidemia in this study, we found that the use of different drugs had no significant effect on the occurrence of hypercholesterolemia; in contrast, TAF treatment (vs. the TDF group) did have an effect on hypertriglyceridemia. In the univariate regression analysis, sex had an effect on hypercholesterolemia, and BMI had an effect on hypertriglyceridemia, but different treatment and duration of treatment did not have any effect. Moreover, after the adjustment of the multivariate regression, the influence of these factors was no longer significant. In contrast, common factors affecting metabolism, such as age, sex, and BMI, were shown to be significantly related to the occurrence of hyperlipidemia. Combined with the finding of a lower blood lipid level in the TDF group, it can be suggested that TDF should be recommended for elderly male patients who have a high BMI after considering the adverse reactions of calcium and phosphorus metabolism and renal dysfunction in treatment decision-making for CHB patients. TAF or ETV is recommended for patients with normal blood lipid levels who are concerned about adverse reactions of TDF.

This study has many limitations. First, only 2 centers were included in this study. The total sample size was not large, and populations in other regions need further study. The sample size of Huashan Hospital Center affiliated to Fudan University was only 405, and some main characteristics (except serum lipid levels of the 3 groups) did not match, which resulted in the interference of several confounding factors other than non-research factors, such as duration of treatment, albumin (ALB), estimated glomerular filtration rate (eGFR), serum creatinine (SCr), and HBeAg status. Moreover, the patients in the ETV group were older, and more patients had a longer treatment time. The data from the Public Health Clinical Center Affiliated to Fudan University were not complete, such as patients' BMI. In addition, this was a retrospective cross-sectional study. We only collected the clinical data of patients at a certain time point after taking medicine, and the treatment times were also different, so we were not able to dynamically evaluate the changes in blood lipid levels before and after taking medicine, but we could only roughly compare the overall blood lipid levels; thus, we cannot indicate which medicine will increase blood lipid levels and which medicine can reduce blood lipid levels. Therefore, these findings cannot be used to evaluate the potential side effects of the 3 drugs on blood lipids. Although both before

and after medicine data were available for some patients, no obvious changes and differences were found. Moreover, when analyzing the factors related to hyperlipidemia, the adjusted multivariate regression rarely reported significant risk factors. It is still unknown whether different drugs and HBV-related indicators will result in the occurrence of hyperlipidemia. In conclusion, according to our research and analysis among Asian CHB patients, the blood lipid levels in the TDF group were lower than those in the TAF group and ETV group, and the occurrence of hyperlipidemia was related to age, sex, and BMI. Further randomized controlled and large-sample trials are needed to verify whether TAF and ETV treatment increases blood lipid levels and whether TDF treatment can reduce blood lipid levels.

Author contributions

JMZ and XYQ designed and revised the study. JWC and XYC analyzed data and wrote the manuscript.
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References

[1] Global hepatitis report 2017. Geneva, Switzerland: World Health Organization. 2017.
[2] Zampino R, Boemio A, Sagnelli C, et al. Hepatitis B virus burden in developing countries. World J Gastroenterol. 2015;21:11941–53.
[3] Electronic address EEE, European association for the study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–98.
[4] 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;67:1560–99.
[5] Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. Hepatology. 2009;49:1503–14.
[6] Verhelst D, Monge M, Meynard JL, et al. Fanconi syndrome and renal failure induced by tenofovir: a first case report. Am J Kidney Dis. 2002;40:1331–3.
[7] Cooper RD, Wiebe N, Smith N, et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis. 2010;51:496–505.
[8] Nishijima T, Kawasaki Y, Tanaka N, et al. Long-term exposure to tenofovir continuously decrease renal function in HIV-1-infected patients with low body weight: results from 10 years of follow-up. AIDS. 2014;28:1903–10.
[9] Wohl D, Oka S, Clumeck N, et al. Brief report: a randomized, double-blind comparison of tenofovir alafenamide versus tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: week 96 results. J Acquir Immune Defic Syndr. 2016;72:58–64.
[10] Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus Placebo to prevent perinatal transmission of hepatitis B. N Engl J Med. 2018;378:911–23.
[11] Balzarini J, Holy A, Jindrich J, et al. Differential antiherpesvirus and antiretrovirus effects of the (S) and (R) enantiomers of acyclic nucleoside phosphonates: potent and selective in vitro and in vivo antiretrovirus activities of (R)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine. Antimicrob Agents Chemother. 1993;37:332–8.
[12] Tsai CC, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. Science. 1995;270:1197–9.
[13] Grossi G, Loglio A, Facchetti F, et al. Tenofovir alafenamide as a rescue therapy in a patient with HBV-cirrhosis with a history of Fanconi syndrome and multidrug resistance. J Hepatol. 2017;68:195–8.
[14] Alves-Bezerra M, Cohen DE. Triglyceride metabolism in the liver. Compr Physiol. 2017;8:1–8.
[15] Babusis D, Phan TK, Lee WA, et al. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. Mol Pharm. 2013;10:459–66.
[16] Lacey A, Savinelli S, Barco EA, et al. Investigating the effect of antiretroviral switch to tenofovir alafenamide on lipid profiles in people living with HIV. AIDS. 2020;34:1161–70.
[17] Arribas J, et al. CROI 2017. Seattle, WA. Poster #453.
[18] 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;56:168–80.
[19] Zhou J, Zhou F, Wang W, et al. Epidemiological features of NAFLD From 1999 to 2018 in China. Hepatology. 2020;71:1851–64.
[20] Wang FS, Fan JG, Zhang Z, et al. The global burden of liver disease: the major impact of China. Hepatology. 2014;60:2099–108.
[21] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Circulation. 2019;139:e1082–143.
[22] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–88.
[23] Choi JS, Han KJ, Lee S, et al. Serum HBV surface antigen positivity is associated with low prevalence of metabolic syndrome in Korean adult men. J Epidemiol. 2015;25:74–9.
[24] Hsu CS, Liu CH, Wang CC, et al. Impact of hepatitis B virus infection on metabolic profiles and modifying factors. J Viral Hepat. 2012;19:e48–57.
[25] Cheng YL, Wang YJ, Kao WY, et al. Inverse association between hepatitis B virus infection and fatty liver disease: a large-scale study in populations seeking for check-up. PLoS One. 2013;8:e72049.
[26] Chen JY, Wang JH, Lin CY, et al. Lower prevalence of hypercholesterolemia and hyperglyceridemia found in subjects with seropositivity for both hepatitis B and C strains independently. J Gastroenterol Hepatol. 2010;25:1763–8.
[27] Wong VW, Wong GL, Chu WC, et al. Hepatitis B virus infection and fatty liver in the general population. J Hepatol. 2012;56:533–40.
[28] Chiang CH, Yang HI, Jen CL, et al. Association between obesity, hypertriglyceridemia and low hepatitis B viral load. Int J Obes (Lond). 2013;37:410–5.
[29] Huang CY, Lu CW, Liu YL, et al. Relationship between chronic hepatitis B and metabolic syndrome: a structural equation modeling approach. Obesity (Silver Spring). 2016;24:483–9.
[30] Wang CC, Chen PN, Kao JH. Systematic review: chronic viral hepatitis and metabolic derangement. Aliment Pharmacol Ther. 2020;51:216–30.