Journal of Clinical and Translational Hepatology **2024**
DOI: 10.14218/JCTH.2024.00237

Original Article

Anti-hepatitis B Virus Treatment with Tenofovir Amibufenamide Has No Impact on Blood Lipids: A Real-world, Prospective, 48-week Follow-up Study

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Received: July 15, 2024 | **Revised:** September 28, 2024 | **Accepted:** October 08, 2024 | **Published online:** October 21, 2024

Abstract

Background and Aims: The effect of tenofovir amibufenamide (TMF) on blood lipid profiles in patients with chronic hepatitis B (CHB) remains unclear. This study aimed to explore whether TMF affects blood lipids during 48 weeks in patients with CHB. ***Methods:*** A total of 91 patients with CHB undergoing TMF treatment for 48 weeks were divided into two groups: Lipid Normal (n = 42) and Lipid Abnormal (n = 49), based on baseline blood lipid levels. Lipid indices, virological responses, and biochemical indicators were compared between the two groups. Clinical observations were further verified through *in vitro* experiments. ***Results:*** After an average follow-up of 373 ± 121 days, lipid indices in all 91 patients had not significantly changed compared with baseline (total cholesterol: 4.67 vs. 4.69 mmol/L, P = 0.2499; triglycerides: 1.08 vs. 1.04 mmol/L, P = 0.4457; high-density lipoprotein cholesterol: 1.25 vs. 1.25 mmol/L, P = 0.3063; low-density lipoprotein cholesterol: 3.03 vs. 3.02 mmol/L, P = 0.5765). Subgroup comparisons showed lipid indices remained stable. Among treatment-naïve patients (n = 82), complete viral suppression rates were 23.2%, 59.8%, 70.7%, and 86.6% at four, 12, 24, and 48 weeks, respectively. Cellular experiments revealed that TMF did not promote lipid metabolism in primary hepatocytes and AML12 cells. ***Conclusions:*** Regardless of baseline blood lipid characteristics, 48 weeks of antiviral treatment with TMF in patients with CHB had no significant lipid-raising effect.

Citation of this article: Chen Y, Gao W, Chu H, Al-Asbahi AAM, Yan S, Yuan H, *et al*. Anti-hepatitis B Virus Treatment with Tenofovir Amibufenamide Has No Impact on Blood Lipids: A Real-world, Prospective, 48-week Follow-up Study. J Clin Transl Hepatol 2024. doi: 10.14218/JCTH.2024.00237.

Keywords: Tenofovir amibufenamide; Antiviral treatment; Chronic hepatitis B; Blood lipid; Virological response; Palmitic acid.

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Introduction

Approximately 254 million people worldwide live with chronic hepatitis B virus (HBV) infection, which is a leading cause of cirrhosis and liver cancer globally. HBV infection resulted in 1.1 million deaths in 2022.[1] Effective strategies to reduce HBV-related medical, physical, psychological, and economic burdens are still needed. Nucleotide/nucleoside analogs (NAs), including entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF), are currently recommended as first-line treatments for chronic hepatitis B (CHB). These drugs have comparable antiviral efficacy and effectively reduce the risks of HBV-related cirrhosis and hepatocellular carcinoma.[2–5] NAs work by competitively inhibiting reverse transcription during viral replication, thereby significantly suppressing HBV DNA replication. However, due to the inability to directly eliminate covalently closed circular DNA in infected hepatocyte nuclei, patients tend to experience virological rebound after discontinuing NAs and may develop fulminant hepatitis. Consequently, patients with CHB typically require long-term or even lifelong treatment, raising concerns about the safety of prolonged medical management.

Dyslipidemia is a significant risk factor for adverse cardiovascular outcomes and a leading cause of morbidity and mortality worldwide. Lipid management should be considered when selecting appropriate antiviral drugs for patients. Among the first-line NAs, entecavir has a neutral effect on lipids,[6] while TDF has a lipid-lowering effect in patients with CHB.[7] However, switching from TDF to TAF has been associated with lipid profile derangements in patients with CHB.[8–10] Tenofovir amibufenamide (TMF), a novel phosphoramidate prodrug of tenofovir, has been demonstrated to be comparable to TDF in antiviral efficacy, with improved bone and renal safety.[11,12] Patients with CHB and metabolic abnormalities have a higher risk of developing hepatocellular carcinoma[13]; whether TMF can lead to dyslipidemia or increase the risk of hepatocellular carcinoma requires further investigation. The present study examined the effect of TMF on lipid profiles during 48 weeks of antiviral treatment.

Methods

Clinical research design

A total of 221 outpatients diagnosed with CHB at Union Hos-

pital, Huazhong University of Science and Technology, from January 2022 to June 2023 were screened for inclusion in this prospective study. Inclusion criteria were confirmed HBV infection, hepatitis B surface antigen positivity for at least 6 months, age between 18–70 years, and compliance with the guidelines for antiviral indications. Exclusion criteria included treatment with oral lipid-lowering medications; coinfection with hepatitis A virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, or human immunodeficiency virus; the presence of other chronic liver diseases, such as alcoholic liver disease, drug-induced liver disease, or autoimmune liver disease; severe systemic diseases, such as lung cancer or heart failure; pregnancy or lactation; or poor compliance.

After applying the inclusion and exclusion criteria, 174 patients were enrolled. Patients were divided into two subgroups based on baseline blood lipid levels according to the 2023 Chinese guidelines for lipid management[14]: those with normal baseline blood lipids (Lipid Normal group) and those with disordered blood lipids (Lipid Abnormal group) (Fig. 1). All patients received treatment with TMF at a dosage of 25 mg daily and were regularly followed up at 4, 12, 24, and 48 weeks after the initiation of antiviral treatment. After 48 weeks of follow-up, clinical data including lipid profile indices [total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)], virological response, liver function, renal function, electrolyte levels, routine blood indices, liver ultrasound, and transient elastography imaging were collected.

This research protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (UHCT21612). It has been registered at ClinicalTrials.gov (NCT05398393).

Outcomes

The primary endpoint was the lipid profile levels after 48 weeks of TMF treatment. The secondary endpoints included the efficacy and safety of TMF for HBV, the proportion of patients who achieved a virologic response (defined as an HBV DNA level of <20 IU/mL), and alterations in alanine transaminase (ALT), aspartate transaminase (AST), liver stiffness measurement (LSM), AST-to-platelet ratio index (APRI), renal function,[15] etc.

AML12 cell culture and treatment

AML12 cell lines were cultured in Dulbecco's Modified Eagle Medium (DMEM)/F12 medium supplemented with 10% fetal bovine serum (FBS) (Gibco, Waltham, MA, USA) and 1% insulin-transferrin-selenium-ethanolamine medium supplement (Beyotime, Shanghai, China). AML12 cells were switched to FBS-free DMEM/F12 medium for overnight starvation. Palmitic acid (PA) was completely dissolved in anhydrous ethanol and then diluted to 10 mM in DMEM/F12 containing 3% (w/v) fatty acid-free bovine serum albumin at 55°C.

Cell models of disordered lipid metabolism were constructed by treating starved AML12 cells with 200 μM PA solution for 24 h. TMF powder was dissolved in DMEM/F12 medium and stored at 200 μM (guided by Jiangsu Hansoh Pharmaceutical Co. Ltd., Lianyungang, China). The starved cells were then divided into four groups: the control group was cultured in complete medium for 48 h; the PA group received 200 μM PA for 24 h, then was switched to complete medium without PA for another 24 h; the TMF group was cultured in complete medium for 24 h, then received 20 μM TMF for 24 h; and the PA + TMF group was first cultured in PA-containing medium for 24 h, then received 20 μM TMF for another 24 h.

Primary hepatocyte isolation and treatment

Primary hepatocytes were isolated from C57BL/6 mice as previously described[16] and cultured in six-well plates containing DMEM supplemented with 10% FBS. After hepatocyte attachment, a medium with 3% FBS was added for 8 h to induce starvation. Other interventions were consistent with those used for the AML12 cells.

Oil red O staining

The oil red working solution was prepared by mixing 60% saturated oil red O solution (Servicebio, Wuhan, China) with 40% distilled water. The solution was allowed to sit overnight at 4°C, then filtered using qualitative filter paper before use. Samples were washed with 1x phosphate-buffered saline (PBS), then fixed with 4% polyformaldehyde for 8–10 m, followed by two washes with PBS. The cells were covered with 60% isopropanol for 15–20 s, stained with oil red working solution for 30 m away from light, then covered with 60% isopropanol for 3–5 s before washing with water. The nuclei were stained using a hematoxylin staining solution (Servicebio, Wuhan, China) and washed with water. Finally, PBS was added for microscopic observation (Nikon, Tokyo, Japan).

TG measurement

Cells in each well were washed with PBS, digested with trypsin, and collected into an Eppendorf tube. The collected cell suspension was centrifuged at 1,000 rpm for 10 m, and the supernatant was discarded. The cell precipitate was resuspended in PBS and centrifuged again. Next, 2% Triton X-100 was added to the cell precipitate for lysis for 30–40 m. The TG concentration was measured using a TG reagent kit (Nanjing JianCheng Bioengineering Institute, Nanjing, China) according to the manufacturer's instructions.

Quantitative real-time polymerase chain reaction (qPCR)

The cellular RNA was extracted using FreeZol Reagent (Vazyme, Nanjing, China) and subjected to reverse transcription (Vazyme, Nanjing, China) to obtain complementary DNA according to the manufacturer's instructions. Real-time qPCR was performed with ChamQ SYBR qPCR Master Mix (Vazyme, Nanjing, China) according to the manufacturer's instructions, with amplification detected over 45 cycles. Supplementary Table 1 lists the primer sequences used in this study.[17] 18S RNA was used as an internal control to normalize gene expression.

Statistical analysis

All statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) or GraphPad Prism version 9.5.1 (GraphPad Software, Boston, MA, USA). Continuous variables were expressed as median (interquartile range) or mean ± standard deviation and analyzed by the Student's t-test or rank-sum test, as appropriate. Categorical variables were presented as frequency and percentage and were compared using the Chi-squared test or Fisher's exact test. Virological response rates were analyzed using the log-rank test. A two-tailed *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics and laboratory examination results

Data from 91 *p*atients with paired lipid profiles before and af-

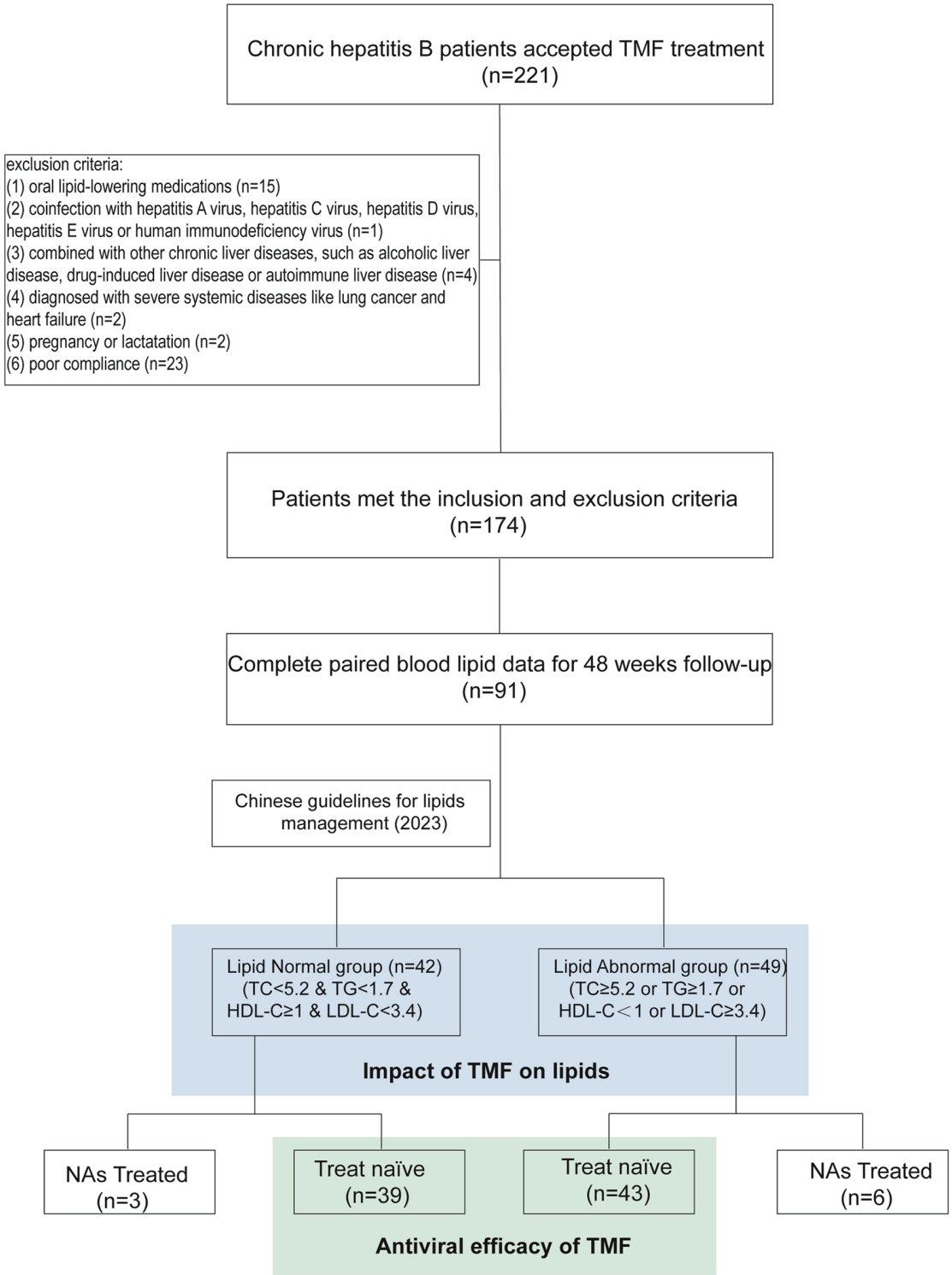

Fig. 1. Flowchart of the screening and grouping process. TMF, tenofovir amibufenamide; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAs, Nucleotide/nucleoside analogs.

ter 48 weeks of TMF treatment were analyzed. The Lipid Normal group comprised 42 patients, while the Lipid Abnormal group comprised 49 patients (Fig. 1). The baseline demographic characteristics of the patients were similar between the two groups (Table 1 and Supplementary Table 2). The mean age was 48 ± 11 years, and 57.1% were male. Cirrhosis and metabolic-associated fatty liver disease (MAFLD) were present in 11 (12.1%) and 34 (37.4%) of the total

patients, respectively. A small percentage of patients also had diabetes, hypertension, and a history of alcohol use. The average follow-up time for all patients was 373 ± 121 days, with the Lipid Normal and Lipid Abnormal groups being 382 ± 125 and 366 ± 118 days, respectively (Table 1).

The baseline lipid indices in the Lipid Abnormal group, including TC, TG, HDL-C, and LDL-C, were significantly higher than those in the Lipid Normal group [TC: 5.19 (4.49–5.61) vs. 4.36 (4.02–4.79) mmol/L, respectively ($P < 0.0001$); TG: 1.25 (0.99–1.60) vs. 0.94 (0.66–1.18) mmol/L ($P < 0.0001$); HDL-C: 1.11 (0.93–1.41) vs. 1.29 (1.14–1.51) mmol/L ($P = 0.0046$); LDL-C: 3.48 (2.94–3.73) vs. 2.65 (2.23–3.06) mmol/L ($P < 0.0001$)].

The serum HBV DNA level (3.66 vs. 3.64 $\log_{10}$ IU/mL, $P = 0.8976$) and the proportion of hepatitis B virus E antigen-positive patients (14.3% vs. 16.3%, $P = 0.7879$) were similar between the Lipid Normal and Lipid Abnormal groups, respectively. No significant differences were noted between the two groups in total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, gamma-glutamyl transferase, total protein, albumin, routine blood indices, renal function, or electrolyte levels at enrollment. We also assessed the LSM, controlled attenuation parameter (CAP), weight, and body mass index (BMI) of all patients, and no significant differences were found between the Lipid Normal and Lipid Abnormal groups (Table 1).

TMF had no lipid-increasing effect during 48 weeks of antiviral treatment

To determine whether antiviral treatment affected blood lipids, paired data before and after antiviral treatment were analyzed to evaluate the impact of TMF on blood lipids. No significant differences were observed after TMF treatment for an average of 373 ± 121 days when compared with baseline [TC: 4.67 (4.09–5.22) vs. 4.69 (4.16–5.23) mmol/L, respectively ($P = 0.2499$); TG: 1.08 (0.86–1.39) vs. 1.04 (0.80–1.45) mmol/L ($P= 0.4457$); HDL-C: 1.25 (1.06–1.46) vs. 1.25 (1.06–1.47) mmol/L ($P = 0.3063$); LDL-C: 3.03 (2.35–3.50) vs. 3.02 (2.40–3.41) mmol/L ($P = 0.5765$)] (Fig. 2A). To explore whether there was a difference in the effect of TMF on patients with normal and abnormal baseline lipid levels, we performed subgroup analyses. In the Lipid Normal group, lipid indices remained stable compared to baseline [TC: 4.36 (4.02–4.79) vs. 4.49 (4.08–4.88) mmol/L, respectively ($P = 0.0972$); TG: 0.94 (0.66–1.18) vs. 0.90 (0.75–1.22) mmol/L ($P = 0.1199$); HDL-C: 1.29 (1.14–1.51) vs. 1.28 (1.20–1.53) mmol/L ($P = 0.5172$); LDL-C: 2.65 (2.23–3.06) vs. 2.67 (2.24–3.09) mmol/L ($P = 0.4257$)] (Fig. 2B). In the Lipid Abnormal group, changes before and after TMF treatment were not significant [TC: 5.19 (4.49–5.61) vs. 4.96 (4.24–5.66) mmol/L, respectively ($P = 0.9251$); TG: 1.25 (0.99–1.60) vs. 1.20 (0.94–1.71) mmol/L ($P = 0.9509$); HDL-C: 1.11 (0.93–1.41) vs. 1.20 (0.98–1.40) mmol/L ($P = 0.3941$); LDL-C: 3.48 (2.94–3.73) vs. 3.31 (2.63–3.84) mmol/L ($P = 0.8883$)] (Fig. 2C).

The Lipid Normal and Lipid Abnormal groups were established by considering the four indicators together; we further analyzed TC, TG, HDL-C, and LDL-C separately to better observe the effect of TMF on individual lipid indices (Supplementary Fig. 1A-D). TC levels in patients with normal baseline TC fluctuated within the reference range [TC: 4.38 (4.00–4.80) vs. 4.45 (4.06–5.00) mmol/L ($P = 0.0207$)] (Supplementary Fig. 1A). HDL-C levels in patients with abnormal baseline values improved after TMF treatment [HDL-C: 0.86 (0.76–0.95) vs. 1.01 (0.83–1.16) mmol/L ($P = 0.0023$)] (Supplementary Fig. 1D). We also evaluated patients diagnosed with hyperlipidemia at baseline who were treated with oral lipid-lowering drugs during TMF therapy (n = 15), and their lipid profiles showed no significant changes (Supplementary Fig. 2), indicating the safety of using TMF in patients with CHB who were taking oral lipid-lowering drugs.

During follow-up, patients in both the Lipid Normal and Lipid Abnormal groups showed no significant changes in BMI before and after TMF treatment [Lipid Normal group (n = 26): 24.00 vs. 23.41 kg/m^2, $P = 0.8119$; Lipid Abnormal group (n = 31): 23.97 vs. 23.99 kg/m^2, $P = 0.5874$] (Supplementary Fig. 3A). Additionally, the variation in the CAP was similar to that in the BMI [Lipid Normal group (n = 27): 234 vs. 225 dB/m, $P = 0.9851$; Lipid Abnormal group (n = 36): 235 vs. 241 dB/m, $P = 0.8494$] (Supplementary Fig. 3B). We followed 86 patients to assess MAFLD before and after TMF treatment. Thirty-one patients had been diagnosed with MAFLD at baseline, which increased to 32 after TMF treatment. The number of MAFLD patients (diagnosed with MAFLD by either liver ultrasound or a CAP value >240 dB/m[18]) did not significantly increase after 48 weeks of TMF treatment [total patients: 31 vs. 32 ($P = 0.8742$); Lipid Normal group: 14 vs. 11 ($P = 0.4717$); Lipid Abnormal group: 17 vs. 21 ($P = 0.3933$); inter-group comparison: $P = 0.3817$] (Supplementary Fig. 3C). Overall, TMF did not increase lipid levels or lead to BMI increase or MAFLD during 48 weeks of antiviral treatment.

Antiviral efficacy of TMF

Of the patients, 90.11% (n = 82) were treatment-naïve patients with CHB, having not received antiviral drugs in the past six months (Fig. 1). A small group of patients (n = 9) who had switched from other oral antiviral drugs to TMF were excluded when evaluating the antiviral efficacy of TMF. Among these treatment-naïve patients, the baseline serum HBV DNA level was 3.77 (3.06–4.95) $\log_{10}$ IU/mL at baseline, with comparable levels between the Lipid Normal [3.87 (3.04–5.15) $\log_{10}$ IU/mL, n = 39] and Lipid Abnormal groups [3.75 (3.13–4.92) $\log_{10}$ IU/mL, n = 43] (Table 2 and Supplementary Table 3). The rate of complete viral suppression (CVS), defined as an HBV DNA level <20 IU/mL, was 23.2%, 59.8%, and 70.7% at 4, 12, and 24 weeks, respectively, with no significant differences between the Lipid Normal and Lipid Abnormal groups at any of these time points [20.5% vs. 25.6% at 4 weeks ($P = 0.5869$), 59.0% vs. 60.5% at 12 weeks ($P = 0.8907$), and 71.8% vs. 69.8% at 24 weeks ($P = 0.8403$)] (Fig. 3A). The log-rank test showed no significant difference in the cumulative CVS rate between the two groups at any time point ($P = 0.8205$) (Fig. 3B). At week 48, HBV DNA levels had significantly decreased following TMF treatment, with 86.6% of patients achieving CVS. No significant differences were observed in either the reduction of HBV DNA (Lipid Normal group: 3.87 vs. 1.30 $\log_{10}$ IU/mL; Lipid Abnormal group: 3.75 vs. 1.30 $\log_{10}$ IU/mL, $P = 0.8625$) or the CVS rate (87.2% vs. 86.0%, respectively, $P > 0.9999$) between the two groups (Table 2).

Considering that anti-HBV therapy can improve hepatic fibrosis, we assessed three common predictive indices: the LSM,[19] Fibrosis-4 index, and APRI.[20] LSM decreased significantly after TMF treatment, but no statistically significant difference in the magnitude of decline was found between the Lipid Normal and Lipid Abnormal groups [Lipid Normal group: 6.8 (6.1–9.0) vs. 6.5 (5.7–7.0) kPa; Lipid Abnormal group: 7.4 (6.3–11.3) vs. 6.9 (5.0–8.2) kPa, $P = 0.3738$]. Changes in APRI were consistent with LSM. Similarly, ALT and AST levels showed statistically significant intra-group differences, but no statistically significant inter-group differences. Eleven patients were hepatitis B virus E antigen-positive at baseline

Table 1. Baseline characteristics and laboratory examinations

	Total (n = 91)	Lipid Normal (n = 42)	Lipid Abnormal (n = 49)	*P*-value
Age, mean ± SD (y)	48 ± 11	48 ± 11	49 ± 11	0.7476
Gender (male)	52 (57.1%)	25 (59.5%)	27 (55.1%)	0.6709
Family history of hepatitis B	28 (30.8%)	14 (33.3%)	14 (28.6%)	0.6237
Family history of hepatocarcinoma/liver cirrhosis	15 (16.5%)	6 (14.3%)	9 (18.4%)	0.6009
Liver cirrhosis	11 (12.1%)	7 (16.7%)	4 (8.2%)	0.3341
MAFLD	34 (37.4%)	14 (33.3%)	20 (40.8%)	0.4620
Alcohol abused	10 (11.0%)	4 (9.5%)	6 (12.2%)	0.7476
Hypertension	7 (7.7%)	3 (7.1%)	4 (8.2%)	>0.9999
Type 2 diabetes	2 (2.2%)	0	2 (4.1%)	0.4974
Positive HBeAg	14 (15.4%)	6 (14.3%)	8 (16.3%)	0.7879
Log10 (HBV DNA) (IU/mL)	3.65 (2.51–4.82)	3.66 (2.51–4.82)	3.64 (2.51–4.86)	0.8976
Follow-µp time, mean ± SD (day)	373 ± 121	382 ± 125	366 ± 118	0.5358
TC (mmol/L)	4.67 (4.09–5.22)	4.36 (4.02–4.79)	5.19 (4.49–5.61)	<0.0001
TG (mmol/L)	1.08 (0.86–1.39)	0.94 (0.66–1.18)	1.25 (0.99–1.60)	<0.0001
HDL-C (mmol/L)	1.25 (1.06–1.46)	1.29 (1.14–1.51)	1.11 (0.93–1.41)	0.0046
LDL-C (mmol/L)	3.03 (2.35–3.50)	2.65 (2.23–3.06)	3.48 (2.94–3.73)	<0.0001
TBil (µmol/L)	14.0 (11.1–18.2)	14.2 (11.5–18.0)	14.0 (10.4–18.3)	0.7649
DBil (µmol/L)	5.2 (4.2–6.8)	5.3 (4.4–6.8)	5.2 (4.0–7.0)	0.6330
ALT (U/L)	22 (15–35)	22 (15–33)	22 (17–39)	0.7466
AST (U/L)	23 (19–31)	23 (19–30)	23 (20–34)	0.6525
ALP (U/L)	74 (63–90)	72 (54–89)	78 (68–93)	0.0787
GGT (U/L)	18 (14–26)	17 (14–21)	19 (13–28)	0.2788
TP (g/L)	74.0 (70.4–77.2)	73.0 (68.1–76.6)	75.2 (71.7–77.7)	0.1313
ALB (g/L)	44.2 (41.8–45.8)	43.8 (40.8–45.1)	44.8 (42.0–46.7)	0.1102
GLO, mean ± SD (g/L)	29.69 ± 4.61	28.88 ± 5.13	30.38 ± 4.04	0.1233
Glu (mmol/L) (36:40)	5.2 (4.8–5.6)	5.2 (4.7–5.6)	5.3 (5.0–5.6)	0.2764
eGFR (38:46) <90 mL/(m/1.73m^2)	20/84 (23.8%)	9/38 (23.7%)	11/46 (23.9%)	0.9804
Cr (38:46) (man > 133, woman > 106µmol/L)	2/84 (2.4%)	1/42 (2.6%)	1/49 (2.2%)	>0.9999
UA, mean ± SD (µmol/L) (38:46)	321.0 ± 95.9	306.5 ± 96.2	333.0 ± 94.9	0.2094
Ca (mmol/L) (37:39)	2.29 (2.21–2.39)	2.32 (2.20–2.39)	2.29 (2.23–2.37)	0.9773
P (mmol/L) (37:39)	1.01 (0.92–1.13)	0.97 (0.94–1.15)	1.02 (0.91–1.10)	0.8060
AFP (µg/L) (37:39)	2.5 (1.7–3.6)	2.5 (1.6–3.7)	2.4 (1.9–3.5)	0.7087
WBC, mean ± SD (10^9/L) (35:45)	5.226 ± 1.297	4.953 ± 1.123	5.438 ± 1.392	0.0966

(continued)

Table 1. *(continued)*

	Total (n = 91)	Lipid Normal (n = 42)	Lipid Abnormal (n = 49)	*P*-value
RBC, mean ± SD (10^{12}/L) (35:45)	4.615 ± 0.519	4.529 ± 0.487	4.687 ± 0.544	0.1840
HGB (g/L) (35:45)	136 (130–150)	140 (130–150)	135 (131–151)	0.927
PLT, mean ± SD (10^9/L) (35:45)	194.7 ± 51.2	182.2 ± 52.9	204.4 ± 48.3	0.0531
NEUT (10^9/L) (35:45)	2.84 (2.29–3.71)	2.77 (2.01–3.34)	2.87 (2.38–3.84)	0.1763
LYMPH (10^9/L) (35:45)	1.733 ± 0.567	1.658 ± 0.515	1.791 ± 0.603	0.2995
EO (10^9/L) (35:45)	0.07 (0.04–0.14)	0.09 (0.04–0.13)	0.07 (0.04–0.16)	0.4376
BASO (10^9/L) (35:45)	0.02 (0.02–0.03)	0.03 (0.02–0.03)	0.02 (0.2–0.03)	0.6052
LSM (kPa) (30:42)	7.1 (6.1–9.6) (n = 72)	6.7 (6.1–9.1) (n = 30)	7.4 (5.6–10.5) (n = 42)	0.7787
CAP (dB/m) (30:41)	236 (222–262) (n = 71)	235 (222–255) (n = 30)	244 (222–266) (n = 41)	0.3739
Hight (cm) (30:39)	162.7 (157.9–168.5) (n = 69)	164.5 (158.1–169.0) (n = 30)	160.1 (157.6–167.4) (n = 39)	0.2242
Weight, mean ± SD (Kg) (30:39)	63.50 ± 9.77 (n = 69)	63.78 ± 10.26 (n = 30)	63.29 ± 9.50 (n = 39)	0.8362
BMI (Kg/m^2) (30:39)	24.10 (21.99–25.43) (n = 69)	24.12 (21.88–25.54) (n = 30)	23.97 (22.42–25.10) (n = 39)	0.8829

Data were represented as numbers (%) or medians (interquartile range), unless otherwise indicated. Chi-square or Fisher's exact test was used for categorical variables, and Student's t-test and rank-sum test were used for continuous data. A two-tailed *p*-value of <0.05 was considered statistically significant. AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BASO, basophil; BMI, body mass index; Ca, calcium; CAP, controlled attenuation parameter; Cr, creatine; DBil, direct bilirubin; eGFR, estimated glomerular filtration rate; EO, eosinophil; GGT, gamma-glutamyl transferase; GLO, globulin; Glu, glucose; HDL-C, high-density lipoprotein cholesterol; HGB, hemoglobin; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; LYMPH, lymphocyte; MAFLD, metabolic associated fatty liver disease; NEUT, neutrophil; P, phosphate; PLT, platelet; RBC, red blood cell; TBil, total bilirubin; TC, total cholesterol; TG, triglycerides; TP, total protein; UA, uric acid; WBC, white blood cell.

(five in the Lipid Normal group and six in the Lipid Abnormal group). By the end of follow-up, only two patients in the Lipid Abnormal group had experienced serological conversion within 48 weeks of TMF treatment, with no significant difference between the Lipid Normal and Lipid Abnormal groups as shown by Fisher's exact test (P = 0.4545) (Table 2). Additionally, no significant changes were observed in the proportion of impaired renal function in patients with CHB after 48 weeks of TMF treatment in either the intra-group or inter-group comparisons. Furthermore, neither calcium nor phosphorus levels were significantly altered after treatment (Table 2).

TMF did not affect lipid metabolism in vitro

To explore the effect of TMF on lipid metabolism in hepatocytes, we constructed cell models of disordered lipid metabolism induced by a 24-h PA intervention in the AML12 cell line (Fig. 4A). TMF intervention alone did not significantly increase the deposition of intracellular lipid droplets compared to the control group in AML12 cells, as validated by oil red staining and a TG concentration test. Additionally, no significant increase in intracellular lipid droplets was observed in the PA+TMF intervention group compared with the PA intervention alone (Fig. 4A, B). We also found no differences in lipogenic gene expression between the control and TMF groups or the PA and PA+TMF groups (Fig. 4C–F). These experiments were repeated in primary hepatocytes, where similar results were observed (Fig. 4G–L). Overall, the experiments successfully demonstrated that TMF does not affect lipid metabolism in AML12 cells or primary hepatocytes in *in vitro* experiments.

Discussion

The World Health Organization is striving to eliminate the epidemic of CHB infections by the year 2030.[21] Increasing research supports expanding antiviral treatment eligibility to ensure that more patients with CHB have access to effective treatment.[22] Considering the increasing emphasis on metabolic syndrome[23] during the long-term administration of NAs, the influence of NAs on lipid profiles has garnered more attention. We investigated the effect of TMF, a novel phosphoramidate pro-drug of tenofovir, on lipid metabolism in patients with CHB.

Lipid indices remained stable in patients with CHB after 48 weeks of TMF treatment in both the Lipid Normal and Lipid Abnormal groups, consistent with a previous study.[12] In the separate analysis of TC, TG, HDL-C, and LDL-C, although there was a slight elevation in post-treatment TC levels in patients with normal baseline levels, the TC levels remained within the normal range. Additionally, HDL-C, a protective factor against cardiovascular disease, showed an unexpected improvement following TMF treatment. Our supplementary results also indicated that using TMF in CHB patients taking oral lipid-lowering medication was safe. In addition, we performed *in vitro* experiments to investigate the effect of TMF treatment on lipid metabolism. TG concentration and RNA expression in the AML12 cell line and primary hepatocytes confirmed the safety of TMF with respect to lipid metabolism. Overall, TMF exhibited no lipid-raising effect in our study.

We also assessed the antiviral efficacy of TMF in treatment-naïve patients. The efficacy of TMF in our study was non-inferior to the results reported for the antivirals TDF and TAF.[7] Additionally, ALT and AST levels significantly decreased after TMF treatment. The values of LSM and APRI, indices that reflect the degree of liver fibrosis,[24] also improved significantly after antiviral therapy. Importantly, patients treat-

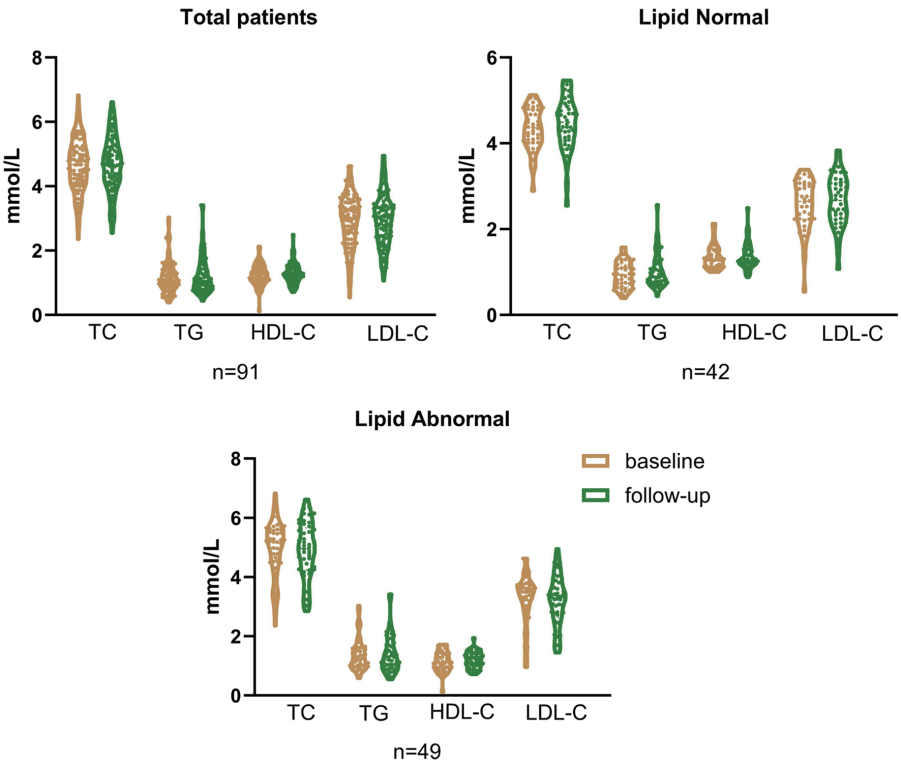

Fig. 2. Lipid spectrum before and after TMF treatment. The mean follow-up times for total patients, the Lipid Normal group, and the Lipid Abnormal group were 373 ± 121, 382 ± 125, and 366 ± 118 days, respectively. Wilcoxon matched-pairs signed rank tests were used to assess variations in lipid parameters before and after TMF treatment. TMF, tenofovir amibufenamide; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

ed with TMF did not exhibit significant bone or renal impairment, which differs from TDF as reported.[25,26] These findings demonstrate the effectiveness and safety of TMF as an antiviral agent, providing an alternative treatment option with non-inferior efficacy.

This study had two main limitations. First, it was a single-center study with a limited number of patients, and the follow-up period was relatively short, which may have affected the accuracy of the results. Second, we only validated the effect of TMF on lipid metabolism in cellular experiments; the findings lacked support from *in vivo* experiments. The effect of TMF on lipid profiles needs further validation in multicenter, large-sample studies.

Conclusions

TMF showed no significant lipid-raising effect after 48 weeks in patients with CHB with either normal or abnormal lipid parameters at baseline. It also demonstrated strong antiviral efficacy in treatment-naïve patients. These results suggest that TMF may serve as an alternative treatment option for patients with CHB.

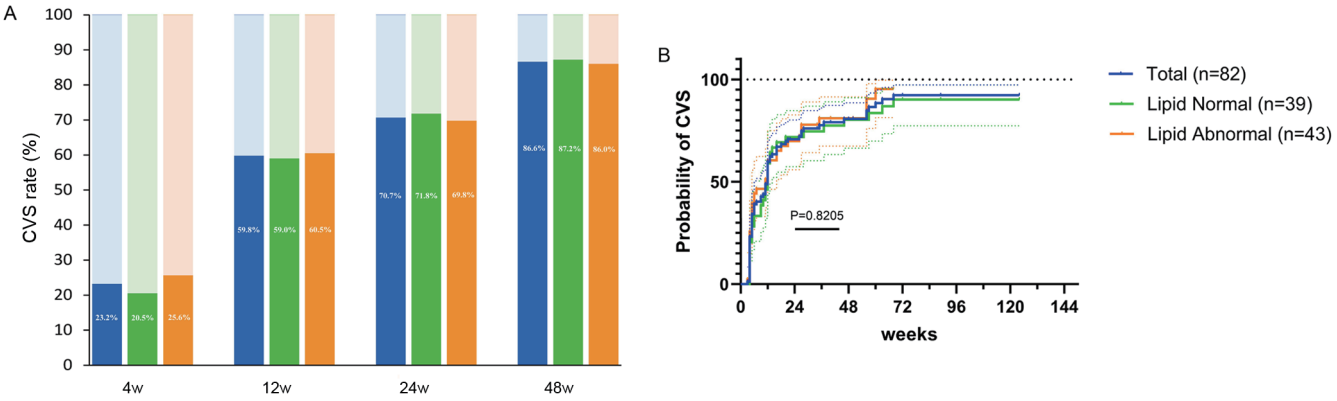

Fig. 3. Complete virological suppression rate after TMF treatment. (A) The cumulative complete virological suppression rate at weeks 4, 12, 24, and 48, with no differences between subgroups. (B) The Log-rank (Mantel-Cox) test showed no significant difference in CVS between subgroups at any time point. Complete virological suppression was defined as HBV DNA <20 IU/mL.

Table 2. Laboratory indications before and after TMF treatment in treatment-naïve CHB patients

	Total patients (n = 82)		
	baseline	**follow-up**	***P*1**
Log10 (HBV DNA) (IU/mL)	3.77 (3.06–4.95)	1.30 (1.30–1.30)	<0.0001
CVS rate (%)		86.6% (71/82)	
CVS time (weeks) (34:37)		10.0 (4.0–16.0)	
HBeAg positive	11 (13.4%)	9 (11.0%)	0.6332
LSM (kPa) (25:31)	7.4 (6.3–10.3)	6.6 (5.4–7.6)	0.0018
FIB-4 (27:29)	1.22 (0.95–1.87)	1.17 (0.81–1.65)	0.0672
APRI (27:29)	0.34 (0.24–0.59)	0.29 (0.20–0.39)	0.0004
Weight, mean ± SD (Kg) (24:27)	64.34 ± 9.30	63.60 ± 9.81	0.2334
BMI (Kg/m2) (24:27)	24.12 (21.89–25.52)	23.75 (21.58–25.76)	0.5196
CAP (dB/m) (25:30)	238 (224–261)	237 (221–259)	0.9766
MAFLD (38:39)	29/77	30/77	0.8683
T-Bil (μmol/L) (39:43)	14.6 (11.6–18.7)	15.0 (11.5–20.1)	0.4777
D-Bil (μmol/L) (39:43)	5.4 (4.3–7.1)	5.2 (4.1–6.3)	0.0710
ALT (U/L) (39:43)	22 (16–38)	18 (14–24)	<0.0001
AST (U/L) (39:43)	23 (19–33)	21 (18–25)	<0.0001
ALP (U/L) (39:43)	75 (64–91)	74 (63–87)	0.3215
GGT (U/L) (39:43)	19 (14–27)	18 (14–23)	0.1082
TP (g/L) (39:43)	73.8 (70.2–77.2)	73.7 (70.4–76.6)	0.8328
ALB (g/L) (39:43)	44.2 (41.0–45.8)	44.7 (42.6–46.9)	0.0122
GLO, mean ± SD (g/L) (39:43)	29.6 ± 4.7	28.9 ± 4.2	0.1555
eGFR (33:40) <90 mL/(m/1.73m^2)	16/73 (21.9%)	19/73 (26.0%)	0.5609
Cr (33:40) (man > 133, woman > 106μmol/L)	2 (2.7%)	1 (1.4%)	>0.9999
UA, mean ± SD (μmol/L) (33:40)	321.5 ± 96.1	342.1 ± 95.7	0.0258
Glu (mmol/L) (28:25)	5.3 (5.0–5.6)	5.4 (5.1–5.7)	0.2502
Ca (mmol/L) (27:28)	2.33 (2.23–2.39)	2.29 (2.24–2.37)	0.2018
P (mmol/L) (27:28)	1.02 (0.94–1.16)	1.09 (0.95–1.18)	0.5227
AFP (μg/L) (21:16)	3 (1.7–3.7)	2.4 (1.7–3.6)	0.1110
WBC, mean ± SD (10^9/L) (27:29)	5.31 ± 1.41	5.33 ± 1.35	0.8783
RBC, mean ± SD (10^{12}/) (27:29)	4.57 ± 0.49	4.62 ± 0.53	0.2693
HGB (g/L) (27:29)	136 (131–150)	140 (130–150)	0.4496
PLT, mean ± SD (10^9/L) (27:29)	190 ± 54	193 ± 64	0.5702
NEUT (10^9/L) (27:29)	2.83 (2.24–3.75)	2.86 (2.27–3.78)	0.8986
LYMPH (10^9/L) (27:29)	1.67 (1.40–2.10)	1.72 (1.37–2.04)	0.8468
EO (10^9/L) (27:29)	0.08 (0.04–0.15)	0.08 (0.05–0.16)	0.9351
BASO (10^9/L) (27:29)	0.02 (0.02–0.03)	0.02 (0.01–0.04)	0.7515

(continued)

Table 2. *(continued)*

	Lipid Normal group (n = 39)		
	baseline	**follow-up**	***P*2**
Log10 (HBV DNA) (IU/mL)	3.87 (3.04–5.15)	1.30 (1.30–1.30)	<0.0001
CVS rate (%)	87.2% (34/39)		
CVS time (weeks) (34:37)	11.0 (4.8–14.5)		
HBeAg positive	5 (12.8%)	5 (12.8%)	>0.9999
LSM (kPa) (25:31)	6.8 (6.1–9.0)	6.5 (5.7–7.0)	0.0798
FIB-4 (27:29)	1.24 (0.97–1.90)	1.21 (0.89–1.91)	0.2148
APRI (27:29)	0.35 (0.25–0.65)	0.31 (0.22–0.49)	0.0122
Weight, mean ± SD (Kg) (24:27)	64.04 ± 9.05	64.45 ± 8.97	0.8253
BMI (Kg/m2) (24:27)	24.00 (21.85–25.27)	23.41 (21.55–25.46)	0.9881
CAP (dB/m) (25:30)	235 (225–253)	225 (215–258)	0.7952
MAFLD (38:39)	13/38	10/38	0.6181
T-Bil (μmol/L) (39:43)	14.8 (11.6–18.6)	13.9 (11.5–19.2)	0.8225
D-Bil (μmol/L) (39:43)	5.4 (4.5–6.8)	5.0 (4.2–6.6)	0.1720
ALT (U/L) (39:43)	22 (15–37)	19 (14–24)	0.0033
AST (U/L) (39:43)	23 (18–30)	20 (18–25)	0.0039
ALP (U/L) (39:43)	72 (55–88)	74 (63–88)	0.3863
GGT (U/L) (39:43)	17 (14–21)	17 (13–23)	0.6383
TP (g/L) (39:43)	73.0 (67.7–76.6)	72.7 (70.4–75.6)	0.6914
ALB (g/L) (39:43)	43.8 (40.7–45.2)	44.5 (42.6–46.9)	0.0260
GLO, mean ± SD (g/L) (39:43)	28.9 ± 5.2	28.3 ± 4.2	0.3979
eGFR (33:40) <90 mL/(m/1.73m^2)	7/33 (21.2%)	7/33 (21.2%)	>0.9999
Cr (33:40) (man > 133, woman > 106μmol/L)	1 (3.0%)	0	>0.9999
UA, mean ± SD (μmol/L) (33:40)	309.3 ± 91.9	329.8 ± 89.7	0.2125
Glu (mmol/L) (28:25)	5.2 (4.7–5.6)	5.4 (5.0–5.7)	0.055
Ca (mmol/L) (27:28)	2.33 (2.22–2.39)	2.28 (2.23–2.37)	0.2083
P (mmol/L) (27:28)	1.01 (0.94–1.22)	1.08 (0.95–1.18)	0.3975
AFP (μg/L) (21:16)	2.6 (1.6–3.8)	2.4 (1.7–3.4)	0.1344
WBC, mean ± SD (10^9/L) (27:29)	5.02 ± 1.16	5.12 ± 1.33	0.6730
RBC, mean ± SD (10^{12}/) (27:29)	4.55 ± 0.49	4.58 ± 0.54	0.6217
HGB (g/L) (27:29)	143 (130–150)	141 (132–153)	0.5259
PLT, mean ± SD (10^9/L) (27:29)	172 ± 53	175 ± 65	0.7607
NEUT (10^9/L) (27:29)	2.77 (2.01–3.47)	2.76 (2.02–3.43)	0.9012
LYMPH (10^9/L) (27:29)	1.69 (1.26–1.91)	1.79 (1.32–1.97)	0.6038
EO (10^9/L) (27:29)	0.09 (0.04–0.13)	0.07 (0.05–0.15)	0.3634
BASO (10^9/L) (27:29)	0.02 (0.02–0.03)	0.02 (0.01–0.03)	0.9183

(continued)

Table 2. *(continued)*

	Lipid Abnormal group (n = 43)			
	baseline	**follow-up**	***P*3**	***P*4**
Log10 (HBV DNA) (IU/mL)	3.75 (3.13–4.92)	1.30 (1.30–1.30)	<0.0001	0.8625
CVS rate (%)	86.0% (37/43)			>0.9999
CVS time (weeks) (34:37)	6.0 (4.0–17.0)			0.4606
HBeAg positive	6 (14.0%)	4 (9.3%)	0.7383	0.4545
LSM (kPa) (25:31)	7.4 (6.3–11.3)	6.9 (5.0–8.2)	0.0105	0.3738
FIB-4 (27:29)	1.18 (0.88–1.87)	1.15 (0.75–1.64)	0.3066	0.6430
APRI (27:29)	0.29 (0.24–0.49)	0.24 (0.20–0.37)	0.0170	0.7914
Weight, mean ± SD (Kg) (24:27)	64.07 ± 9.69	62.85 ± 10.62	0.1726	0.4053
BMI (Kg/m2) (24:27)	24.36 (22.42–26.67)	24.08 (21.58–25.82)	0.3802	0.5335
CAP (dB/m) (25:30)	247 (222–271)	245 (227–264)	0.7493	0.6118
MAFLD (38:39)	16/39	20/39	0.4959	0.3655
T-Bil (μmol/L) (39:43)	14.6 (11.4–19.2)	16.4 (11.3–20.2)	0.2262	0.2172
D-Bil (μmol/L) (39:43)	5.3 (4.2–7.1)	5.5 (3.8–6.2)	0.2214	0.9834
ALT (U/L) (39:43)	22 (17–42)	18 (14–25)	0.0037	0.9908
AST (U/L) (39:43)	24 (20–34)	21 (17–26)	0.0005	0.6287
ALP (U/L) (39:43)	78 (67–95)	74 (63–87)	0.0338	0.0260
GGT (U/L) (39:43)	20 (13–30)	19 (14–25)	0.0954	0.4427
TP (g/L) (39:43)	74.6 (71.0–77.2)	74.3 (70.0–77.5)	0.9361	0.6692
ALB (g/L) (39:43)	44.5 (41.1–46.6)	44.8 (42.4–46.6)	0.2170	0.4360
GLO, mean ± SD (g/L) (39:43)	30.2 ± 4.2	29.4 ± 4.1	0.2511	0.8942
eGFR (33:40) <90 mL/(m/1.73m^2)	9/40 (22.5%)	12/40 (30.0%)	0.6120	>0.9999
Cr (33:40) (man > 133, woman > 106μmol/L)	1 (2.5%)	1 (2.5%)	>0.9999	>0.9999
UA, mean ± SD (μmol/L) (33:40)	331.6 ± 99.4	352.2 ± 100.3	0.0446	0.9975
Glu (mmol/L) (28:25)	5.4 (5.1–5.7)	5.4 (5.1–5.7)	0.735	0.0974
Ca (mmol/L) (27:28)	2.33 (2.27–2.37)	2.3 (2.25–2.38)	0.5738	0.7036
P (mmol/L) (27:28)	1.05 (0.92–1.13)	1.11 (0.90–1.18)	0.8974	0.4541
AFP (μg/L) (21:16)	3 (1.8–3.6)	2.7 (1.7–4.3)	0.4150	0.5794
WBC, mean ± SD (10^9/L) (27:29)	5.57 ± 1.59	5.52 ± 1.36	0.7943	0.6183
RBC, mean ± SD (10^{12}/) (27:29)	4.59 ± 0.50	4.66 ± 0.51	0.3417	0.6666
HGB (g/L) (27:29)	134 (132–150)	138 (129–147)	0.6492	0.9060
PLT, mean ± SD (10^9/L) (27:29)	206 ± 50	209 ± 59	0.6230	0.9198
NEUT (10^9/L) (27:29)	2.87 (2.32–3.95)	3.01 (2.385–3.88)	>0.9999	0.9449
LYMPH (10^9/L) (27:29)	1.62 (1.41–2.25)	1.67 (1.38–2.05)	0.7372	0.6515
EO (10^9/L) (27:29)	0.07 (0.04–0.15)	0.08 (0.05–0.22)	0.4423	0.3006
BASO (10^9/L) (27:29)	0.02 (0.02–0.04)	0.03 (0.01–0.04)	0.7195	0.8575

Data were represented as numbers (%) or medians (interquartile range), unless otherwise indicated. Comparisons within the group before and after treatment were analyzed using a paired t-test. A two-tailed *p*-value of <0.05 was considered statistically significant. P1: comparison between baseline and follow-up for all patients; P2: comparison between baseline and follow-up for the Lipid Normal group; P3: comparison between baseline and follow-up for the Lipid Abnormal group; P4: comparison between the Lipid Normal group and the Lipid Abnormal group. A two-tailed *p*-value of <0.05 was considered statistically significant. AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; APRI, AST-to-platelet ratio index; AST, aspartate transaminase; BASO, basophil;BMI, body mass index; Ca, calcium; CAP, controlled attenuation parameter; Cr, creatine; CVS, complete viral suppression; DBil, direct bilirubin; eGFR, estimated glomerular filtration rate; EO, eosinophil; FIB-4, fibrosis-4 index; GGT, gamma-glutamyl transferase; GLO, globulin; Glu, glucose; HGB, hemoglobin; LSM, liver stiffness measurement; LYMPH, lymphocyte; MAFLD, metabolic associated fatty liver disease ; NEUT, neutrophil; P, phosphate; PLT, platelet; RBC, red blood cell; TBil, total bilirubin; TP, total protein; UA, uric acid; WBC, white blood cell.

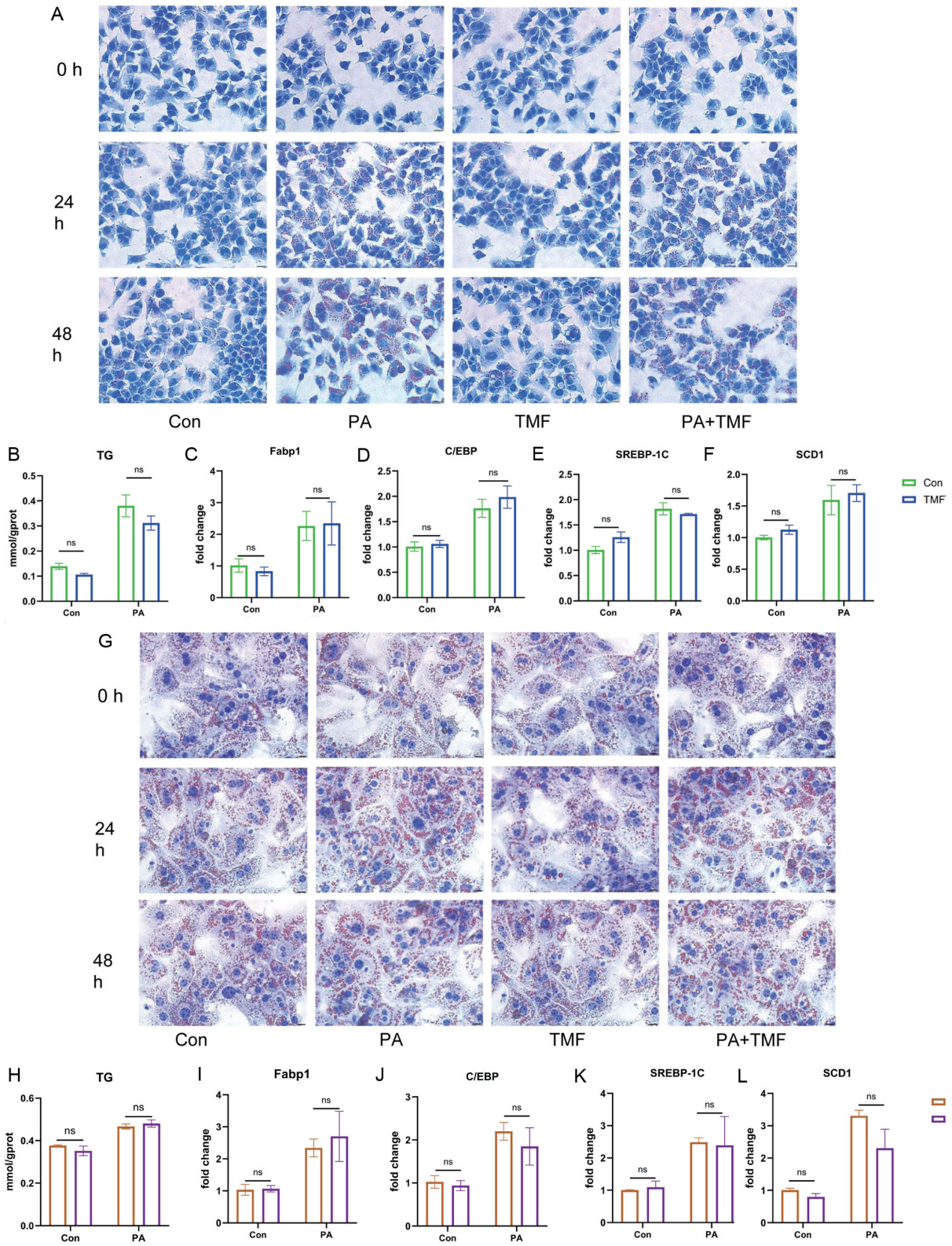

Fig. 4. Effect of TMF on lipid accumulation and lipogenic gene expression in AML12 cell lines and primary hepatocytes *in vitro*. (A–F) AML12 cell lines. (A) Oil red staining (original magnification, ×400). Control group: normal AML12 cells, PA group: PA intervention for 24 h, TMF group: TMF intervention for 24 h, PA+TMF group: PA intervention for 24 h followed by TMF intervention for another 24 h. (B) TG concentration of the four groups. (C–F) Lipogenic gene expression of Fabp1, C/EBP, SREBP-1c, and SCD1 in the four groups. (G–L) Results from primary hepatocytes. Con, control; TMF, tenofovir amibufenamide; PA, Palmitic acid.

Acknowledgments

This work was financially and pharmacologically supported by Jiangsu Hansoh Pharmaceutical Co., Ltd. (Lianyungang, China). Zhizhen Hu and Fanru Nie (Medical Affairs of Jiangsu Hansoh Pharmaceutical Group Co., Ltd.) provided assistance with the preparation of the manuscript. The figure in the graphical abstract was created using Figdraw (www.figdraw.com).

Funding

This study was funded by the National Natural Science Foundation of China [82270614, 81974078, 81570530, and 81370550 to LY, 82000561to HC]; the National Key R&D Program of China [2023YFC2413804 to LY and 2022YFA1305600 to HC]; the Science Foundation of Hubei Province [2019ACA133 to LY] and the Science Foundation of Union Hospital [2021xhyn005] to HC.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Design of the research (LY, FD), data collection (YC, WG, AAMAA, SY, HY, JC, ZC, ZL), data analysis and visualization (YC, WG), drafting of the manuscript (YC), revising and improving the manuscript (HC, WG), critical revision of the important intellectual content in this manuscript (LY, FD, XH, RL, JY). All authors reviewed and approved the final version and publication of the manuscript.

Ethical statement

This research protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (UHCT21612). It has been registered at ClinicalTrials.gov (NCT05398393). Written informed consent was obtained from the patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the corresponding authors without undue reservation.

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