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Efficacy and safety of sequential or combined therapy with tenofovir amibufenamide in entecavir-treated patients with low-level viremia: A propensity score-matched cohort study

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Research Article

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Abstract

Background

Low-level viremia (LLV) in chronic hepatitis B (CHB) patients receiving entecavir (ETV) therapy is associated with increased risk of hepatic fibrosis progression and hepatocellular carcinoma. Optimal management strategies for LLV remain debated. This study aimed to compare the efficacy and safety of sequential tenofovir amibufenamide (TMF) monotherapy versus ETV plus TMF combination therapy in CHB patients with LLV after prior ETV treatment.

Methods

This retrospective cohort study enrolled 212 CHB patients with LLV (HBV DNA 20-2000 IU/mL) after ≥ 48 weeks of ETV treatment at the Third People's Hospital of Yunnan Province between January 2022 and December 2024. Patients were allocated to either sequential TMF monotherapy (TMF group, n = 118) or ETV plus TMF combination therapy (combination group, n = 94). Propensity score matching (1:1 ratio, caliper 0.02) was performed to balance baseline covariates, yielding 60 patients per group. Virological response (HBV DNA < 20 IU/mL), HBeAg seroconversion, liver function (ALT, AST), renal function (Cr, eGFR), liver stiffness measurement (LSM), lipid profiles (TC, TG, HDL-C, LDL-C), and adverse events were assessed at 48 weeks.

Results

After PSM, baseline characteristics were well-balanced between groups. At week 48, the combination group demonstrated significantly higher HBV DNA undetectable rate (86.67% vs. 63.33%, χ^2=8.711, P = 0.003) and HBeAg seroconversion rate (58.33% vs. 36.67%, χ^2=5.682, P = 0.017) compared with the TMF group. The combination group showed significantly lower ALT (24.85 ± 6.94 vs. 29.36 ± 8.17 U/L, t = 3.254, P = 0.001), AST (22.67 ± 5.83 vs. 27.41 ± 7.26 U/L, t = 3.917, P < 0.001), and LSM (6.58 ± 1.46 vs. 7.48 ± 1.72 kPa, t = 3.081, P = 0.003) levels post-treatment. However, the TMF group exhibited better renal preservation with higher eGFR (101.35 ± 10.84 vs. 96.28 ± 11.53 ml/min/1.73m², t = 2.489, P = 0.014). Both groups experienced mild elevations in TC from baseline (TMF group: 5.21 ± 0.94 vs. 4.82 ± 0.89 mmol/L, P = 0.018; combination group: 5.16 ± 0.91 vs. 4.78 ± 0.86 mmol/L, P = 0.022), with no significant between-group differences. Adverse event rates were comparable (TMF group: 20.00%; combination group: 18.33%; χ^2=0.055, P = 0.815).

Conclusions

In ETV-treated CHB patients with LLV, adding TMF to ongoing ETV therapy achieves superior virological response and greater improvements in liver fibrosis compared with switching to TMF monotherapy,

whereas sequential TMF monotherapy offers better renal protection. Both regimens are associated with modest TC elevation, warranting regular lipid monitoring during long-term follow-up.

Background

Chronic hepatitis B virus (HBV) infection remains a major global health burden, affecting approximately 296 million individuals worldwide and contributing substantially to cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [1]. The primary therapeutic goal for chronic hepatitis B (CHB) is sustained suppression of HBV replication to prevent disease progression and improve clinical outcomes [2]. Nucleos(t)ide analogues (NAs) with high potency and high genetic barrier to resistance, particularly entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF), are recommended as first-line antiviral agents by current clinical practice guidelines [3, 4].

Despite the efficacy of ETV in achieving virological suppression in most patients, a subset of individuals experiences low-level viremia (LLV) during long-term therapy, typically defined as detectable HBV DNA between 20 and 2000 IU/mL [5]. The reported prevalence of LLV among NA-treated CHB patients ranges from 20% to 40% [6]. Accumulating evidence suggests that persistent LLV is not a benign condition; it is associated with accelerated hepatic fibrosis progression and significantly increased risk of HCC. Kim et al. demonstrated that CHB patients with LLV during ETV therapy had substantially higher 5-year cumulative HCC incidence compared to those achieving maintained virological response [7]. A recent study by Tamaki et al. further confirmed that untreated LLV in compensated cirrhosis patients confers comparable HCC risk to untreated high-level viremia [8].

The optimal management strategy for LLV remains incompletely defined. Current approaches include switching to an alternative potent NA or combining two NAs with complementary resistance profiles [9]. Tenofovir amibufenamide (TMF), a novel prodrug of tenofovir developed in China, incorporates structural optimizations that enhance hepatic-targeting delivery while minimizing systemic tenofovir exposure [10]. Peng et al. reported that TMF demonstrates comparable efficacy to TAF in achieving virological response at 48 weeks, with potential advantages in lipid profiles [11]. However, data specifically addressing TMF use in the LLV population are limited.

The metabolic effects of NA therapy have garnered increasing attention as CHB patients experience prolonged survival. Emerging evidence indicates that different NAs exert distinct influences on lipid metabolism, with potential implications for cardiovascular risk [12]. Shin et al. found that TAF was associated with increased total cholesterol (TC) levels, whereas TDF exhibited TC-lowering effects [13]. Lin et al. similarly demonstrated that TAF induces dyslipidemia characterized by elevations in TC, triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) [14]. Whether TMF shares similar metabolic effects with TAF, given its structural relationship, requires systematic evaluation.

Therefore, this study aimed to compare the efficacy and safety profiles of two therapeutic strategies—sequential TMF monotherapy versus ETV plus TMF combination therapy—in ETV-treated CHB patients with LLV. Using propensity score matching to minimize confounding, we comprehensively evaluated

virological response, liver and renal function parameters, hepatic fibrosis indices, and lipid metabolic changes over 48 weeks of treatment.

Methods

Study design and participants

This retrospective cohort study was conducted at the Department of Gastroenterology, The Third People's Hospital of Yunnan Province, Kunming, China. Consecutive CHB patients who received ETV treatment between January 2022 and December 2024 were screened for eligibility.

Inclusion criteria were: (1) diagnosis of CHB according to the Chinese Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2022 version) [15]; (2) age 18–75 years; (3) received continuous ETV monotherapy (0.5 mg daily) for ≥ 48 weeks; (4) documented LLV, defined as serum HBV DNA between 20 and 2000 IU/mL on at least two consecutive measurements separated by ≥ 3 months during ETV therapy; (5) complete medical records available for review.

Exclusion criteria were: (1) co-infection with hepatitis A, C, D, or E virus, or human immunodeficiency virus; (2) concurrent alcoholic liver disease, drug-induced liver injury, autoimmune liver disease, or hereditary metabolic liver diseases; (3) decompensated cirrhosis (presence of ascites, variceal bleeding, or hepatic encephalopathy) or HCC; (4) severe cardiac, renal, pulmonary, or systemic diseases; (5) pregnancy or lactation; (6) poor medication adherence (< 90% of prescribed doses) during follow-up; (7) prior exposure to interferon, TDF, TAF, or other NAs besides ETV.

The study protocol was approved by the Ethics Committee of The Third People's Hospital of Yunnan Province (Approval No. YN2022-056-01) and conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study.

Treatment regimens

Eligible patients were allocated to two groups based on the treatment regimen initiated after LLV detection:

TMF group: Patients discontinued ETV and received TMF monotherapy (Jiangsu Haosen Pharmaceutical Co., LTD, China; National Drug Approval Number H20233067; 25 mg tablet), 25 mg once daily orally.

Combination group: Patients continued ETV (Jiangsu Tianqing Pharmaceutical Co., LTD, China; National Drug Approval Number H20212264; 0.5 mg tablet), 0.5 mg once daily orally, and additionally received TMF (25 mg once daily orally).

Both groups were treated for 48 weeks with regular follow-up assessments at 12-week intervals.

Data collection and outcome measures

Data collection and outcome measures
Demographic characteristics, clinical history, and laboratory parameters were extracted from electronic medical records. Propensity score matching was employed to minimize selection bias.

Virological assessment

Serum HBV DNA levels were quantified using high-sensitivity real-time PCR assay (Cobas AmpliPrep/Cobas TaqMan HBV Test, Roche Diagnostics, Switzerland) with a lower detection limit of 20 IU/mL. HBV DNA undetectable rate was defined as the proportion of patients with serum HBV DNA < 20 IU/mL at week 48. Hepatitis B e antigen (HBeAg) and antibody (HBeAb) were measured using chemiluminescence immunoassay (Abbott Architect i2000, Abbott Laboratories, USA). HBeAg seroconversion was defined as loss of HBeAg with appearance of HBeAb.

Liver and renal function

Fasting venous blood samples were collected for biochemical analysis. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Cr), and lipid profiles were measured using an automated biochemical analyzer (Beckman Coulter AU5800, USA). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation.

Liver fibrosis assessment

Liver stiffness measurement (LSM) was performed using transient elastography (FibroScan 502 Touch, Echosens, France) by experienced operators blinded to clinical data. Examinations were considered reliable if at least 10 valid measurements were obtained with an interquartile range/median ratio < 30% and success rate ≥ 60%. The FIB-4 index was calculated as: (age × AST) / (platelet count × √ALT).

Lipid profiles

Fasting serum lipid parameters including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were assessed at baseline and week 48.

Safety monitoring

Adverse events during the 48-week treatment period were recorded, including gastrointestinal symptoms (nausea, diarrhea), headache, renal function abnormalities (Cr elevation > 20% from baseline or eGFR decline > 20%), and other treatment-emergent adverse events.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and compared using independent samples t-test for between-group comparisons and paired t-test for within-group comparisons. Categorical variables were presented as frequencies (percentages) and compared using χ^2 test or Fisher's exact test as appropriate.

To address potential confounding by indication, propensity score matching (PSM) was performed. Propensity scores were calculated using logistic regression incorporating baseline variables including age, sex, body mass index (BMI), HBV DNA level, HBeAg status, ALT, AST, Cr, LSM, and lipid parameters. Patients were matched 1:1 using nearest-neighbor matching with a caliper width of 0.02. Standardized mean differences were examined to assess covariate balance after matching.

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided P-values < 0.05 were considered statistically significant.

Sample size estimation

Based on previous studies [16, 17], the expected HBV DNA undetectable rates at 48 weeks were approximately 70% for TMF monotherapy and 90% for combination therapy. Using a two-sided α of 0.05 and power of 80%, the required sample size was calculated as 52 patients per group. Accounting for potential loss to follow-up and matching efficiency, we aimed to include at least 60 patients per group after PSM.

Results

Baseline characteristics and propensity score matching

A total of 212 patients met the inclusion criteria and were enrolled, comprising 118 patients in the TMF group (sequential therapy) and 94 patients in the combination group (ETV + TMF). Before matching, significant differences were observed between groups in baseline HBV DNA levels (P = 0.038), HBeAg positivity rate (P = 0.029), and ALT levels (P = 0.045), indicating potential selection bias (Supplementary Table S1).

After 1:1 propensity score matching, 60 well-matched pairs were successfully generated. Table 1 presents the baseline characteristics of the matched cohort. All covariates were well-balanced between the two groups, with no statistically significant differences and standardized mean differences < 0.1 for all variables, confirming the adequacy of the matching procedure.

Table 1
Baseline characteristics of study patients after propensity score matching

Characteristic	TMF group (n = 60)	Combination group (n = 60)	t/χ²	P-value	SMD
Age (years)	50.32 ± 11.45	51.08 ± 11.27	0.364	0.717	0.067
Male, n (%)	43 (71.67)	45 (75.00)	0.170	0.680	0.075
BMI (kg/m²)	23.41 ± 2.68	23.65 ± 2.73	0.485	0.629	0.089
Smoking history, n (%)	10 (16.67)	9 (15.00)	0.063	0.802	0.046
Alcohol history, n (%)	8 (13.33)	7 (11.67)	0.076	0.783	0.050
Hypertension, n (%)	12 (20.00)	11 (18.33)	0.055	0.815	0.043
Diabetes mellitus, n (%)	7 (11.67)	6 (10.00)	0.086	0.769	0.054
HBV DNA (log_{10} IU/mL)	3.08 ± 0.79	3.02 ± 0.76	0.425	0.672	0.078
HBeAg positive, n (%)	32 (53.33)	34 (56.67)	0.134	0.714	0.067
ALT (U/L)	43.85 ± 14.72	44.21 ± 14.56	0.135	0.893	0.025
AST (U/L)	37.92 ± 12.84	38.45 ± 13.06	0.224	0.823	0.041
Total bilirubin (μmol/L)	14.36 ± 5.28	14.12 ± 5.19	0.251	0.802	0.046
Cr (μmol/L)	67.85 ± 9.93	67.41 ± 9.86	0.244	0.808	0.045
eGFR (ml/min/1.73m²)	103.28 ± 11.45	103.85 ± 11.62	0.270	0.788	0.049
LSM (kPa)	8.41 ± 2.18	8.35 ± 2.14	0.152	0.879	0.028
Platelet count (×10⁹/L)	176.54 ± 45.32	179.28 ± 46.15	0.327	0.744	0.060
TC (mmol/L)	4.82 ± 0.89	4.78 ± 0.86	0.250	0.803	0.046
TG (mmol/L)	1.38 ± 0.62	1.35 ± 0.60	0.269	0.788	0.049
HDL-C (mmol/L)	1.24 ± 0.31	1.26 ± 0.32	0.348	0.728	0.064
LDL-C (mmol/L)	2.79 ± 0.72	2.76 ± 0.70	0.231	0.818	0.042

Data are presented as mean ± SD or n (%). SMD, standardized mean difference; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; LSM, liver stiffness measurement; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Virological response at week 48

After 48 weeks of treatment, the combination group demonstrated significantly superior virological outcomes compared with the TMF group. The HBV DNA undetectable rate was 86.67% (52/60) in the combination group versus 63.33% (38/60) in the TMF group (χ^2=8.711, P = 0.003). Among HBeAg-positive patients at baseline, the HBeAg seroconversion rate was significantly higher in the combination group (58.33%, 21/36) compared with the TMF group (36.67%, 11/30) (χ^2=5.682, P = 0.017) (Table 2).

Table 2
Virological response at week 48

Outcome	TMF group (n = 60)	Combination group (n = 60)	χ^2	P-value
HBV DNA undetectable, n (%)	38 (63.33)	52 (86.67)	8.711	0.003
HBeAg seroconversion[1], n (%)	11/30 (36.67)	21/36 (58.33)	5.682	0.017

[1]Denominator represents number of HBeAg-positive patients at baseline (TMF group: 30 patients; combination group: 36 patients).

Liver biochemical and fibrosis parameters

Both groups showed significant improvements in liver biochemical parameters and fibrosis indices at week 48 compared with baseline (P < 0.05 for all). However, the combination group achieved significantly better outcomes. Post-treatment ALT levels were 24.85 ± 6.94 U/L in the combination group versus 29.36 ± 8.17 U/L in the TMF group (t = 3.254, P = 0.001). Similarly, AST levels were significantly lower in the combination group (22.67 ± 5.83 vs. 27.41 ± 7.26 U/L, t = 3.917, P < 0.001) (Table 3).

Table 3
Liver biochemical and fibrosis parameters at week 48

Parameter	TMF group (n = 60)	Combination group (n = 60)	t-value	P-value
ALT (U/L)	29.36 ± 8.17*	24.85 ± 6.94*	3.254	0.001
AST (U/L)	27.41 ± 7.26*	22.67 ± 5.83*	3.917	< 0.001
Total bilirubin (μmol/L)	13.28 ± 4.85	12.76 ± 4.63	0.602	0.548
Albumin (g/L)	42.35 ± 4.28	43.12 ± 4.35	0.981	0.329
Platelet count (×10⁹/L)	197.35 ± 41.67*	211.46 ± 43.28*	1.823	0.071
LSM (kPa)	7.48 ± 1.72*	6.58 ± 1.46*	3.081	0.003
FIB−4 index	2.08 ± 0.82*	1.85 ± 0.74*	1.614	0.109

Data are presented as mean ± SD. *P < 0.05 compared with baseline within the same group. ALT, alanine aminotransferase; AST, aspartate aminotransferase; LSM, liver stiffness measurement; FIB-4, fibrosis-4 index.

Regarding fibrosis parameters, the combination group exhibited significantly lower LSM values at week 48 (6.58 ± 1.46 vs. 7.48 ± 1.72 kPa, t = 3.081, P = 0.003). Platelet counts were higher in the combination group, although the difference did not reach statistical significance (211.46 ± 43.28 vs. 197.35 ± 41.67 ×10⁹/L, t = 1.823, P = 0.071). FIB-4 index showed greater improvement in the combination group but the between-group difference was not significant (1.85 ± 0.74 vs. 2.08 ± 0.82, t = 1.614, P = 0.109).

Renal function outcomes

Renal function parameters showed differential changes between the two groups. At week 48, the TMF group demonstrated better preserved renal function with significantly higher eGFR (101.35 ± 10.84 vs. 96.28 ± 11.53 ml/min/1.73m², t = 2.489, P = 0.014) and lower Cr levels (69.24 ± 10.18 vs. 73.56 ± 11.35 μmol/L, t = 2.202, P = 0.030) compared with the combination group (Table 4).

Table 4
Renal function parameters at baseline and week 48

Parameter	Time point	TMF group (n = 60)	Combination group (n = 60)	Between-group P
Cr (μmol/L)				
	Baseline	67.85 ± 9.93	67.41 ± 9.86	0.808
	Week 48	69.24 ± 10.18	73.56 ± 11.35	0.030
	Change	1.39 ± 6.24	6.15 ± 7.82	0.001
	Within-group P	0.095	0.004	
eGFR (ml/min/1.73m²)				
	Baseline	103.28 ± 11.45	103.85 ± 11.62	0.788
	Week 48	101.35 ± 10.84	96.28 ± 11.53	0.014
	Change	−1.93 ± 7.15	−7.57 ± 9.24	< 0.001
	Within-group P	0.068	0.002	

Data are presented as mean ± SD. Cr, creatinine; eGFR, estimated glomerular filtration rate.

Within-group comparisons revealed that the combination group experienced a significant decline in eGFR from baseline (103.85 ± 11.62 to 96.28 ± 11.53 ml/min/1.73m², P = 0.002) and significant Cr elevation (67.41 ± 9.86 to 73.56 ± 11.35 μmol/L, P = 0.004). In contrast, changes in renal parameters in the TMF group were modest and not statistically significant (P > 0.05 for both).

Lipid profile changes

Lipid profiles at baseline and week 48 are presented in Table 5. Both groups experienced significant increases in TC levels from baseline to week 48. In the TMF group, TC increased from 4.82 ± 0.89 to 5.21 ± 0.94 mmol/L (mean change: 0.39 ± 0.62 mmol/L, P = 0.018). In the combination group, TC increased from 4.78 ± 0.86 to 5.16 ± 0.91 mmol/L (mean change: 0.38 ± 0.58 mmol/L, P = 0.022). However, between-group comparison of post-treatment TC levels showed no significant difference (P = 0.768).

Table 5
Lipid profiles at baseline and week 48

Parameter	Time point	TMF group (n = 60)	Combination group (n = 60)	Between-group P
TC (mmol/L)				
	Baseline	4.82 ± 0.89	4.78 ± 0.86	0.803
	Week 48	5.21 ± 0.94	5.16 ± 0.91	0.768
	Change	0.39 ± 0.62	0.38 ± 0.58	0.927
	Within-group P	0.018	0.022	
TG (mmol/L)				
	Baseline	1.38 ± 0.62	1.35 ± 0.60	0.788
	Week 48	1.44 ± 0.68	1.41 ± 0.65	0.805
	Change	0.06 ± 0.35	0.06 ± 0.32	1.000
	Within-group P	0.217	0.204	
HDL-C (mmol/L)				
	Baseline	1.24 ± 0.31	1.26 ± 0.32	0.728
	Week 48	1.27 ± 0.33	1.29 ± 0.34	0.743
	Change	0.03 ± 0.18	0.03 ± 0.19	1.000
	Within-group P	0.246	0.235	
LDL-C (mmol/L)				
	Baseline	2.79 ± 0.72	2.76 ± 0.70	0.818
	Week 48	2.91 ± 0.79	2.88 ± 0.76	0.831
	Change	0.12 ± 0.45	0.12 ± 0.42	1.000
	Within-group P	0.082	0.075	

Data are presented as mean ± SD. TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

TG, HDL-C, and LDL-C levels remained relatively stable in both groups, with no significant within-group changes or between-group differences at week 48. The proportion of patients developing dyslipidemia

(TC ≥ 6.2 mmol/L or TG ≥ 2.3 mmol/L) was comparable between groups (TMF group: 11.67% vs. combination group: 10.00%, χ^2=0.086, P = 0.769).

Safety assessment

Adverse events during the 48-week treatment period are summarized in Table 6. The overall incidence of adverse events was comparable between groups (TMF group: 20.00% vs. combination group: 18.33%, χ^2=0.055, P = 0.815). Most adverse events were mild in severity and did not require treatment discontinuation.

Table 6
Adverse events during 48-week treatment period

Adverse event	TMF group (n = 60)	Combination group (n = 60)	χ^2	P-value
Any adverse event, n (%)	12 (20.00)	11 (18.33)	0.055	0.815
Nausea	3 (5.00)	3 (5.00)	0.000	1.000
Diarrhea	2 (3.33)	2 (3.33)	0.000	1.000
Headache	4 (6.67)	3 (5.00)	0.000	1.000
Fatigue	1 (1.67)	0 (0.00)	-	1.000[1]
Renal abnormality	2 (3.33)	3 (5.00)	0.000	1.000
Serious adverse events	0 (0.00)	0 (0.00)	-	-
[1]Fisher's exact test.				

Gastrointestinal symptoms (nausea, diarrhea) and headache were the most frequently reported events in both groups. Renal function abnormalities, defined as Cr elevation > 20% from baseline or eGFR decline > 20%, occurred in 2 patients (3.33%) in the TMF group and 3 patients (5.00%) in the combination group, all of which were transient and resolved without intervention. No cases of proximal tubulopathy, Fanconi syndrome, or significant bone density changes were observed. No deaths or HCC occurrences were recorded during the 48-week follow-up.

Discussion

This propensity score-matched cohort study provides comprehensive comparative data on two clinically relevant strategies—sequential TMF monotherapy versus ETV plus TMF combination therapy—for managing LLV in ETV-treated CHB patients. Our findings reveal a trade-off between virological efficacy and renal safety: combination therapy achieved superior virological response and greater improvement in hepatic fibrosis, while sequential TMF monotherapy offered better preservation of renal function. Both regimens were associated with mild TC elevation, highlighting the need for metabolic monitoring during long-term follow-up.

Virological efficacy

The significantly higher HBV DNA undetectable rate in the combination group (86.67% vs. 63.33%) underscores the advantage of dual-mechanism viral suppression. ETV inhibits HBV reverse transcriptase and blocks negative-strand DNA synthesis, whereas TMF, as a tenofovir prodrug, is hydrolyzed intracellularly to tenofovir diphosphate, which competitively inhibits HBV DNA polymerase and terminates DNA chain elongation [18]. The complementary mechanisms likely provide more complete suppression of viral replication, particularly in patients with pre-existing low-level resistance or quasispecies variants. Our findings align with Kong et al., who reported superior virological response with combination therapy in LLV patients [16]. The higher HBeAg seroconversion rate in the combination group (58.33% vs. 36.67%) suggests that more profound viral suppression may facilitate immune-mediated clearance of infected hepatocytes.

Liver fibrosis regression

The greater reduction in LSM observed in the combination group (from 8.35 to 6.58 kPa) compared with the TMF group (from 8.41 to 7.48 kPa) represents a clinically meaningful difference. Each 1-kPa reduction in LSM corresponds to decreased risk of hepatic decompensation and HCC [19]. The association between sustained virological suppression and fibrosis regression is well-established; our data extend this concept by demonstrating that achieving complete viral suppression through combination therapy may accelerate fibrosis reversal. Wu et al. recently demonstrated that modified regimens achieving complete virological response in LLV patients were associated with better long-term outcomes [20].

Renal safety considerations

The differential renal effects observed—preserved eGFR in the TMF group versus modest eGFR decline in the combination group—warrant careful consideration. TMF's enhanced hepatic targeting and reduced systemic tenofovir exposure theoretically minimize renal tubular toxicity [11]. However, ETV is primarily excreted renally, and concurrent administration may increase cumulative renal burden. Ma et al. reported that ETV-treated patients exhibited greater eGFR decline compared with TAF-treated patients over 48 weeks [21]. Our findings suggest that in patients with baseline renal impairment or additional risk factors (e.g., diabetes, hypertension), sequential TMF monotherapy may represent a safer long-term strategy.

Lipid metabolic effects

The modest but significant TC elevations observed in both groups (approximately 0.38–0.39 mmol/L increase) are consistent with emerging evidence regarding tenofovir prodrugs and lipid metabolism. TMF, like TAF, lacks the lipid-lowering effect characteristic of TDF [14]. The underlying mechanism may involve differential modulation of hepatic lipid transporters or scavenger receptors. Shin et al. demonstrated that TAF was associated with TC increases of approximately 2.88 mg/dL/year, whereas TDF exhibited TC-lowering effects [13]. Our TC elevation magnitude is comparable to previous TMF reports [11]. Importantly, TC/HDL-C ratio, a cardiovascular risk predictor, remained stable in both groups,

suggesting that the clinical significance of isolated TC elevation may be modest. However, for patients with pre-existing dyslipidemia or high cardiovascular risk, lipid monitoring and appropriate intervention are warranted.

Safety profile

Both regimens demonstrated favorable safety profiles with comparable adverse event rates (approximately 19–20%) and no serious adverse events. The absence of proximal tubulopathy or Fanconi syndrome confirms TMF's improved renal safety relative to TDF. Gastrointestinal symptoms were mild and transient, consistent with previous reports [22].

Clinical implications and personalized approach

Our findings support a personalized approach to LLV management. For patients without renal risk factors, combination therapy offers superior virological and fibrosis-related benefits. For patients with baseline renal impairment, diabetes, hypertension, or concomitant nephrotoxic medications, sequential TMF monotherapy may provide adequate virological response while preserving renal function. Regular monitoring of lipid profiles and cardiovascular risk assessment should be incorporated into long-term follow-up for all patients receiving TMF-containing regimens.

Limitations

Several limitations should be acknowledged. First, the retrospective design introduces potential selection bias despite rigorous PSM adjustment. Unmeasured confounders (e.g., dietary habits, physical activity, genetic polymorphisms) may influence outcomes. Second, the 48-week follow-up period is relatively short for assessing long-term outcomes such as HCC incidence, cardiovascular events, or progressive renal impairment. Third, the single-center nature may limit generalizability to other populations with different ethnic compositions or healthcare settings. Fourth, we did not assess novel biomarkers such as HBV RNA or hepatitis B core-related antigen, which may provide additional prognostic information [20]. Fifth, the sample size, while adequate for primary outcomes, may be insufficient for subgroup analyses or rare adverse event detection. Finally, cost-effectiveness analysis was not performed but is relevant for treatment selection in resource-limited settings.

Future directions

Prospective multicenter studies with extended follow-up (≥ 96 weeks) are needed to confirm our findings and evaluate long-term hard outcomes. Investigation of optimal treatment duration (e.g., whether combination therapy can be de-escalated after sustained virological response) would inform clinical practice. The role of novel biomarkers in guiding treatment decisions in LLV patients merits exploration. Additionally, head-to-head comparisons between TMF and TAF in the LLV population would clarify whether observed differences represent class effects or molecule-specific properties.

Conclusions

In CHB patients with LLV after ETV therapy, ETV plus TMF combination therapy achieves superior virological response and greater hepatic fibrosis regression compared with switching to TMF monotherapy. However, sequential TMF monotherapy offers better renal preservation. Both regimens are associated with mild TC elevation, necessitating regular lipid monitoring during long-term follow-up. These findings support individualized treatment selection based on patient characteristics, particularly renal function and cardiovascular risk profile.

Abbreviations

ALT
Alanine aminotransferase
AST
Aspartate aminotransferase
BMI
Body mass index
CHB
Chronic hepatitis B
Cr
Creatinine
eGFR
Estimated glomerular filtration rate
ETV
Entecavir
HBeAg
Hepatitis B e antigen
HBV
Hepatitis B virus
HCC
Hepatocellular carcinoma
HDL-C
High-density lipoprotein cholesterol
LDL-C
Low-density lipoprotein cholesterol
LLV
Low-level viremia
LSM
Liver stiffness measurement
NAs
Nucleos(t)ide analogues
PSM

Propensity score matching
TAF
Tenofovir alafenamide
TC
Total cholesterol
TDF
Tenofovir disoproxil fumarate
TG
Triglycerides
TMF
Tenofovir amibufenamide.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The Third People's Hospital of Yunnan Province. The requirement for informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Zhengdeng Li and Sheng Zheng conceived and designed the study. Zhengdeng Li, Xue Su, and Yanfang Wei collected the clinical data. Zhengdeng Li and Xue Su performed the statistical analyses. Zhengdeng Li drafted the manuscript. Sheng Zheng critically revised the manuscript for important intellectual

content. All authors read and approved the final manuscript. Sheng Zheng is responsible for the overall content as guarantor.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to patient privacy protection but are available from the corresponding author on reasonable request and with approval from the hospital ethics committee.

References

1. Global Burden of Disease Collaborative Network. Global, regional, and national burden of hepatitis B, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Gastroenterol Hepatol. 2024;9(5):415–32.
2. European Association for the Study of the Liver. EASL 2024 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2024;81(4):678–721.
3. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560–99.
4. Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases, Chinese Medical Association. Guidelines for the prevention and treatment of chronic hepatitis B (2022 version). Zhonghua Gan Zang Bing Za Zhi. 2022;30(12):1309–31.
5. Zhang Q, Cai DC, Hu P, Ren H. Low-level viremia in nucleoside analog-treated chronic hepatitis B patients. Chin Med J (Engl). 2021;134(23):2810–7.
6. Li ZB, Chen DD, Jia YF, Wang YJ, Zhang L, Liu XE, et al. Risk factors related to low-level viraemia in chronic hepatitis B patients receiving entecavir treatment. Front Cell Infect Microbiol. 2024;14:1413589.
7. Kim JH, Sinn DH, Kang W, Gwak GY, Paik YH, Choi MS, et al. Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment. Hepatology. 2017;66(2):335–43.
8. Tamaki N, Huang DQ, Lee HW, Yasui Y, Kurosaki M, Izumi N, et al. Head-to-head comparison of long-term HCC risk of antivirals-treated versus untreated low-level viremia in HBV-compensated cirrhosis. J Gastroenterol Hepatol. 2025;40(6):1595–601.

9. Wang B, Liu Y, Zhang X. Unveiling low level viremia in chronic hepatitis B: challenges and new horizons. Front Cell Infect Microbiol. 2025;15:1568234.
10. Liu Z, Jin Q, Zhang Y, Gong L, He X, Zhang D, et al. 96-Week treatment of tenofovir amibufenamide and tenofovir disoproxil fumarate in chronic hepatitis B patients. J Clin Transl Hepatol. 2023;11(3):649–60.
11. Peng WT, Jiang C, Yang FL, Wang XF, Liang XH, Zhou Y, et al. Tenofovir amibufenamide vs tenofovir alafenamide for treating chronic hepatitis B: A real-world study. World J Gastroenterol. 2023;29(44):5907–18.
12. Tong K, Chen M, Wang D, Dai H, Peng J, Zhang J, et al. Effects of first-line nucleot(s)ide analogues on lipid profiles in patients with chronic hepatitis B: a network meta-analysis. Eur J Clin Pharmacol. 2024;80(3):335–54.
13. Shin H, Lim GS, Yoon JW, Ko Y, Park Y, Park J, et al. Metabolic effects and cardiovascular disease risks of antiviral treatments in patients with chronic hepatitis B. J Med Virol. 2024;96(7):e29760.
14. Lin S, Huang W, Liao Z, Ma H, Wu W, Lin M, et al. Comparison of lipid profile alterations in chronic hepatitis B patients receiving tenofovir alafenamide or tenofovir disoproxil fumarate. Sci Rep. 2024;14(1):27369.
15. Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases, Chinese Medical Association. Guidelines for the prevention and treatment of chronic hepatitis B (2022 version). Zhonghua Gan Zang Bing Za Zhi. 2023;31(1):3–28.
16. Kong LX, Chen XF, Xu Y, Zhang L, Wang H, Liu Y, et al. Sequential or combined rescue antiviral therapy by tenofovir amibufenamide in entecavir-treated chronic hepatitis B patients with low-level viremia. J Pract Hepatol. 2025;28(3):334–7.
17. Wang L, Chen Y, Zhang H, Liu J, Zhao X, Li M, et al. Adding pegylated interferon-α to nucleos(t)ide analogs improves HBsAg clearance in chronic hepatitis B with low-level viremia. Front Med (Lausanne). 2025;12:1642961.
18. Huang YJ, Lee SW, Tung CF, Hsieh YY, Chang KC, Chen MJ, et al. HBV relapse after discontinuation of tenofovir alafenamide or entecavir in non-cirrhotic hepatitis B e antigen-negative patients. Dig Dis. 2025;43(3):336–44.
19. Wu S, Kong Y, Piao H, Jiang W, Xie W, Chen Y, et al. On-treatment changes of liver stiffness at week 26 could predict 2-year clinical outcomes in HBV-related compensated cirrhosis. Liver Int. 2018;38(6):1045–54.
20. Wu Y, Zhang L, Chen X, Wang J, Li H, Liu Y, et al. Serum hepatitis B virus RNA in low-level viremia of chronic hepatitis B: clinical features and association with virological response. Virol J. 2025;22(1):132.
21. Ma SP, Yu YQ, Zou XP, Chen L, Wang H, Zhang Y, et al. Changes in renal function in chronic hepatitis B patients treated initially with entecavir versus tenofovir alafenamide fumarate and related influencing factors. J Clin Hepatol. 2025;41(1):44–51.

22. Li L, Zhou J, Li Y, Wang F, Zhang D, Wang M, et al. Effectiveness and safety of tenofovir amibufenamide and its comparison with tenofovir alafenamide in patients with chronic hepatitis B: results from a retrospective real-world study. Front Pharmacol. 2023;14:1165990.
23. Li W, Huang R, Wang J, Zhang B, Wang Q, Feng J, et al. Development and validation of a new predictive model for the immune tolerance stage of chronic HBV infection based on the liver histopathological changes. BMC Gastroenterol. 2025;25(1):408.
24. Zhou YH, Cai N, Chen YX, Su YL, Hu P. Metabolic effects and cardiovascular disease risks of TDF or TAF in patients with chronic hepatitis B: a systematic review and meta-analysis. Front Pharmacol. 2025;16:1604972.
25. Meng LY, Yang CT, Bao JF, Huang JS. Effectiveness and safety of tenofovir amibufenamide in chronic hepatitis B patients. World J Gastroenterol. 2024;30(26):3261–3.