Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Efficacy and Cost-Effectiveness Analyses of Entecavir versus Tenofovir Amibufenamide in Patients with Chronic Hepatitis B

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Purpose: To evaluate the efficacy and cost-effectiveness of entecavir (ETV) versus tenofovir amibufenamide (TMF) in patients with chronic hepatitis B.

Patients and methods: In this retrospective study, patients diagnosed with chronic hepatitis B between January 2022 and June 2024 were screened. Those receiving ETV as first-line therapy were 1:1 propensity score-matched to TMF recipients. The primary endpoint was HBV-DNA negativity conversion at week 48.

Results: Of 50,645 screened patients, 182 met eligibility criteria (TMF, n=91 [48 HBeAg-positive, 43 HBeAg-negative]; ETV, n=91 [36 HBeAg-positive, 55 HBeAg-negative]). HBeAg status was balanced between groups (P = 0.074). At week 48, HBV-DNA negativity was 54.95% for TMF and 76.92% for ETV (P = 0.002; OR 95% CI, 0.193–0.693). Among HBeAg-negative patients, ETV achieved significantly higher negativity at week 24 (P = 0.028) and week 48 (P = 0.041); subgroup findings are exploratory. Treatment costs over 48 weeks were $14060.62 for TMF and $13334.70 for ETV, largely due to national health insurance coverage of ETV. The ICER of TMF versus ETV was -36.28, indicating ETV is more cost-effective. The substantial cost difference is primarily attributable to ETV being covered by national health insurance. Adverse event rates were comparable between the two drugs, indicating similar safety profiles.

Conclusion: ETV showed better virologic response and lower drug-related costs than TMF in this single-center retrospective study, especially in HBeAg-negative patients. Further validation in multicenter prospective studies is needed.

Plain Language Summary: Question: Comparative efficacy of entecavir (ETV) versus tenofovir amibufenamide (TMF) and their cost-effectiveness in antiviral therapy for patients with chronic hepatitis B (CHB): which treatment regimen is more advantageous in terms of clinical outcomes and economic value?

Findings: In this retrospective cohort study that includes 182 patients with CHB, ETV demonstrated significant advantages in terms of both efficacy and cost-effectiveness compared to TMF, with better clinical outcomes and higher economic value.

Meaning: These results suggest that ETV may be considered a potentially preferred antiviral regimen for patients with CHB; however, findings should be interpreted cautiously due to the retrospective design and limited sample size.

Ethical approval: This study has been formally approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, ensuring that the study design, implementation process, and data handling all comply with medical ethical standards and relevant laws and regulations. In addition, this study has been registered in the platform of China Clinical Trial Registry Center, registration number: ChiCTR2500097387.

https://doi.org/10.2147/DDDT.S553277
Received: 12 July 2025
Accepted: 18 November 2025
Published: 8 January 2026

Keywords: hepatitis B, tenofovir amibufenamide, entecavir, efficacy, cost-effectiveness evaluation

Introduction

Hepatitis B virus (HBV) infection affects over 250 million people worldwide and accounted for more than one million deaths in 2022, largely as a result of cirrhosis and hepatocellular carcinoma (HCC).[1] The burden is particularly heavy in the Asia-Pacific region, with an estimated 80 million people infected in China alone, accounting for a substantial proportion of global cases.[2] HBV also poses a significant public health challenge in sub-Saharan Africa, the Middle East, and parts of Eastern Europe, highlighting the worldwide relevance of effective prevention and management strategies.[3] Long-term antiviral therapy is essential to suppress viral replication, reduce hepatic inflammation, and prevent disease progression.[4] First-line nucleoside analogs, including entecavir (ETV) and tenofovir-based regimens, demonstrate potent antiviral efficacy and favorable safety profiles.[5]

Tenofovir amibufenamide (TMF) is a novel tenofovir prodrug with improved plasma stability and enhanced delivery efficiency, resulting in lower systemic tenofovir exposure and reduced renal and bone toxicity compared with tenofovir disoproxil fumarate (TDF).[6] While TDF and tenofovir alafenamide (TAF) are widely used, real-world data on TMF's efficacy and cost-effectiveness are limited.

Previous pharmacoeconomic studies of nucleoside analogs generally report comparable efficacy, but cost-effectiveness outcomes vary, and most analyses are model-based or limited to drug acquisition costs, neglecting outpatient visits, laboratory monitoring, and adverse event management.[7–9] Amid recent healthcare policy reforms and drug pricing adjustments in China, a timely pharmacoeconomic evaluation is particularly urgent.

This retrospective cohort study was designed to test the hypothesis that, as a well-established long-term therapy, ETV may provide comparable or superior antiviral efficacy and safety, with a favorable cost-effectiveness profile, relative to TMF in patients with CHB.

Methods

Study Design

This retrospective cohort study was approved by the Institutional Review Board of the First Affiliated Hospital of Wenzhou Medical University, Zhejiang, China (Approval No. KY2024-R193; approved on August 20, 2024). The requirement for informed consent was waived, as the exposures analyzed were part of routine clinical practice. Data were collected from January 2022 to June 2024, encompassing 50,645 patients with CHB who received either ETV or TMF at the hospital during this period. Retrospective analysis commenced in mid-2024, once sufficient clinical and economic data had been accrued and adequate follow-up had been achieved to permit a meaningful comparison between ETV and TMF. Data access and analyses were conducted only after obtaining ethical approval. The study was performed in accordance with the ethical principles outlined in the Declaration of Helsinki and adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Although this investigation is a retrospective observational study rather than an interventional clinical trial, it was retrospectively registered with the Chinese Clinical Trial Registry (ChiCTR2500097387) on February 18, 2025, prior to data analysis.

Inclusion criteria were patients aged 18 years and older, meeting the CHB diagnostic criteria from the Chinese Society of Hepatology and the Chinese Society of Infectious Diseases Guidelines for the Prevention and Control of CHB (2022 edition), HBeAg-positive or negative and HBV-DNA-positive, first-time use of nucleoside analogs, having completed 48 weeks of treatment with TMF or ETV and having complete clinical data records. The Exclusion criteria were patients with concomitant HIV, hepatitis C, or tuberculosis infection, concomitant tumors, and women who were pregnant or breastfeeding.

Eligible patients were matched using propensity score matching (PSM) to reduce confounding. The variables used for matching included age, sex, baseline HBV-DNA level, HBeAg status, ALT level, AST level, total bilirubin level, and albumin level. Matching was performed using 1:1 nearest neighbor matching without replacement with a caliper of 0.2 standard deviations.

Exposures

Patients received ETV (entecavir, 0.5 mg×21 tablets per pack) at a dose of 0.5 mg/day for 48 weeks.

Patients received TMF (tenofovir amibufenamide, 25 mg×30 tablets per pack) at a dose of 25 mg/day for 48 weeks.

Data Collection

Before and after 12, 24, and 48 weeks of treatment, liver function (ALT and AST were measured by continuous monitoring method (Beckman Coulter) and values ranging from 3 to 40 U/L were classified as negative; total bilirubin was measured by the diazo method (Beckman Coulter) and values < 20 μmol/L were considered normal; albumin was measured by the bromocresol green dye-binding method (Beckman Coulter) and values ranging from 40 to 55 g/L were considered normal; liver transient elastography was measured by FibroScan Pro (Echosens) and values < 7.3 kPa were considered normal), fasting blood glucose (fasting blood glucose was measured by the hexokinase method (Beckman Coulter) and values ranging from 3.9 to 6.1 mmol/L were considered normal) and HBV-DNA (HBV-DNA was measured by real-time PCR (Roche COBAS) and values < 20 IU/mL were classified as negative) were assessed in the patients and collected.

Treatment efficacy evaluation: the primary endpoint was the conversion rate to HBV-DNA negativity at week 48. The secondary endpoints were HBV-DNA negativity conversion rate and ALT normalization rate at week 12 and 24.

Safety evaluation: an adverse event (AE) was defined as any untoward medical occurrence and abnormal laboratory testing values in patients receiving ETV or TMF, regardless of causal relationship to treatment.[10] AEs were collected at each visit via patient self-reporting and investigator inquiry and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, ranging from mild (Grade 1; eg, nausea, headache) to severe (Grade 3–5; eg, anaphylactic shock).

Cost: in this pharmacoeconomic analysis, the following direct medical costs were considered: (1) drug acquisition costs for ETV and TMF; (2) outpatient registration fees; (3) laboratory testing fees required for routine monitoring; and (4) costs associated with the diagnosis and management of drug-related adverse events. These cost components were selected to provide a comprehensive evaluation of the economic impact of antiviral therapy from a healthcare system perspective. Indirect costs, such as productivity loss, transportation, or other non-medical expenses, were excluded because they were beyond the scope of the present study, and relevant data were unavailable. All drug-related costs were obtained from hospital procurement records. To ensure consistency in the economic analysis, all prices were standardized to the same reference year. The median exchange rate for 2023–2024 (7.073 Chinese yuan [¥] per US dollar [$]) was applied to convert all costs into US dollars. The exchange rate data were obtained from the China Foreign Exchange Trade System (CFETS, https://www.chinamoney.com.cn/chinese/forsddshis/index.html?dataType=3).

All costs reported in the analysis were adjusted to this price year to allow for direct comparison between treatments.

Cost-effectiveness evaluation: the objective was to identify the treatment regimen that achieves the optimal balance between efficacy and cost. In this study, effectiveness was defined as the proportion of responders with HBV-DNA negativity at week 48. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in the mean drug costs between two groups divided by the absolute difference in the week-48 HBV-DNA negativity rate, ie, the cost per additional responder achieving HBV-DNA negativity. In addition, the cost per additional responder achieving HBV-DNA negativity (C/E) was determined for each treatment group as a supplementary measure. This approach is consistent with standard pharmacoeconomic methodology and provides a more interpretable assessment of cost-effectiveness.

Sensitivity analysis: to assess the robustness of the cost-effectiveness results, one-way sensitivity analyses were performed on key cost parameters. Specifically, the impact of a 10% reduction in drug prices and a 10% decrease in the USD-to-local currency exchange rate was evaluated. These analyses allowed us to determine how fluctuations in medication costs and currency conversion could influence total direct medical costs and the ICER.

Subgroup analysis: a post hoc exploratory subgroup analysis was conducted according to HBeAg status. Patients were categorized as HBeAg-positive or HBeAg-negative, and the rates of HBV-DNA negativity conversion at week 12, 24, and 48 were compared between the TMF and ETV groups.

Statistical analysis: the statistical processing of all data and matching analysis was conducted using SPSS version 25.0. For measurement data, t-tests were conducted and the results are presented as mean ± standard deviation. Chi-

square tests were applied for count data, with the outcomes expressed as percentages (%). A P-value less than 0.05 was considered to indicate a statistically significant difference.

Results

Baseline Characteristics

After applying the inclusion/exclusion criteria and PSM, 182 patients were included in the final analysis from an initially screened cohort of 50,645 individuals (Figure 1). Among them, 91 patients received TMF and 91 received ETV. The two treatment groups were comparable in terms of demographic and clinical characteristics, including age, sex distribution, HBV-DNA level, total bilirubin level, albumin level, and aspartate transaminase levels (all P>0.05), indicating that the baseline characteristics were well balanced between groups and potential confounding was minimized. The baseline characteristics of both treatment groups before and after PSM are summarized below. The matching process effectively balanced key covariates, further ensuring the comparability of the two cohorts for subsequent outcome analyses (Table 1).

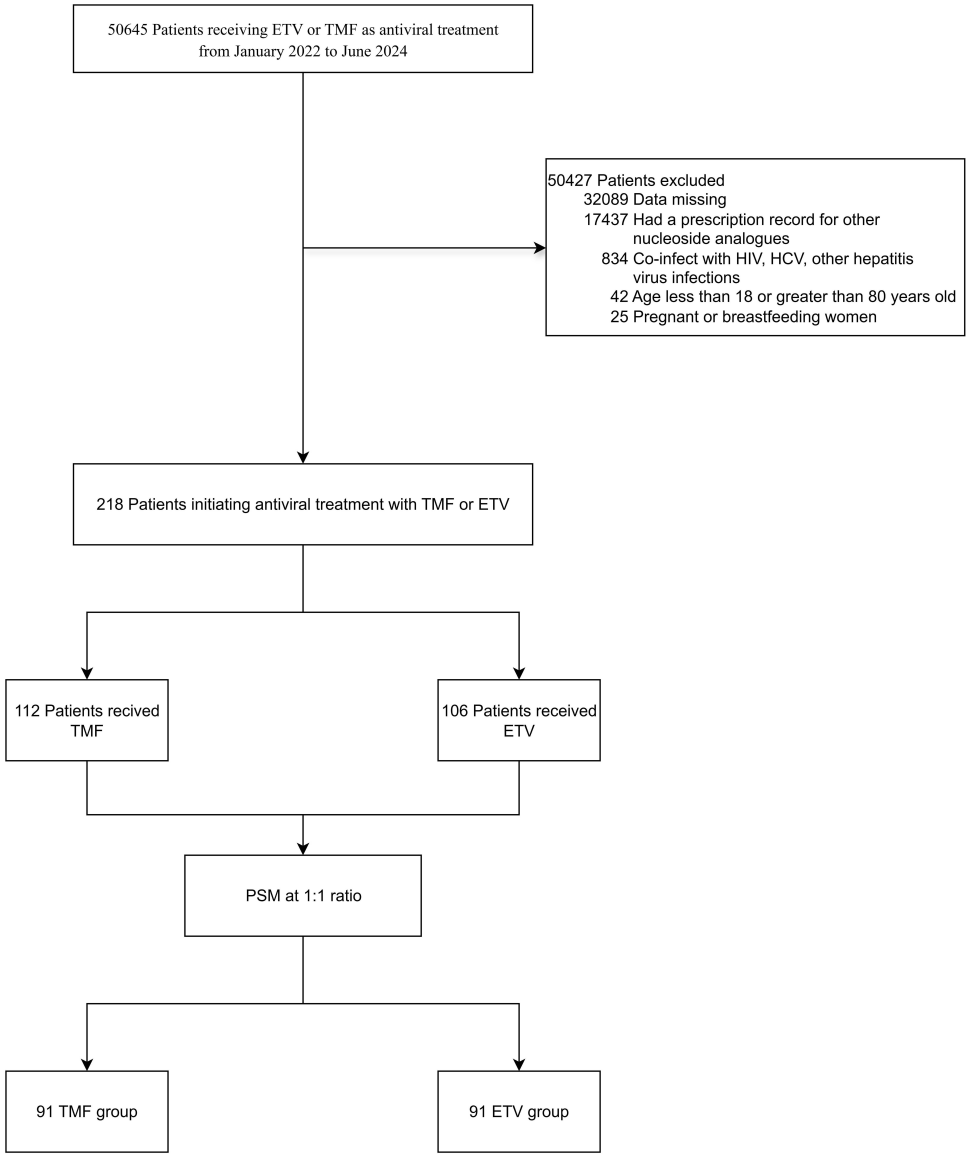

Figure 1 Flowchart of patient selection, showing the number of patients screened, excluded, and included in the final analysis.

Table 1 Baseline Characteristics of Patients Before and After Propensity Score Matching, Showing Balanced Demographic and Clinical Variables Between Groups

Characteristics	Unmatched Cohort				Matched Cohort			
	Patients, No. (%)				Patients, No. (%)			
	TMF (112)	ETV (106)	SMD	P-value	TMF (91)	ETV (91)	SMD	P-value
Age, mean (SD), years	42.08(13.38)	41.48(12.99)	0.078	0.638	42.36(9.42)	43.98(9.76)	0.17	0.257
Sex								
Male	82	62			63	52		
Female	30	44		0.333	28	39		0.091
HBV-DNA, median (IQR), IU/mL [a]	1300 (66,500–2,000,000)	1700 (20,500–10,500,000)	0.178	0.147	38,000 (1000–780,000)	7300 (1300–470,000)	0.083	0.572
ALT, mean (SD), U/L	127.16(282.65)	104.08(291.7)	0.098	0.413	59.08(41.30)	60.40(59.89)	0.026	0.281
AST, mean (SD), U/L	81.95(140.05)	62.03(148.3)	0.183	0.132	48.56(42.41)	50.87(77.70)	0.037	0.078
TBIL, mean (SD), mg/dL	14.16(32.37)	17.55(33.36)	0.138	0.292	14.97(5.08)	15.68(8.59)	0.101	0.642
ALB, mean (SD), g/L	44.16(5.08)	44.19(4.80)	0.011	0.955	44.36(3.31)	44.46(3.02)	0.032	0.674
Liver fibrosis								
F0-F1	9(8.04)	10(9.43)		0.714	7(7.69)	8(8.79)		>0.99
F2	6(5.36)	4(3.57)		0.814	5(5.49)	4(4.40)		>0.99
F3	2(1.79)	1(0.94)		>0.99	1(1.10)	0(0)		NA
F4	5(4.46)	6(5.66)		0.687	2(2.20)	3(3.30)		>0.99
Hypertension	8(7.14)	5(4.72)		0.450	4(4.40)	2(2.20)		0.678
Diabetes	4(3.57)	1(0.94)		0.430	2(2.20)	0(0)		NA

Notes: Liver fibrosis is classified according to the METAVIR scoring system; data are presented as n (%). [a], HBV-DNA measurements are reported as median with interquartile range (IQR) due to non-normal distribution.
Abbreviations: HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; ALB, albumin; SMD, standardized mean difference.

Treatment Efficacy Evaluation

Primary Endpoint

At week 48, the HBV-DNA negativity rate increased in both treatment groups, reaching 54.95% (50/91) in the TMF group and 76.92% (70/91) in the ETV group. This difference remained statistically significant (P = 0.002; OR 95% CI, 0.193–0.693; Table 2), indicating a more favorable virological response with ETV.

Secondary Endpoint

During the first 24 weeks of treatment, ETV consistently achieved higher rates of both virological and biochemical responses compared with TMF. At week 12, HBV-DNA negativity was observed in 32.97% (30/91) of TMF-treated and 47.25% (43/91) of ETV-treated patients (P = 0.049; OR 95% CI, 0.301–1.001; Table 2), increasing to 40.66% and 60.44% by week 24 (P = 0.008; OR 95% CI, 0.248–0.811). Similarly, ALT normalization was achieved in 49.45% (45/91) of TMF-treated and 71.43% (43/91) of ETV-treated patients at week 12 (P = 0.002; OR 95% CI, 0.212–0.722; Table 3), rising to 60.44% and 75.82% by week 24 (P = 0.026; OR 95% CI, 0.257–0.922), remained significantly higher in the ETV group at week 48 (P = 0.021; OR 95% CI, 0.209–0.890). These findings indicate that ETV provides superior virological and biochemical responses compared with TMF during the early phase of therapy.

Table 2 HBV-DNA Negativity Conversion Rates in TMF and ETV Groups at week 12, 24, and 48, Showing Higher Virological Response in the ETV Group

HBV-DNA Negativity Conversion Rate (%)	TMF (n=91)	ETV (n=91)	χ^2	P-value	OR	OR (95% CI)
12 Weeks of Treatment	32.97(30)	47.25(43)	3.866	0.049	0.549	0.301–1.001
24 Weeks of Treatment	40.66(37)	60.44(55)	7.122	0.008	0.448	0.248–0.811
48 Weeks of Treatment	54.95(50)	76.92(70)	9.785	0.002	0.366	0.193–0.693

Notes: OR>1 indicates a higher likelihood of HBV-DNA negativity conversion in the TMF group compared with the ETV group.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

https://doi.org/10.2147/DDDT.S553277

Table 3 ALT Normalization Rates in TMF and ETV Groups at week 12, 24, and 48, Showing Higher Normalization Rates in the ETV Group

ALT Normalization Rate (%)	TMF (n=91)	ETV (n=91)	χ^2	P-value	OR	OR (95% CI)
12 Weeks of Treatment	49.45(45)	71.43(65)	9.192	0.002	0.391	0.212–0.722
24 Weeks of Treatment	60.44(55)	75.82(69)	4.960	0.026	0.487	0.257–0.922
48 Weeks of Treatment	70.33(64)	84.62(77)	5.321	0.021	0.431	0.209–0.890

Notes: OR>1 indicates a higher likelihood of ALT normalization in the TMF group compared with the ETV group.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

Cost

The examination-related expenditures incurred by patients included costs for abdominal ultrasonography ($9.19 per session), quantitative hepatitis B serological assays ($10.60), hepatitis B DNA quantification ($9.19), and hepatic function evaluations ($4.38), all of which were performed during the treatment period. The unit cost of examinations per patient per visit was $33.37. As both the TMF and ETV groups underwent four examinations over the course of treatment, the total examination expenditure amounted to $12146.70 per patient in each group (Table 4).

Safety Evaluation

The most common adverse events in the TMF group were gastrointestinal disorders, hyperlipidemia, hyperthyroidism, and reduced bone density,[11] whereas in the ETV group, they primarily included gastrointestinal disorders, abdominal pain, and fatigue.[12] Importantly, no severe adverse events leading to treatment discontinuation were observed in either group. Overall, the incidence of adverse events was low, and most events gradually resolved or completely disappeared during the course of treatment. These findings indicate that both TMF and ETV are generally well-tolerated, with no statistically significant difference in the incidence of adverse events between the two groups (Tables 5 and 6).

Cost-Effectiveness Evaluation

Patients received ETV (0.5 mg per tablet, 21 tablets per pack) at 0.5 mg/day for 48 weeks. A total of 16 packs were required, at a unit price of $0.5 per pack, resulting in a total 48-week cost of $7.9 per patient. Patients received TMF (25 mg per tablet, 30 tablets per pack) at 25 mg/day for 48 weeks, with a total 48-week cost of $721.9 per patient based on the per-tablet price. Prices were obtained from the hospital electronic medical record system (2024).

The HBV-DNA negativity conversion rate at week 48 was used as the indicator of treatment effectiveness. Responders were defined as patients who achieved HBV-DNA negativity at week 48. The average cost per patient was $154.51 in the TMF group and $146.54 in the ETV group. The ICER was calculated as the difference in cost per patient between the two treatment groups divided by the absolute difference in the proportion of responders. The results showed that the ICER for TMF versus ETV was -$36.28 per additional responder, indicating that ETV treatment was more cost-effective compared with TMF (Table 7).

Sensitivity Analysis

The sensitivity analysis results show that when drug prices are reduced by 10%, the cost-effectiveness analysis results remain largely consistent with the original findings. The cost-effectiveness ratio (C/E) for the ETV treatment remains lower than that for the TMF treatment, indicating that despite the price reduction, the ETV group maintains a significant

Table 4 Components of Direct Medical Costs (USD) for Each Treatment Group, Including Drug Costs, Registration Fees, Laboratory Examination Fees, and Costs for Managing Adverse Events

Group	Drug Cost	Registration Fee	Laboratory Testing Fee	Cost for Managing Adverse Events	Total Cost
TMF Group	721.9	995.92	12,146.70	196.1	14,060.62
ETV Group	7.9	1003.1	12,146.70	177	13,334.70

Notes: All costs are expressed in US dollars (USD). The median exchange rate during 2023–2024 (7.073 Chinese yuan [¥] per USD [$]) was used for conversion.

Table 5 Adverse Events Before PSM: Type and Frequency in the ETV and TMF Treatment Groups

Adverse Events	TMF (n=112)	ETV (n=106)	χ^2	P-value	OR	OR (95% CI)
Gastrointestinal	5(4.5)	8(7.5)	0.923	0.337	0.572	0.180–1.809
Disorders Vertigo	0(0)	5(4.7)	NA	NA	NA	NA
Fatigue	2(1.8)	5(4.7)	0.710	0.399	0.367	0.070–1.935
Hyperlipidemia	5(4.5)	1(0.9)	1.378	0.240	4.907	0.564–42.709
Hypophosphatemia	4(3.6)	1(0.9)	0.711	0.399	3.889	0.428–35.369
Hyperthyroidism	6(5.4)	2(1.9)	1.003	0.316	2.943	0.581–14.918
Bone density reduction	3(2.7)	0(0)	NA	NA	NA	NA
Grade 1–2 (mild-moderate)	25(22.3)	22(20.8)	0.079	0.779	1.097	0.575–2.095
Grade 3–4 (severe)	0(0)	0(0)	NA	NA	NA	NA
Total	25(22.3)	22(20.8)	0.079	0.779	1.097	0.575–2.095

Notes: AEs were graded according to CTCAE v5.0 (Grades 1–2: mild–moderate; Grades 3–4: severe). Both clinical symptoms and lab abnormalities were included. OR>1 indicates a higher likelihood of adverse events in the TMF group compared with the ETV group. Data are expressed as n (%). P-values were obtained using the χ^2-test or Fisher's exact test. More than one AE per patient could be counted.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

Table 6 Adverse Events After PSM: Type and Frequency in the ETV and TMF Treatment Groups

Adverse Events	TMF (n=91)	ETV (n=91)	χ^2	P-value	OR	OR (95% CI)
Gastrointestinal	4(4.4)	8(8.8)	1.427	0.232	0.477	0.138–1.644
Disorders Vertigo	0(0)	5(5.5)	NA	NA	NA	NA
Fatigue	0(0)	4(4.4)	NA	NA	NA	NA
Hyperlipidemia	3(3.3)	0(0)	NA	NA	NA	NA
Hypophosphatemia	2(2.2)	0(0)	NA	NA	NA	NA
Hyperthyroidism	6(6.6)	0(0)	NA	NA	NA	NA
Bone Density Reduction	3(3.3)	0(0)	NA	NA	NA	NA
Grade 1–2 (mild-moderate)	18(19.8)	17(18.7)	0.035	0.851	1.073	0.513–2.244
Grade 3–4 (severe)	0(0)	0(0)	NA	NA	NA	NA
Total	18(19.8)	17(18.7)	0.035	0.851	1.073	0.513–2.244

Notes: AEs were graded according to CTCAE v5.0 (Grades 1–2: mild–moderate; Grades 3–4: severe). Both clinical symptoms and lab abnormalities were included. OR>1 indicates a higher likelihood of adverse events in the TMF group compared with the ETV group. Data are expressed as n (%). P-values were obtained using the χ^2-test or Fisher's exact test. More than one AE per patient could be counted.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

Table 7 Cost-Effectiveness Analysis for TMF and ETV Treatment Groups, Including Total Costs, Effectiveness, and ICER

Group	N	Cost (USD/Patient)	Responders, n (%)	ICER
TMF Group	91	154.51	50(54.95)	
ETV Group	91	146.54	70(76.92)	-36.28

Notes: ICER was calculated as the difference in cost per patient between the two treatment groups divided by the absolute difference in the proportion of responders. A negative ICER indicates that the ETV group is more effective and less costly than the TMF group. All costs are expressed in US dollars (USD).

cost-effectiveness advantage. Similarly, when the exchange rate decreases by 10%, the ETV treatment continues to demonstrate superior cost-effectiveness compared with TMF (Tables 8 and 9).

Subgroup Analysis

To further evaluate the efficacy of the treatment regimens, patients were stratified by HBeAg status. Of the 182 patients, 84 were HBeAg-positive (48 receiving TMF and 36 receiving ETV) and 98 were HBeAg-negative (43 receiving TMF

Table 8 Sensitivity Analysis of Cost-Effectiveness with a 10% Reduction in Drug Prices, Including Changes in Total Costs, Effectiveness, and ICER

Group	N	Cost (USD/Patient)	Responder, n (%)	ICER
TMF Group	91	153.72	50(54.95)	
ETV Group	91	146.53	70(76.92)	-32.73

Notes: ICER was calculated as the difference in cost per patient between the two treatment groups divided by the absolute difference in the proportion of responders. A negative ICER indicates that the ETV group is more effective and less costly than the TMF group. All costs are expressed in US dollars (USD).

Table 9 Sensitivity Analysis of Cost-Effectiveness with a 10% Reduction in Exchange Rate, Including Changes in Total Costs, Effectiveness, and ICER

Group	N	Cost (USD/Patient)	Responder, n (%)	ICER
TMF Group	91	139.06	50(54.95)	
ETV Group	91	131.88	70(76.92)	-32.68

Notes: ICER was calculated as the difference in cost per patient between the two treatment groups divided by the absolute difference in the proportion of responders. A negative ICER indicates that the ETV group is more effective and less costly than the TMF group. All costs are expressed in US dollars (USD).

and 55 receiving ETV). Baseline characteristics were well balanced between treatment groups within each HBeAg subgroup (all P > 0.05; Table 10).

In the HBeAg-positive subgroup, HBV-DNA negativity rates did not differ significantly between TMF and ETV at week 12, 24, or 48 (all P > 0.05; Table 11), indicating comparable efficacy of the two treatments in this population.

In HBeAg-negative patients, ETV achieved higher HBV-DNA negativity rates at weeks 24 and 48, with the differences reaching statistical significance (P = 0.028 and P = 0.041; Table 11). These subgroup findings are exploratory and should be interpreted with caution, given the limited sample size and retrospective study design.

Table 10 Baseline Characteristics of HBeAg-Positive and HBeAg-Negative Patients, Including Gender, Age, AST, TBIL, Albumin, and HBV-DNA Levels

Characteristics	HBeAg-Positive Patients				HBeAg-Negative Patients			
	Patients, No. (%)				Patients, No. (%)			
	TMF (48)	ETV (36)	SMD	P-value	TMF (43)	ETV (55)	SMD	P-value
Age, mean (SD), years	38.56(9.19)	40.19(9.85)	0.171	0.453	42.36(9.42)	43.98(9.76)	0.018	0.900
Sex								
Male	30	20			33	32		
Female	18	16		0.521	10	23		0.054
HBV-DNA, median (IQR), IU/mL [a]	450000 (7150–57,750,000)	675,000 (24,500–88,250,000)	0.18	0.206	5800 (850–23,000)	3900 (1100–12,000)	0.15	0.221
ALT, mean (SD), U/L	75.75(45.52)	83.22(80.99)	0.12	0.641	51.45(34.87)	45.45(33.95)	0.18	0.705
AST, mean (SD), U/L	55.31(52.4)	69(108.31)	0.161	0.635	48.56(42.41)	50.87(77.70)	0.054	0.131
TBIL, mean (SD), mg/dL	13.98(4.62)	14.52(6.18)	0.099	0.662	14.97(5.08)	15.68(8.59)	0.036	0.185
AlB, mean (SD), g/L	43.52(3.50)	43.57(3.14)	0.015	0.94	44.36(3.31)	44.46(3.02)	0.088	0.667

Notes: Liver fibrosis is classified according to the METAVIR scoring system; data are presented as n (%). [a], HBV-DNA measurements are reported as median with interquartile range (IQR) due to non-normal distribution.

Abbreviations: HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; ALB, albumin; SMD, standardized mean difference.

Table 11 HBV-DNA Negativity Conversion Rates at week 12, 24, and 48 in HBeAg-Positive and HBeAg-Negative Patients, Including the Proportion of Patients Achieving Virological Response in Each Group

HBV-DNA Negativity Conversion Rate (%)	HBeAg-Positive Patients			HBeAg-Negative Patients		
	TMF (48)	ETV (36)	P-value	TMF (43)	ETV (55)	P-value
Treatment at 12 Weeks	4.17(2)	4.55(1)	>0.999	65.12(28)	76.36(42)	0.221
Treatment at 24 Weeks	10.42(5)	18.18(5)	0.884	74.42(32)	90.91(50)	0.028
Treatment at 48 Weeks	27.08(13)	45.45(16)	0.098	86.05(37)	98.18(54)	0.041

Discussion

CHB remains a major global health concern, particularly in resource-limited regions where access to long-term antiviral therapy poses clinical and economic challenges.[13] In this study, both TMF and ETV effectively suppressed HBV replication, but ETV achieved a significantly higher HBV-DNA negativity conversion rate after 48 weeks.

Global studies indicate that ETV demonstrates superior efficacy and lower risk of resistance compared to drugs such as TDF and TAF,[14,15] while TMF exhibits better renal safety.[16]

The superior efficacy of ETV, particularly in HBeAg-negative patients, may be explained by its high affinity for HBV polymerase and potent viral inhibition, supporting rapid and sustained viral suppression. Its low mitochondrial toxicity also improves long-term tolerability, reducing treatment interruptions.[17] These mechanisms align with real-world and Asian cohort studies reporting slightly higher virological suppression rates with ETV compared to tenofovir derivatives.[18]

HCC is the most common primary liver cancer and a leading cause of cancer-related death worldwide, often arising from CHB infection.[19,20] Both ETV and tenofovir effectively reduce HCC risk in CHB patients, with some studies suggesting a slightly lower incidence with tenofovir, particularly in Asian populations.[21] Overall, both agents provide strong viral suppression and HCC prevention, and treatment choice should be individualized.

An economic paradox emerges in that ETV, though older, remains markedly less expensive than TMF. This cost difference likely results from ETV's loss of patent protection and wide generic availability, while TMF remains under patent exclusivity. In addition, procurement systems and reimbursement negotiations differ across health systems, contributing to international price variation. Understanding these market and policy mechanisms is important when interpreting pharmacoeconomic results.

ETV-treated patients had better cost-effectiveness, even under a hypothetical reduction in TMF price. However, this finding should be interpreted with caution. Given the retrospective single-center design, potential confounding by indication and selection bias cannot be excluded. Therefore, recommending ETV as a universally preferred regimen would be premature; instead, ETV may be considered a cost-effective option under current pricing conditions pending further multicenter prospective validation.

The incidence of adverse events was low in both groups, with no statistically significant between-group difference. Nevertheless, retrospective data collection could underestimate mild-to-moderate adverse events, suggesting possible underreporting bias. All included patients demonstrated full medication adherence (100%), as confirmed through pharmacy dispensing records and clinical follow-up, which minimizes adherence-related bias and strengthens the reliability of antiviral response comparisons. However, we acknowledge that adherence monitoring based solely on prescription data may not fully capture real-time medication behavior.

From a policy standpoint, these findings have implications for cost management and reimbursement decisions. Incorporating real-world cost-effectiveness data into formulary and pricing policies may optimize healthcare resource allocation, enhance treatment affordability, and improve long-term access to antiviral therapy.

This study has several limitations. The retrospective, single-center nature introduces risks of confounding by indication, immortal time bias, and incomplete data capture. Missing data were handled through complete-case analysis, which may not fully eliminate bias. Prospective multicenter studies with standardized data collection and adherence assessment are warranted to confirm and extend these results.

Conclusion

In this single-center retrospective cohort, ETV demonstrated better virologic efficacy than TMF, particularly among HBeAg-negative patients, with higher HBV-DNA negativity rates at week 24 and 48. Both agents were generally well tolerated, with no significant differences in safety outcomes. ETV was associated with lower overall direct medical costs, suggesting potential economic advantages within the conditions studied. However, given the retrospective design and the single-center nature of this analysis, these findings should be interpreted with caution. Future multicenter prospective studies employing broader pharmacoeconomic modeling are warranted to validate these findings and inform evidence-based decision-making in the management of CHB.

Data Sharing Statement

Due to strict patient confidentiality and privacy protections required by our institutional ethics committee, the raw data generated and analyzed during this study are not publicly available. However, de-identified data may be provided by the corresponding author upon reasonable request and after approval from the ethics review board.

Ethics Approval

This study has been formally approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, ensuring that the study design, implementation process, and data handling all comply with medical ethical standards and relevant laws and regulations. In addition, this study has been registered in the platform of China Clinical Trial Registry Center, registration number: ChiCTR2500097387.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflict of interest.

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