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Comparative Effectiveness and Safety of Entecavir vs. Tenofovir in Hepatitis B: A Systematic Review

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ABSTRACT

Chronic hepatitis B (CHB) remains a critical global health issue, often progressing to hepatocellular carcinoma (HCC) and liver-related mortality. Entecavir (ETV) and tenofovir (TDF/TAF) are established first-line antiviral therapies; however, their comparative efficacy and long-term safety profiles require further evaluation to inform clinical decision-making. This systematic review aims to compare the effectiveness and extrahepatic safety of entecavir and tenofovir in managing CHB, with a focus on long-term clinical outcomes and treatment-related complications. A systematic review was conducted based on PRISMA guidelines, identifying studies published between 2020 and 2025 from PubMed and ScienceDirect. The selection included 13 peer-reviewed clinical studies that met strict inclusion criteria related to efficacy outcomes, renal and bone safety, and patient-specific prognostic indicators. Both entecavir and tenofovir demonstrated significant virological suppression and reduction in HCC risk. Tenofovir was associated with improved overall survival, particularly in patients with decompensated liver disease. However, renal impairment was more frequently reported among tenofovir users, suggesting a need for careful monitoring or consideration of alternative agents such as TAF. While both agents are effective, treatment selection should be individualized based on renal function, HCC risk, and previous therapy history. Clinicians are encouraged to balance efficacy with safety considerations to optimize patient outcomes in CHB management.

INTRODUCTION

Chronic hepatitis B infection (CHB) is a significant global health problem, causing severe liver diseases such as cirrhosis and hepatocellular carcinoma (HCC), especially in countries with high prevalence, such as Indonesia (Shen et al., 2023; Alberts et al., 2022). Studies show a high prevalence of infection in vulnerable groups, including garbage workers and the population in Nigeria, who face limited access to health (Souza-Silva et al., 2022; Awoyinka et al., 2023). Studies in India, Iran, and other countries underscore the importance of early detection and preventive measures to reduce the spread of the virus (Palewar et al., 2022; Pouri et al., 2020). Among the available antiviral therapies, entecavir (ETV), tenofovir alafenamide (TAF), and tenofovir disoproxil fumarate (TDF) are widely used due to their strong antiviral activity and high genetic resistance to resistance (Chan et al., 2024; Kumamoto et al., 2023). Recent research has attempted to compare these agents' efficacy and safety profiles to inform optimal treatment strategies.

Cao et al. (2025) conducted a systematic review and meta-analysis evaluating the efficacy and safety of ETV and TDF in patients with CHB-associated cirrhosis. The study concluded that TDF significantly reduced the cumulative incidence of HCC and overall mortality compared to ETV. At the same time, the two drugs were comparable in terms of HBV DNA clearance and hepatic encephalopathy. Notably, TDF does not significantly cause renal dysfunction and even improves the estimated glomerular filtration rate compared to ETV.

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Similarly, the efficacy of TDF and ETV in CHB patients who have never received nucleus(t)ide analogs was compared. The findings suggest that both drugs are equally effective regarding HBV DNA suppression, HBeAg clearance, and seroconversion rates at 24 and 48 weeks of therapy. In addition, no significant differences were observed in the short-term safety profiles between the two treatments (Chen et al., 2019).

However, the risk of developing antiviral resistance differs between the two drugs. In 2024, the authors conducted a systematic review and meta-analysis to estimate the risk of HBV resistance to ETV and TDF. The study found that resistance to ETV increased over time in individuals who had never received treatment, reaching 0.9% at five years. TDF showed an excellent resistance profile with no significant resistance detected during the same period (Lumley et al., 2024).

Although this review primarily focuses on comparing ETV and TDF, TAF is also included in the discussion due to its emergence as a safer alternative to TDF, particularly in terms of renal and bone safety. Several recent studies have examined its clinical relevance in the context of long-term CHB treatment.

Given the evolving landscape of antiviral therapy and the need for evidence-based treatment strategies, this review seeks to address the following research questions:

1. What are the long-term comparative outcomes of ETV and TDF in various patient populations, including those with differing levels of liver disease severity and comorbid conditions?
2. How do ETV, TDF, and TAF compare in terms of extrahepatic safety profiles, particularly concerning kidney and bone health during extended treatment durations?

Answering these questions through a systematic review of recent literature will help inform clinical decision-making and contribute to improved patient outcomes in CHB management.

RESEARCH METHODS

Systematic Literature Review (SLR) is a rigorous method for synthesizing research evidence, designed to minimize bias and provide comprehensive insights into specific research questions. In scientific inquiry, SLR is essential for evaluating existing research, identifying gaps in knowledge, and guiding future research efforts (Moher et al., 2009). This section outlines the research methods used in this systematic review, detailing the search strategy, inclusion and exclusion criteria, data extraction, and analysis process.

The systematic review methodology follows established guidelines, such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009). These guidelines emphasize the importance of a transparent and replicable approach, ensuring that reviews can be independently verified. The initial step involves defining a clear research question, a basis for selecting relevant research (O'Connor et al., 2008). Furthermore, a comprehensive search strategy was developed to identify relevant literature. This involves searching several databases using predefined keywords and Boolean operators (Bramer et al., 2018). Inclusion and exclusion criteria were then applied to filter studies based on relevance, quality, and methodological rigor.

Data extraction uses standard forms to ensure consistency and accuracy in capturing important information from each study. This data is then synthesized and analyzed, often using qualitative or quantitative methods, depending on the nature of the evidence and the research questions present (Sutton & Higgins, 2008).

This study employed a Systematic Literature Review (SLR) methodology to compare the effectiveness and safety profiles of Entecavir (ETV) and Tenofovir (TDF/TAF) in patients with chronic hepatitis B (CHB). The review process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring methodological transparency and reproducibility.

Search Strategy

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To achieve the in-depth understanding required in the context of the effectiveness and safety of the treatment of Entecavir and Tenofovir for Hepatitis B, the review criteria have been established by including appropriate selection criteria for publication. Regarding this, the databases used are Science Direct and Pubmed. This database was chosen because of its broad publication coverage and focus on the health field. In addition, and important for this study, this database includes international publishers (Journal of the Formosan Medical Association, Clinical Gastroenterology and Hepatology, BMC Infectious Diseases, International Journal of Surgery, Alimentary Pharmacology & Therapeutics, Medicine, BMC Gastroenterology, Annals of Hepatology, JHEP Reports, Liver Research, and Scientific Reports).

A comprehensive literature search was conducted across two major electronic databases: PubMed and ScienceDirect. The search was limited to articles published in English between 2020 and 2025, using the following Boolean keyword combinations:

- "tenofovir" AND "entecavir" AND "hepatitis B"

The search initially yielded 5,326 articles, which were screened for relevance and duplication using Mendeley reference manager.

Study Selection Process

Screening and selection followed four PRISMA stages: identification, screening, eligibility, and inclusion, as visualized in Figure 1 (PRISMA Diagram Flow).

After eliminating duplicates and irrelevant studies, a total of 237 articles remained for full-text assessment. Following a rigorous evaluation based on eligibility criteria, 13 studies were included in the final synthesis.

Inclusion Criteria

- Peer-reviewed clinical studies (RCTs, cohort studies, or comparative analyses)
- Focus on the efficacy or safety of ETV and/or TDF/TAF in CHB treatment
- Full-text articles available in English
- Published between 2020 and 2025

Exclusion Criteria

- Publications before 2020
- Non-English language studies
- Reviews, editorials, letters, case reports, or animal studies
- Studies lacking clear outcome data relevant to efficacy or extrahepatic safety

Data Extraction and Synthesis

A standardized data extraction form was used to collect key variables from each study, including:

- Author and year
- Study design
- Patient population
- Treatment arms
- Outcomes (virological suppression, HCC incidence, renal and bone safety)
- Follow-up duration

Due to substantial heterogeneity in study designs, populations, and outcome metrics, meta-analysis was not feasible. Thus, the findings were synthesized using a qualitative thematic approach.

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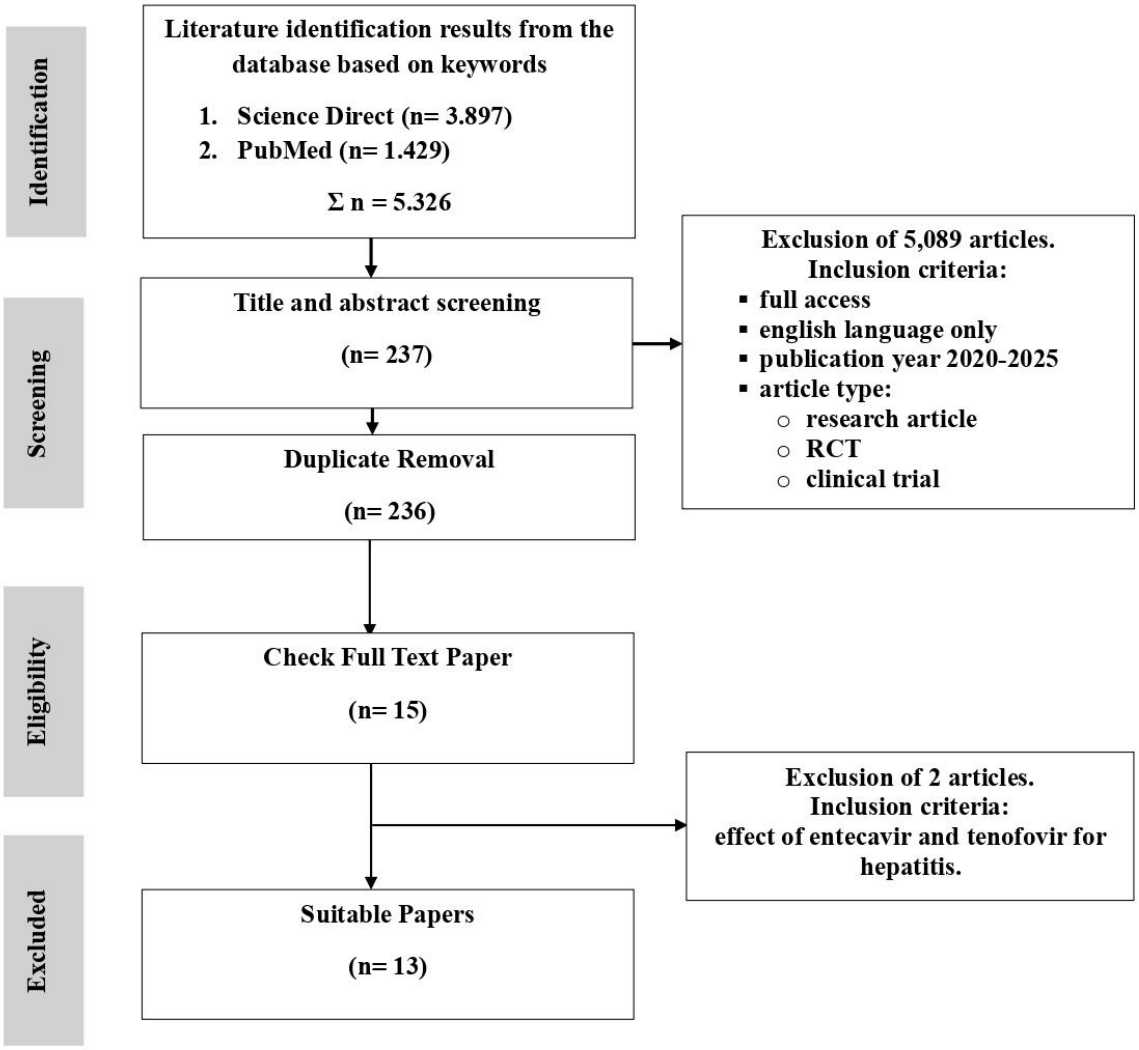

Figure 1. PRISMA Diagram Flow

RESULTS

A total of 13 studies met the predefined inclusion criteria and were analyzed. These studies included randomized controlled trials, prospective cohort studies, and multicenter observational designs involving diverse patient populations across different clinical settings. Due to methodological heterogeneity—differences in population characteristics, follow-up durations, outcome definitions, and reporting formats—a quantitative meta-analysis was not performed. Instead, findings were synthesized thematically.

The findings of several articles are presented in Table 1 below.

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Table 1. Data Extraction

No.	Author, Year of Publication	Title	Objectives	Dataset	Method	Findings
1	Pol & group, 2021	Similar 5-year HCC occurrence in Tenofovir- and Entecavir-treated HBV chronic infection in the French AFEF/ANRS CO22 Heather cohort.	Comparing the impact of TDF and ETV in Hepatitis B (HBV) patients	The ANRS CO22 Heather cohort (a nationalmulticenter observational study of hepatitis B and C patients) included 1,800 patients, with 986 receiving Tenofovir and 814 receiving Entecavir	Prospective cohort studies	The risk of liver-related events or death did not differ significantly between patients treated with tenofovir and those treated with entecavir in a large group of patients who were largely not cirrhosis patients.
2	Li et al., 2021	Short-term and long-term safety and efficacy of tenofovir alafenamide, tenofovir disoproxil fumarate, and entecavir treatment of acute-on-chronic liver failure associated with hepatitis B.	To evaluate the outcomes (safety and efficacy) of three first-line antivirals—TAF, TDF, and ETV—in treating patients with acute chronic hepatitis B virus-related liver failure (HBV-ACLF).	Forty eligible subjects, according to gender and age, were recruited and divided into three groups: the TAF group, the TDF group, and the ETV group. At week 48, 8 (80%) patients in the TAF group, 6 (60%) patients in the TDF group, and 17 (85%) patients in the ETV group survived without liver transplantation (P = 0.251).	Prospective cohort studies	By week 48, survival rates were similar among all three groups, with 80% on TAF, 60% on TDF, and 85% on ETV surviving without liver transplantation. TAF showed better total bilirubin reduction and maintained higher albumin and cholesterol levels than TDF and ETV. TDF showed poor renal safety, even in short-term treatment, while no serious drug-related adverse events were reported in all groups.
3	Suzuki et al., 2021	Switching from entecavir to tenofovir disoproxil fumarate for HBeAg-positive chronic hepatitis B patients: a phase 4, prospective study.	Evaluate the decrease in HBsAg after switching from ETV to TDF at week 48 in HBeAg-positive patients.	Seventy-five participants treated with ETV 0.5 mg once daily were switched to TDF 300 mg once daily for 96 weeks.	Multicenter Clinical Study	Efficacy and safety of switching from ETV to TDF in HBeAg-positive chronic hepatitis B patients who underwent virologic suppression. At week 48, only 4% of participants achieved a decrease in HBsAg levels of 0.25 log10, with a mean decrease of -0.14 log10 IU/mL at week 96.
4	Choi et al., 2023	Differential Relapse Patterns After Discontinuation of Entecavir vsand Tenofovir Disoproxil Fumarate in Chronic Hepatitis B	To compare recurrence patterns after discontinuation of TDF vsand ETV treatment, to assess HBsAg loss and retreatment rates after discontinuation of TDF or ETV therapy.	Included 1402 virus-suppressed CHB patients who discontinued ETV (n = 981) or TDF (n = 421) therapy between 2001 and 2020 from 13 participating centers across North America, Europe, and Asia.	Prospective cohort studies	TDF shows a higher rate of HBsAg loss than ETV, but not significant after adjustment, The virologic recurrence rate was higher in patients treated with TDF at the baseline, and the clinical recurrence rate remained higher in the TDF group during follow-up.
5	Zeng et al., 2022	Tenofovir Alafenamide for Pregnant Chinese Women with Active Chronic Hepatitis B: A Multicenter Prospective Study	Evaluate TAF therapy for pregnant women with active CHB.	One hundred three and 104 pregnant women were registered, and 102 and 104 babies were born in the TAF and TDF groups, respectively. The TAF group's mean age, gestational age, alanine aminotransferase levels, and viral load at baseline were 29.3 years, 1.3 weeks, 122.2 U/L, and 5.1 log10 IU/mL.	Multicenter prospective study	TAF treatment is safe for pregnant women with active CHB and their babies; No infants tested positive for hepatitis B at 7 months of age; TAF is well tolerated; nausea is the most common side effect; no congenital defects are observed at birth; babies have normal growth parameters.
6	T.-S. Chang et al., 2021	Long-term risk of primary liver cancers in entecavir versus tenofovir treatment for chronic hepatitis B	This study compares the long-term risks of ETV versus TDF in hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) in CHB patients from a large multi-institutional database in Taiwan.	Using a large multi-institution database in Taiwan, 21,222 CHB patients were screened for eligibility. A total of 7248 patients were associated with the National Cancer Registry database for the development of HCC or ICC. Patients were matched using a 2:1 ratio of matching scores (PSM).	Prospective cohort studies	The ETV and TDF groups did not differ in the ICC occurrence. Treatment with ETV and TDF shows a comparable long-term risk of HCC and ICC in CHB patients.

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No.	Author, Year of Publication	Title	Objectives	Dataset	Method	Findings
7	Zhang et al., 2024	Long-term efficacy and safety of tenofovir alafenamide, tenofovir disoproxil fumarate, and entecavir in treating hepatitis B virus-related acute-on-chronic liver failure: A 144-week data analysis	To investigate the efficacy and long-term safety of three nucleos(t)ide analogues in treating HBV-ACLF.	A total of 199 patients completed follow-up for 144 weeks. After propensity score matching, 44 patients remained in each group for further analysis of survival status, hepatocellular carcinoma (HCC) incidence, virological response, and liver and kidney function indicators.	Prospective cohort studies	There were no significant differences in survival rates, HCC incidence, efficacy, or safety associated with the use of these three nucleo(t)ide analogues (tenofovir alafenamide, tenofovir disoproxil fumarate, and entecavir) in treating hepatitis B virus (HBV-ACLF).
8	K.-C. Chang et al., 2024	Tenofovir versus entecavir on recurrence and mortality of hepatitis B virus-related hepatocellular carcinoma after curative therapy	Compare the difference between ETV and TDF on HCC recurrence risk and mortality in patients with HBV-associated HCC after curative treatment.	Identified 390 HBV-related HCC patients with curative treatment for HCC and treated with ETV (n = 328) or TDF (n = 62) between January 2011 and December 2020. The mean age was 60, and 90.7% of patients were male.	Prospective cohort studies	TDF therapy was associated with a reduced risk of HCC-related outcomes among patients with HBV-associated HCC after curative treatment compared to the use of ETV.
9	Da Wang et al., 2023	Improved bone and renal safety in younger patients with chronic hepatitis B after switching to tenofovir alafenamide or entecavir	To assess the incidence of renal and bone disorders in CHB patients with long-term TDF therapy and to identify changes in bone mineral density and renal function after switching to ETV or TAF.	154 patients who received TDF monotherapy for 96 weeks were enrolled, with a younger mean age of 36.75 years.	Single-center retrospective study	Younger CHB patients on long-term TDF therapy are at high risk of bone and kidney impairment, with reduced risk when switching to ETV or TAF.
10	Lin et al., 2023	Serum cytokine profiles predict outcomes of chronic hepatitis B patients discontinuing entecavir or tenofovir therapy	To compare serum cytokine levels in patients with HBV who discontinued ETV or TDF therapy was performed to predict virologic and clinical recurrence, as well as to investigate post-cytokine expression between two types of Nucleoside Analogues (NA).	A total of 80 non-cirrhosis CHB patients were enrolled, with 51 patients discontinuing ETV therapy and 29 patients discontinuing TDF therapy. Serum cytokine measurements were performed at the end of therapy (EOT) and the third month after discontinuation of therapy.	Prospective cohort studies	ETV plugs have higher levels of cytokines than TDF plugs in EOT. Old age and high HBsAg EOT increase the risk of virological recurrence. This study is the first to compare post-therapy cytokine expression between NAs, and the mechanism of cytokine differentiation warrants further investigation.
11	Yoo et al., 2025	Lower incidence of hepatocellular carcinoma with tenofovir alafenamide in chronic hepatitis B: Evidence from a large-scale cohort	This study compared the efficacy of TAF, TDF, and ETV in reducing the incidence of HCC to support clinical decision-making and treatment guidelines for chronic hepatitis B patients.	Seventy-five thousand eight hundred sixteen patients were eligible for analysis, ensuring that only previously untreated individuals were included. This data comes from the Health Insurance Review and Assessment (HIRA) in South Korea. It was collected from January 1, 2018, to December 31, 2022.	Prospective cohort studies	TAF significantly reduces the incidence of hepatocellular carcinoma (HCC) in chronic hepatitis B patients, especially those with cirrhosis. Larger sample sizes and longer follow-ups improve the reliability of the study. However, diabetes affects the incidence of HCC differently in each antiviral treatment. The study also noted limitations, such as the small patient group and its observational nature.
12	Linye et al., 2023	Tenofovir versus entecavir on the prognosis of hepatitis B-related hepatocellular carcinoma after surgical resection: a randomised controlled trial	To evaluate the efficacy of TDF and ETV on tumor recurrence in HBV-related HCC patients after liver resection.	A total of 528 patients underwent curative liver resection for HCC-related HBV. Of these, 148 patients met the inclusion criteria and were randomized into two groups: TDF (n = 74) and ETV (n = 74).	Randomized controlled trials (RCTs)	TDF therapy significantly reduced tumor recurrence compared to ETV therapy in HBV-related HCC patients after curative liver resection. TDF therapy was identified as an independent protective factor against advanced tumor recurrence but not against early tumor recurrence. HBV genotype C is associated with worse disease progression and a higher risk of recurrence in HBV-related HCC patients.

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No.	Author, Year of Publication	Title	Objectives	Dataset	Method	Findings
13	Sato et al., 2022	Switching tenofovir alafenamide versus continued therapy into chronic hepatitis patients who were treated with entecavir: prospective, multicenter, randomized controlled study	To evaluate the efficacy and safety of switching from Entecavir (ETV) to Tenofovir Balafenamide fumarate (TAF) in patients with chronic hepatitis B virus (HBV) infection.	Thirty-three patients were initially enrolled, and 30 were evaluated after three were excluded due to unscheduled treatment. Patients were observed over 24 months, and clinical data were collected at multiple time points (3, 6, 9, 12, 18, and 24 months).	Randomized controlled trials (RCTs)	Changes in the mean levels of hepatitis B surface antigen (HBsAg) did not differ significantly between the TAF diversion group and the ETV sustained group (-0.08 vs -0.20 log IU/mL, P = 0.07). Both groups showed comparable efficacy and safety profiles, although larger studies were needed to validate these findings due to the limited sample size. None of the patients developed liver cancer during the observation period.

Virological Efficacy and HCC Suppression

All included studies confirmed that both Entecavir (ETV) and Tenofovir (TDF/TAF) effectively suppressed HBV DNA and reduced the incidence of hepatocellular carcinoma (HCC). Several studies (e.g., Pol & group, 2021; T.-S. Chang et al., 2021) reported no statistically significant difference in HCC occurrence between ETV and TDF. However, TDF was associated with superior outcomes in subgroups, especially in decompensated patients and those with a history of curative HCC treatment.

Renal and Bone Safety

Safety outcomes varied across treatment arms. While TDF showed improved overall survival, it also exhibited a higher risk of renal impairment and decreased bone mineral density in long-term use (Da Wang et al., 2023; Zhang et al., 2024). In contrast, TAF and ETV demonstrated more favorable renal and skeletal safety profiles, making them preferable in patients with pre-existing comorbidities.

Patient Subgroups and Special Populations

Studies such as Zeng et al. (2022) and Linye et al., (2023) explored outcomes in pregnant women and post-resection HCC patients, respectively. TAF appeared to be safe for both mothers and infants, while TDF showed a protective effect against tumor recurrence in surgical cases.

DISCUSSION

This systematic review synthesized current evidence regarding the comparative effectiveness and safety of Entecavir (ETV) and Tenofovir (TDF/TAF) in the management of chronic hepatitis B (CHB). While both drugs demonstrated robust antiviral activity and favorable outcomes in hepatocellular carcinoma (HCC) prevention, nuanced differences in safety and long-term benefits underscore the need for individualized therapeutic decision-making.

In research by Pol & group (2021), The incidence rate for the composite endpoint, which included HCC, decompensated cirrhosis, and all causes of mortality, was 4.1 per 1,000 person-years for the Tenofovir group and 5.0 per 1,000 person-years for the Entecavir group, with no significant difference (P=0.20). As shown in Table 1, the incidence of HCC was similar between the two groups, with a rate of 1.8 per 1,000 person-years for Tenofovir and 1.6 per 1,000 person-years for Entecavir. Other outcomes, such as decompensated cirrhosis and liver-related death, also showed no significant difference. During the follow-up period, 21 cases of HCC, 8 cases of decompensated cirrhosis, and 28 all-cause deaths (including eight liver-related deaths) were reported, with detailed characteristics of the HCC cases occurring provided in the supplemental material. Overall, the study's results showed that Tenofovir and Entecavir had comparable results in terms of HCC incidence and other liver-related events in patients with chronic HBV infection.

Research Li et al. (2021) showed that all three treatment groups showed comparable liver transplant-free survival rates at week 48, suggesting similar effectiveness among treatments. At week 4, all three groups showed similar biochemical responses; however, patients treated with TAF showed a prominent advantage in reducing total bilirubin levels and maintaining albumin and cholesterol levels

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compared to other groups. Meanwhile, TDF showed a poor trend of renal safety, even in the short term. However, there was no significant difference in changes in kidney function among the three groups at week 4, indicating potential concerns regarding the renal safety profile of TDF. The findings suggest that TAF, TDF, and ETV effectively manage HBV-ACLF.

Furthermore, T.-S. Chang et al. (2021) stated that patients who received TDF generally had a lower prevalence of diabetes and were more often in a compensatory state compared to patients undergoing ETV therapy. They also had more exposure to nucleus(t)ide analogs (NAs) and were more likely to be positive for hepatitis B e antigen (HBeAg). The analysis showed that the annual incidence of hepatocellular carcinoma (HCC) was similar between the two groups, with a rate of 2.03 per 100 person-years for ETV and 1.67 per 100 person-years for TDF ($p = 0.102$), with no significant difference in HCC incidence on multivariable analysis. However, in decompensated patients, TDF was associated with a significantly lower risk of HCC than ETV (HR 0.54; 95% CI 0.30-0.98, $p = 0.043$). Independent risk factors for HCC include older age, male gender, cirrhosis of the liver, low platelet count, low albumin levels, and high FIB-4 score. TDF patients also showed better overall survival ($p < 0.001$), although there was no significant difference in liver-related mortality between the two groups in the adjusted cohort ($p = 0.99$). However, TDF patients had lower overall liver-related mortality ($p = 0.009$). These results suggest that although TDF may improve overall survival, the risk of HCC remains comparable to that of ETV, with some additional benefits for certain subgroups.

These studies are reinforced by recent research from K.-C. Chang et al. (2024) showed that TDF was more effective in lowering the risk of all-cause and HCC-related mortality than the ETV group. The study concluded that TDF treatment was associated with better survival outcomes and lower recurrence rates in patients with HBV-associated HCC who had undergone curative treatment than those treated with ETV.

K.-C. Chang et al. (2024) demonstrated that TDF users had a substantially lower risk of all-cause mortality (aHR = 0.38, P = 0.003) and HCC-related mortality (aHR = 0.23, P = 0.005) compared to ETV users in patients with HBV-related HCC. These findings suggest that TDF may confer a survival advantage beyond viral suppression in certain high-risk populations.

In this regard, the latest research from Yoo et al. (2025) involving 105,751 chronic hepatitis B patients treated with antivirals (TAF, TDF, or ETV). The results showed that TAF had a lower incidence rate of hepatocellular carcinoma (HCC) (25.79) compared to TDF (42.91) and ETV (40.51). TDF and ETV have a higher risk of HCC than TAF, with incidence rates of 1.66 and 1.57, respectively. Even in patients without cirrhosis, TAF still showed a lower incidence of HCC than TDF. These findings emphasize the importance of choosing antiviral therapies based on their impact on the incidence of HCC.

Research Suzuki et al. (2021) concludes that a temporary switch of treatment from ETV to TDF results in some hepatitis B e-antigens (HBeAg) becoming undetectable in the blood of individuals infected with the hepatitis B virus (HBV) and a decrease in HBsAg levels to moderate levels.

In addition, research Sato et al. (2022) evaluate the efficacy and safety of switching from ETV to TAF in patients with chronic hepatitis B (HBV) infection. Results showed that after two years, the change in the mean level of hepatitis B surface antigen (HBsAg) did not differ significantly between the TAF and ETV groups, i.e., -0.08 log IU/mL for TAF and -0.20 log IU/mL for ETV (P-value 0.07). However, the analysis showed that the duration of previous ETV treatment was shorter in the group with decreased HBsAg compared to those without (49 months vs. 92 months, P 0.03), indicating the effect of treatment duration on outcomes. In addition, the estimated glomerular filtration rate (eGFR) tended to decrease more in the TAF group than in the ETV group. However, there was no significant difference in patients with an initial eGFR < 60. Overall, the efficacy and safety profiles between TAF and ETV are comparable, although Sato et al. (2022) noted the need for further research with a larger cohort to confirm these findings.

In this regard, research by Da Wang et al. (2023) investigated the effects of switching from TDF to TAF or ETV in hepatitis B patients already on long-term TDF therapy, resulting in the finding that renal function significantly decreased in patients who continued TDF, while renal function

improved in patients who switched to ETV or TAF. These findings suggest that hepatitis patients undergoing long-term TDF therapy are at high risk of developing bone and kidney disorders, but switching to ETV or TAF may significantly reduce this risk.

Further, the research Zhang et al. (2024) investigated the long-term efficacy and safety of TAF, TDF, and ETV in treating acute liver failure associated with hepatitis B virus (HBV-ACLF), resulting in a survival of 144 weeks of 56.82% for the TAF group, 75.00% for the TDF group, and 59.09% for the ETV group, with no statistically significant differences between the groups. Meanwhile, no significant differences were found in the virological response rate or indicators of liver and kidney function among the three groups. However, the levels of aspartate aminotransferase (AST) indicating liver health were significantly higher in the TDF group compared to the ETV group.

In research, Choi et al. (2023) explained that the results of the analysis showed that 6.8% of chronic hepatitis B (CHB) patients experienced HBsAg loss, with cumulative ratios for TDF of 1.2%, 3.0%, and 6.4% at the 6th, 12th, and 24th months, while for ETV were 0.7%, 1.9%, and 6.7%. Patients who discontinue TDF have a higher clinical recurrence rate than ETV. In the race analysis, 6.1% of ETV patients were Caucasian, while 6.7% were of TDF, with 93.9% of ETV and 93.3% of TDF of Asian race. At the end of therapy, the mean alanine aminotransferase (ALT) level was 0.53 times the external link for ETV and 0.61 times the external link for the TDF. Patients undergoing TDF therapy showed a higher rate of recurrence compared to those taking ETV. In addition, factors such as race, HBeAg status, and HBsAg levels at the end of therapy affect the risk of relapse.

In addition, the research by Lin et al. (2023) focuses on chronic hepatitis B (CHB) patients who discontinue ETV or TDF therapy by examining the relationship between serum cytokine profiles and patient end outcomes. The results revealed that patients who stopped ETV had significantly higher levels of several cytokines, including interleukin 5 (IL-5), IL-12 p70, IL-13, IL-17 A, and tumor necrosis factor-alpha (TNF-alpha), compared to those who stopped TDF. Overall, the study concluded that specific cytokine profiles in EOT may help predict the likelihood of virologic and clinical recurrence in CHB patients after stopping NA therapy, emphasizing the importance of cytokine monitoring in managing these patients.

Comparison of effect sizes in Lin et al. (2023) showed that baseline levels of certain cytokines may predict relapse after discontinuation of therapy. Lin et al. (2023) reported that in the ETV group, each additional year of age increased the risk of virological relapse by 3% (HR = 1.03, 95% CI: 1.00–1.07), while higher EOT HBsAg levels also significantly raised this risk (HR = 1.68, 95% CI: 1.07–2.66). Comparable cytokine predictors were also identified for patients who received TDF, suggesting distinct immunological patterns may mediate relapse between these two treatment groups.

In the research, Zeng et al. (2022) A study shows that Tenofovir Alafenamide (TAF) is safe and effective for pregnant women with active chronic hepatitis B. Of the 103 women who received TAF, their average age was 29.3 years. TAF was well tolerated, with nausea as a common side effect (29.1%) and no birth defects. The HBeAg seroconversion rate reached 20.7% by the sixth month after delivery, and all babies were born HBsAg negative by 7 months of age. Babies from mothers who get TAF grow and develop normally until 18 months. This research supports TAF as a safe treatment alternative for pregnant women.

Research Linye et al. (2023) comparing the efficacy of TDF and ETV in 148 patients with hepatitis B-associated hepatocellular carcinoma (HCC) after surgical resection. Of the 148 patients, 37 had a tumor recurrence, and 16 died or received liver transplants. Results showed that the overall survival rate (OS) at 1, 3, and 5 years was significantly higher in the TDF group (100.0%, 95.9%, and 90.8%) than in the ETV (98.6%, 91.1%, and 78.5%). Similarly, recurrence-free survival rates (RFS) at 3 and 5 years were also better for TDF (82.38% and 75.3%) than for ETV (70.4% and 55.2%). Statistical analysis showed that TDF was associated with a lower risk of tumor recurrence (P = 0.026, HR = 0.497) and was identified as an independent protective factor against advanced tumor recurrence.

Linye et al. (2023) demonstrated that TDF therapy was associated with significantly improved recurrence-free survival (HR 0.497; 95% CI: 0.269–0.922; P = 0.026) and a trend toward better overall survival (HR 0.385; 95% CI: 0.143–1.051; P = 0.062) compared to ETV. In the intention-to-treat

population, ETV users had more than triple the risk of tumor recurrence (RR 3.056; P = 0.047) and over twice the risk of death or liver transplantation (RR 2.566; P = 0.009). These findings suggest that TDF may offer superior prognostic benefits for HBV-related HCC patients post-resection. In conclusion, TDF therapy significantly improved overall survival and recurrence-free survival in HBV-related HCC patients after surgical resection compared to ETV therapy.

Comparative Effectiveness of ETV and TDF

The reviewed studies consistently demonstrated that both ETV and TDF effectively suppress HBV DNA replication and reduce HCC incidence across diverse patient populations. Notably, Tenofovir—especially in the disoproxil fumarate (TDF) form—was associated with improved overall survival, particularly in high-risk patients, including those with decompensated cirrhosis or who underwent curative HCC resection (K.-C. Chang et al., 2024; Linye et al., 2023). These findings suggest that while virological efficacy is equivalent, survival benefits may be more pronounced in TDF-treated cohorts under certain clinical conditions.

Safety Profiles and Special Populations

A critical consideration in CHB management is the long-term safety of antiviral therapy. TDF has been associated with nephrotoxicity and bone mineral loss, especially in younger or long-term users (Da Wang et al., 2023). In contrast, Tenofovir alafenamide (TAF), a newer formulation, has demonstrated comparable efficacy with improved renal and skeletal safety, making it more suitable for patients with pre-existing comorbidities or those at risk of organ damage.

Importantly, studies involving special populations provide additional insight. For instance, pregnant women treated with TAF exhibited positive maternal and neonatal outcomes without significant safety concerns (Zeng et al., 2022). Likewise, TDF was shown to reduce tumor recurrence risk post-HCC resection, highlighting its potential role in oncological risk mitigation (Linye et al., 2023).

Interpretation of Heterogeneity and Study Limitations

The inability to perform meta-analysis in this review stems from substantial heterogeneity in study designs, outcome definitions, follow-up durations, and patient characteristics. While all studies adhered to acceptable methodological standards, the inclusion of observational cohorts introduces a risk of selection bias. Moreover, regional disparities in healthcare access, clinical guidelines, and patient demographics may limit the broader applicability of the findings.

Future systematic reviews should consider subgroup meta-analyses where homogeneity allows, and explore meta-regression techniques to account for variability in effect sizes.

Clinical and Public Health Implications

The findings of this review carry significant implications for clinical practice and public health policy. Physicians should adopt a risk-stratified approach, considering factors such as renal function, liver disease stage, comorbidities, and treatment goals when selecting antiviral agents. From a policy perspective, health systems should ensure the availability of safer alternatives like TAF, particularly in vulnerable populations, and promote guidelines that encourage personalized CHB therapy.

Directions for Future Research

To address the remaining gaps, we recommend the following:

- Conducting head-to-head randomized trials comparing ETV, TDF, and TAF across ethnically and clinically diverse populations.
- Generating real-world evidence through large, multicenter cohort studies focusing on long-term safety and survival.
- Performing cost-effectiveness analyses to guide sustainable national treatment programs, particularly in low-resource settings.

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CONCLUSION

This systematic review highlights the comparable antiviral efficacy of Entecavir (ETV) and Tenofovir (TDF/TAF) in managing chronic hepatitis B, with both agents demonstrating substantial suppression of viral replication and a reduction in hepatocellular carcinoma (HCC) risk. Notably, Tenofovir, particularly in its disoproxil fumarate form, appears to offer additional survival advantages in high-risk populations, such as patients with decompensated liver disease or those who have undergone curative therapy for HCC. However, its long-term use is associated with an increased risk of renal impairment and bone mineral loss, which underscores the need for vigilant patient monitoring and individualized treatment decisions. In contrast, Tenofovir alafenamide (TAF) emerges as a safer alternative for patients with comorbid conditions affecting renal or skeletal systems, offering similar antiviral benefits with improved tolerability. These distinctions reinforce the importance of tailoring treatment strategies to patient-specific factors, including disease stage, organ function, and comorbidity profile.

The findings of this review have important implications for clinical practice and health policy. Physicians are encouraged to incorporate risk stratification and long-term safety assessments into routine decision-making. At the policy level, ensuring the accessibility of diverse antiviral agents—particularly newer, safer options such as TAF—should be prioritized to enhance treatment outcomes and minimize adverse effects. To further inform evidence-based hepatitis B management, future research should prioritize head-to-head randomized controlled trials comparing ETV, TDF, and TAF in varied patient populations. Additionally, longitudinal real-world studies and cost-effectiveness evaluations are essential to guide sustainable, personalized care strategies that address both clinical efficacy and resource allocation in diverse healthcare settings.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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