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Review Article

Current Clinical Applications of Entecavir in Hepatitis B Viruses Infection

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Abstract

Entecavir (ETV) is a guanosine nucleoside analogue widely used in the management of chronic Hepatitis B Virus (HBV) infection. It demonstrates consistent antiviral activity, favourable tolerability, and a high genetic barrier to resistance, making it a reliable option across diverse clinical settings. Evidence from clinical trials and real-world studies confirms that ETV achieves sustained viral suppression, alanine aminotransferase (ALT) normalization, and histological improvement, contributing to reduced long-term risks of cirrhosis and hepatocellular carcinoma. Its pharmacokinetic properties and antiviral effectiveness have been established in both treatment-naïve and lamivudine-resistant patients. ETV maintains clinical utility in various special populations, including individuals with decompensated cirrhosis, chronic kidney disease, post-transplant status, and those receiving immunosuppressive therapy. In these groups, ETV retains efficacy with limited drug-drug interactions and a generally mild adverse-event profile. Optimal adherence to therapy remains essential to ensure sustained viral suppression and minimize the risk of treatment failure. In addition to established clinical roles, emerging research has explored new formulations and potential therapeutic applications of ETV, including long-acting delivery strategies and its possible relevance in oncologic contexts. These developments highlight continued interest in optimizing the use of ETV in HBV management. Overall, ETV remains a well-supported antiviral agent that combines durable efficacy, safety, and broad applicability in the treatment of chronic HBV infection.

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1. Introduction

The introduction plays an important role in providing background information (including relevant references), emphasizing the importance of the study, and outlining its objectives. In 1995, Bristol-Myers Squibb discovered that the compound SQ-34676, which was previously developed for herpes simplex virus treatment but found ineffective, worked effectively for hepatitis B virus (HBV) treatment, particularly chronic HBV. Thus, it was deemed as the most powerful compound to be discovered thus far that year (Scheme 1). The compound was then called BMS 200475, and subsequently, named entecavir (ETV) [1]. With the molecular formula of $C_{12}H_{15}N_5O_3$, ETV weighs 277.28 g/mol [2]. ETV is guanine substituted with a 4-hydroxy-3-(hydroxymethyl)-2-methylidencyclopentyl group at position 9 and is a synthetic analog of 2′-deoxyguanosine [2].

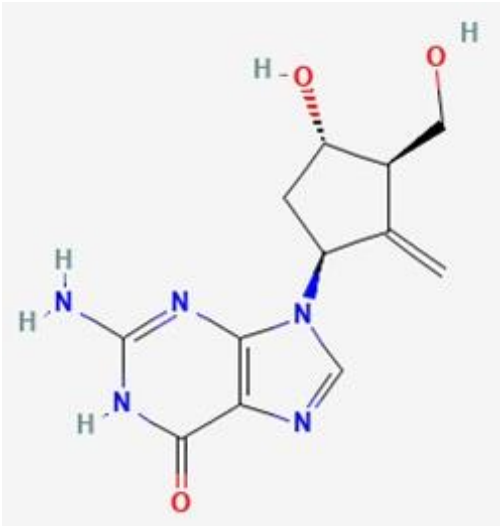
The nucleos(t)ide analogs (NA) are classified based on their barrier for HBV resistance as “low barrier NA,” including lamivudine (LAM), adefovir (ADV), telbivudine (LdT), or “high barrier NA,” including ETV, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). High barrier NA use is recommended by the international guidelines as the first-line drug. Moreover, high barrier NAs are highly efficient in controlling viral replication (HBV DNA) and inflammatory activity (alanine aminotransferase [ALT] level) [3].

2. Pharmacodynamic and Pharmacokinetic Properties

ETV is a nucleoside reverse transcriptase inhibitor with selective antiviral activity against HBV. ETV is intracellularly phosphorylated to its active triphosphate form. It is also a nucleoside analog with activity against HBV polymerase. Furthermore, it competes with the natural substrate deoxyguanosine triphosphate, and with its active triphosphate form, it inhibits all three activities of HBV polymerase (reverse transcriptase; base priming and reverse transcription of the negative strand from pregenomic messenger RNA; and synthesis of the positive strand of HBV DNA) through intracellular phosphorylation. ETV triphosphate is a weak inhibitor of cellular DNA polymerases alpha, beta, and delta as well as mitochondrial DNA polymerase gamma, with Ki values of 18->160 μm. It is not a substrate, inhibitor, or inducer of the cytochrome P450 enzyme system [2].

Half-life of the ETV active triphosphate form is approximately 15 hours. Moreover, when taken orally, 100% of ETV is absorbed through the intestines. It reaches peak concentration in plasma within 0.5-1.5 hours. When taken with meals, absorption is reduced by 44%-46%. Therefore, ETV should be taken on an empty stomach [2-4]. The half-life is 24 hours, and it is recommended to be taken once a day. It reaches steady state in plasma after 10 days of use [2].

ETV is metabolized in the liver and converted to inactive metabolites. It is mainly excreted through the kidneys; 62%-73% of the excreted portion is recovered in the urine. The renal clearance is independent of dose, suggesting that ETV undergoes both glomerular filtration (GFR) and tubular secretion, and thus, patients with renal impairment require dose adjustment [2, 4, 5] ETV is characterized by higher bioavailability as it features better absorption and longer plasma elimination half-life compared to LAM and ADV [6].



Scheme 1. *Entekavir formula.*

3. Clinical Indications

3.1. Acute HBV Infection

Acute HBV infection resolves spontaneously in over 95% of immunocompetent adults, requiring no treatment; however, primary supportive treatment can be provided. Antiviral therapy is recommended if there are a risk of acute liver

failure and a requirement for liver transplantation [7]. Treatment is recommended for patients with fulminant acute HBV infection, those with severe acute HBV (who meet at least two of the following criteria: hepatic encephalopathy, serum bilirubin > 10.0 mg/dl, and international normalized ratio [INR] > 1.6), and those with acute HBV with a prolonged course (persistent symptoms for more than 4 weeks after presentation or marked jaundice [bilirubin > 10 mg/dl]). Treatment can be discontinued once HBsAg clearance is confirmed. TDF, ETV, LAM, LdT, and ADV are the accepted parameters [8].

The 2018 Hepatitis B Guideline by the American Association for the Study of Liver Diseases (AASLD) recommends treatment of acute HBV infection in cases of acute liver failure or total bilirubin level of >3 mg/dL (or direct bilirubin > 1.5 mg/dL), INR of >1.5, and encephalopathy or ascites. ETV, TDF, or TAF are the antiviral drugs of choice [9].

3.2. Chronic Viral Hepatitis B

ETV was approved by the US Food and Drug Administration (FDA) in 2005 for the treatment of children aged 2 years and older and adults with chronic HBV infection [2] Clinical trial results suggested that treatment with ETV was associated with an improvement in liver histology. A study, which analyzed histologic improvement in 57 patients that received ETV for a median of 6 years (3-7 years) and had baseline Knodell necro inflammatory scores of ≥2, reported that 96% of patients showed histologic improvement, defined as a ≥2-point reduction in Knodell necro inflammatory score without worsening of fibrosis score, and 88% had ≥1-point improvement in the Ishak fibrosis score [10].

In the ETV-901 study, 146 patients were treated with ETV for 5 years. In this study, which also included 19 patients without a virologic response in the first year of treatment, all patients received ETV at 1 mg/day from year 3 onward, and 94% of patients had HBV DNA of <300 copies/mL and 80% had normal ALT levels at year 5. Additionally, a further 33 patients (23%) had HBeAg seroconversion, and two patients (1.4%) lost HBsAg during ongoing treatment. These data suggest that extended treatment with ETV was associated with an increase in the rates of HBV DNA suppression, ALT normalization, and HBeAg seroconversion [11].

3.3. Treatment-naive Chronic Viral Hepatitis B

The World Health Organization guidelines of March 2024 recommended TDF or ETV regimens if there was an indication for treatment.(12) The international guidelines recommend treatment in all HBeAg-positive or -negative chronic HBV patients, defined by HBV DNA of >2,000 IU/ml, ALT of >upper limit of normal (ULN) and/or at least moderate liver necroinflammation or fibrosis, in patients with compensated or decompensated cirrhosis with any detectable HBV DNA level, and in patients with HBV DNA of >20.000 IU/ml and ALT >2xULN, regardless of the degree of fibrosis. The preferred regimens are ETV, TDF, and TAF as monotherapy. ETV is recommended at a dose of 0.5 mg tablets/day in cases of treatment-naive chronic HBV. Dose adjustment is required for patients with GFR of <50 ml/min [8, 13].

A study, which reviewed the complete virologic response and long-term outcomes of treatment-naive chronic HBV patients after at least 3 years of NA use, reported that there was no difference in efficacy between TDF, ETV, LAM, and LdT, and that 40 years of age and below and low baseline HBV DNA value were independent factors for complete virologic response. Drug resistance was observed in the LAM group and side effects were observed in the LdT group. ETV and TDF were highly effective treatment options [14].

ETV provides sustained viral suppression during long-term treatment of treatment-naive HBeAg-positive chronic HBV cases and achieves HBeAg seroconversion in approximately 20%-45% of patients. Patients were treated with ETV 0.5 mg/day or LAM 100 mg/day for a minimum of 52 weeks in a phase III, double-blind study of 715 treatment-naive, HBeAg-positive patients. Significantly more patients on ETV compared to those on LAM had undetectable serum HBV DNA levels (67% vs. 36%) and serum ALT normalization (68% vs. 60%). Moroever, the mean reduction in serum HBV DNA from baseline to week 48 was greater in the ETV group compared to the LAM group. HBeAg seroconversion was observed in 21% of the ETV group and 18% of the LAM group at week 48 [15].

Another clinical trial that investigated 222 treatment-naive patients (40.5% HBeAg positive), who received continuous ETV therapy for 3 years, reported that 76.5%-100% of patients had undetectable levels of HBV DNA at 3 years. The rates of undetectable HBV DNA, HBeAg seroconversion, and ALT normalization increased to 92.1%, 43.9%, and 90.4%, respectively, at 3 years [16]. In a study from Turkey, 49 HBeAg-positive treatment-naive patients received ETV treatment, and at the end of the 4-year study HBV DNA decreased to undetectable levels with ALT normalization in 90% of the patients. Moreover, HBeAg and HBsAg seroconversion rates were 7.5% and 2.5%, respectively [17].

Another study with 82 HBeAg-positive patients on ETV reported HBeAg seroconversion at a rate of 31.7% after 3 years of treatment. As another result of the above study, HBV DNA and HBeAg levels during treatment were better predictors of subsequent clinical outcomes in HBeAg-positive chronic HBV patients on ETV therapy compared to HBsAg levels at baseline [18].

A clinical trial with 305 patients, who were enrolled in ETV-022, a randomized phase III study comparing ETV with LAM in NA-naive, HBeAg-positive patients, compared changes in hepatic HBV covalently closed circular DNA (cccDNA) and total hepatic HBV DNA at week 48 of ETV or LAM treatment. Forty-eight weeks of ETV was associated with greater reductions in cccDNA and total hepatic HBV DNA compared to LAM, but it was concluded that long-term

treatment was needed for cccDNA elimination [19].

ETV treatment has faster, and more potent antiviral activity was observed compared to ADV in NA-naive patients with HBeAg-positive chronic HBV. In a randomized clinical trial, 69 NA-naive patients with HBV DNA of ≥108 copies/mL at baseline were randomly assigned to ETV 0.5 mg/day or ADV 10 mg/day for a minimum of 52 weeks. Mean HBV DNA change from baseline to week 48 was significantly higher in ETV and HBV DNA levels of <300 copies/mL were achieved between weeks 2-48 in the majority of patients that received ETV. Consequently, only 3% of ETV-treated patients had HBV DNA of ≥105 copies/mL compared to 47% of ADV-treated patients at week 48 [20].

In a 24-week, parallel-group, open-label, randomized clinical trial, which compared the early antiviral efficacy of LdT and ETV in the treatment of HBeAg-positive chronic HBV infection in adult Chinese treatment-naive patients, HBV DNA level reduction, HBeAg loss, and seroconversion rates and ALT normalization were similar at 12 and 24 weeks, and no statistically significant difference was observed in efficacy or tolerability between 600 mg LdT and 0.5 mg ETV at the end of 24-week treatment [21].

3.4. Acute Exacerbation of Chronic Hepatitis B Infection

NA treatment is recommended for patients with chronic HBV-associated acute exacerbations and acute-chronic liver failure. A study in China compared patients with acute-chronic liver failure, who did not receive ETV, LAM, or NA. It was reported that significant viral suppression was achieved with LAM and ETV after 3 months, there was no difference by survival, it did not improve the short-term prognosis, and yet it could significantly reduce the relapse rate [22, 23]. Another multicenter study with patients with HBV exacerbation due to immunosuppressive therapies reported that there was no significant difference between ETV and TDF by treatment initiation time, time to normalization of serum transaminases, undetectability of HBV DNA, length of hospital stays, development of acute liver failure, and mortality [24].

In a clinical study investigating the efficacy of ETV in acute hepatic exacerbation owing to chronic HBV in HBeAg-negative patients, 84 patients received 0.5 mg/day ETV and routine supportive treatment regimen, whereas 99 patients in the control group received only supportive treatment. Antiviral treatment with ETV significantly improved survival in HBeAg-negative patients [25].

3.5. LAM-resistant Chronic HBV

In chronic HBV patients, it was reported that the cumulative probability of ETV resistance after 5 years of ETV treatment was 1.2%-1.5%, whereas in LAM-resistant individuals, the resistance rate reached to as high as 51% after 5 years of treatment [26, 27].

In ETV-023, a phase III study, 525 NA-naive Chinese patients with chronic HBV were randomized 1:1 to receive ETV 0.5 mg/day or LAM 100 mg/day. After a total of 12 weeks of treatment, the mean reduction in serum HBV DNA and mean change in HBV DNA from baseline to week 48 were significantly greater in the ETV group compared to the LAM group. The virological response and ALT normalization rates were significantly higher in patients treated with ETV compared to patients treated with LAM. Similar HBeAg seroconversion rates were seen in ETV and LAM groups at week 48 in HBeAg-positive patients [28].

The results of clinical trials suggested that switching to ETV was an effective and safe treatment option in patients with chronic HBV resistant to LAM treatment. In ETV-056, a randomized, double-blind, placebo-controlled phase III study, 145 chronic HBV patients who were resistant to LAM treatment were randomized to receive ETV 1 mg/day in 116 patients and placebo in 29 patients. Upon completion of the 12-week blinded treatment phase, 144 patients received ETV 1 mg/day for 36 weeks. At week 12, i.e., the end of the blinded treatment phase, the mean change from baseline in HBV DNA level and ALT normalization rates were significantly higher in patients on ETV compared to patients who received placebo. At week 48 of ETV treatment, 27% of patients initially randomized to receive ETV had undetectable levels of HBV DNA, and 8% of the patients who were HBeAg positive at onset developed HBeAg loss and 6% developed HBeAg seroconversion [29].

3.6. Prophylaxis in Patients Who Receive Immunosuppressive or Cytotoxic Therapy

In cases that are HBsAg-positive, anti-HBc-positive, or HBsAg-negative, anti-HBc-positive patients receive immunosuppressive or cytotoxic treatment, prophylaxis with NA is recommended to prevent HBV reactivation if medium/high risk treatment is administered, and this should be started before or simultaneously with immunosuppressive treatment, if possible. Prophylactic first-line NAs (ETV, TDF or TAF) should be preferred over other NAs owing to their high barrier to resistance. The recommended duration of prophylactic antiviral therapy is 6-12 months upon discontinuation of immunosuppressive therapy [9, 30].

In a study that reviewed HBsAg-positive or anti-HBc positive patients who received immunosuppressive treatment due to hematological malignancy, it was reported that ETV should be used instead of LAM in chronic HBV patients with detectable initial HBV DNA levels [31]. Another Chinese multicenter randomized clinical trial compared the efficacy of ETV and LAM in patients who received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy regimen for diffuse large B-cell lymphoma who were HBsAg positive, had normal liver function, serum HBV DNA levels below 103 copies/mL, and did not receive

prior antiviral therapy. It was reported that the rate of HBV-related hepatitis, HBV reactivation, and the need for chemotherapy discontinuation were significantly lower in the ETV group compared to the LAM group [32].

In a meta-analysis of 10 studies, which reviewed allogeneic hematopoietic stem cell transplant patients, long-term LAM use was associated with drug resistance and ETV was very effective against HBV reactivation. It was reported that there was little or no data regarding use of ADV, LdT or TDF/TAF as prophylaxis in this specific patient population [33].

4. Safety and Side Effects Profile

The most prevalent side effects of ETV include headache, insomnia, fatigue, dizziness, drowsiness, vomiting, diarrhea, nausea, indigestion, and elevated liver enzyme levels [34] Safety data from long-term ETV use in chronic HBV suggested that it was well tolerated, except for a low incidence of side effects, and most of the adverse incidents were of mild or moderate severity. A very low rate of patients with side effects (Table 1) had to discontinue treatment [35, 36].

Table 1. *Side effects and frequency of ETV.*

Frequency	Symptom
Very common	Elevated lipase (up to 18%)
Common	Headache (9%), insomnia, fatigue (6%), dizziness (4%), somnolence, nausea (3%), diarrhea, dyspepsia, vomiting, elevated liver enzymes (>3 ULN up to 5%), elevated amylase (2%)
Uncommon	Rash, hair loss
Rare	Serious allergic reactions

ULN = Upper Limit of Normal

Although increased creatinine was reported in 2% of patients with compensated liver disease and in up to 11% of patients with liver decompensation, it was suggested that dose adjustment was not necessary unless GFR falls below 50. Other likely metabolic side effects include fasting hyperglycemia, low bicarbonate, lactic acidosis, and elevated alkaline phosphatase. Genitourinary system side effects include hematuria, glucosuria, and dysuria. Musculoskeletal side effects include arthralgia, myalgia, and back pain. Dermatologic side effects include photosensitivity, hair loss, and rash [6, 37-39].

In a Korean ETV safety study of 3367 patients, only 19 events in nine cases (0.27%) were reported as serious side effects and three events in two cases (0.06%) were reported as serious adverse drug reactions [36]. Headache, upper respiratory tract infection, cough, nasopharyngitis, fatigue, dizziness, upper abdominal pain, and nausea were reported as the most prevalent side effects in several clinical trials with ETV [40].

Elevated ALT was reported in 3% of patients in a study with 1051 individuals on ETV for 184 weeks. In this study, 4% of adverse events were attributed to ETV, and 1% of patients had to discontinue the drug. Lactic acidosis, a side effect, which could be associated with NA, was not observed. Mortality due to hepatic encephalopathy and liver-related causes (such as liver failure, hepatic encephalopathy, hepatorenal syndrome, and upper gastrointestinal bleeding) was reported in patients with decompensated cirrhosis [41]. A study, which compared 0.5 and 1 mg doses of ETV, concluded that the frequency of drug-related side effects did not increase with dose [42].

Regarding the hematologic side effects, hypoalbuminemia, thrombocytopenia, and neutropenia were reported, specifically in the pediatric population. Elevated lipase, diarrhea, nausea and vomiting, elevated amylase, upper abdominal pain, and upper gastrointestinal bleeding were reported as gastrointestinal side effects. Although hepatocellular carcinoma (HCC) was reported in patients with decompensated cirrhosis, a 10-year treatment experience in 24 countries reported that ETV treatment was not associated with an increased risk of malignant neoplasms, including HCC, non-HCC malignancies, and general malignancies, compared with non-ETV treatment [35].

4.1. Combination Therapy

A study, which investigated the efficacy of NA combination therapies, reported that the antiviral efficacy of ETV monotherapy was similar to ETV + TDF combination therapy in NA-naive patients with chronic HBV over 96 weeks of treatment. It was reported that the superiority of ETV + TDF combination therapy over ETV monotherapy was observed only in HBeAg-positive patients with baseline HBV DNA levels of ≥108 IU/mL, and not in patients with HBV DNA levels of <108 IU/mL [43].

Clinical trial results suggested that there was no clear benefit of combination therapy with ETV and pegylated interferon (peg-IFN) in HBeAg-positive chronic HBV patients. In a randomized, open-label study in China, 218 HBeAg-positive treatment-naive patients were treated with peg-IFN alfa-2a monotherapy for 48 weeks, or with the addition of ETV at week 13, or with a 24-week ETV pretreatment prior to peg-IFN alfa-2a. Post-treatment HBeAg seroconversion rates at week 24 were similar in all three groups, 33% in the peg-IFN monotherapy group, 25% in the ETV add-on group, and 26% in the ETV pretreatment group. A significantly greater reduction in HBV DNA was achieved with the addition of ETV during treatment, but this reduction was not secured after treatment [44].

In another randomized, multicenter, open-label study, peg-IFN alfa-2a was added to the treatment of 85 out of 175 HBeAg-positive ETV-treated patients between weeks 24 and

48, whereas 90 patients were continued with ETV monotherapy. Patients with HBV DNA levels of <200 IU/mL at week 48 and HBeAg loss discontinued ETV at week 72, and all patients were followed up until week 96. Compared with the monotherapy group, no significant increase in the proportion of patients with HBeAg loss and HBV DNA of <200 IU/mL at week 48 in the peg-IFN alfa-2a group were observed. At week 96 of the study, 24 weeks of peg-IFN add-on therapy was associated with a significantly higher rate of HBeAg seroconversion response compared to ETV monotherapy (26% vs. 13%) [45].

A meta-analysis included studies of treatment-naive/NA-resistant/HBV-DNA undetectable patients who received ETV or ETV-based combination regimens. ETV monotherapy was more effective compared to the ETV-based combination therapy for improving the rate of undetectable HBV DNA. In patients on ETV with undetectable HBV DNA, ETV monotherapy was more effective compared to the combination group in maintaining the treatment effect [46].

In the same study, HBeAg loss and HBeAg seroconversion rates were similar between ETV and ETV-based combination regimen, and the monotherapy group exhibited better HBsAg loss rates compared to the combination therapy group. ETV-based combination therapy was more effective in reducing AST and total bilirubin levels compared to the monotherapy group, but ALT levels and ALT normalization rates were similar between the two groups at the end of treatment.(47) In chronic hepatitis B (CHB) patients with partial virologic response to ETV, viral response rate and HBeAg seroconversion rate at week 48 were higher in the TDF + ETV group compared to the TDF group [47].

4.2. Interactions

ETV should be administered on an empty stomach 2 hours before or after a meal, because food delays ETV absorption and reduces the area under the curve by 18%-20%. Nevertheless, it was reported by a study that in patients who have achieved a virologic response with ETV therapy, administration of ETV in the fed state had comparable efficacy to fasting in terms of virologic, biochemical, and serologic responses [48].

There are 156 known medicines that interact with ETV, but most of these are associated with mild to moderate interactions, and ETV does not require drug discontinuation or dose adjustment. ETV may increase the risk of visual disturbances, diarrhea, and vomiting by reducing the elimination of crizotinib used in patients with lung cancer [49]. It is not affected by the cytochrome P450 enzyme system and is unlikely to interact with agents affected by the cytochrome P450 enzyme system. Nevertheless, as it is eliminated by renal tubular secretion, it is expected that drugs, which inhibit tubular secretion (e.g., probenecid), can increase ETV serum concentration [40].

5. Special Patient Groups

5.1. Pregnancy

ETV is a group C medicine in the pregnancy medicine category. Considering the lack of controlled studies involving pregnant women, this population can only be included in cases where the benefit outweighs the risk [2]. Although ETV is contraindicated in pregnant women due to the risk of congenital anomalies and embryotoxicity, rat studies have been conducted with 10-1000 times the human dose. Several studies have reported that there was no increase in maternal complications and side effects in accidental pregnancies during long-term ETV use [50].

In a study, which analyzed adverse events associated with ETV and ADV during pregnancy based on cases reported to the FDA adverse event reporting system, there was an increased risk of spontaneous abortion with ETV. Nevertheless, it was also stated that there was no increase in adverse events with ETV use in pregnancy when the reports were limited to the indication of HBV infection [51]. Management of chronic HBV during pregnancy and strategies in place to prevent mother-to-child transmission are considered an important step in eliminating or reducing the global burden of chronic HBV. Thus, due care should be taken for the impact of placental transfer of ETV on pregnancy, although antivirals are recommended to reduce perinatal transmission in the third trimester [52].

5.2. Cirrhotic Patients

Approximately 15%-40% of HBV carriers are at risk of severe sequelae, including cirrhosis, hepatic decompensation, and HCC. ETV treatment is effective in controlling chronic HBV infection and preserving liver function in cirrhotic HBV patients with or without decompensated liver disease. All practical guidelines recommend that antiviral treatment should be considered in patients with HBV-associated decompensated cirrhosis regardless of HBV DNA levels [13, 53].

It was reported that ETV markedly improved underlying hepatic reserve in patients with decompensated cirrhosis, mostly within 6 months of treatment [54]. Previous studies reported regression of fibrosis and even reversal of cirrhosis with prolonged suppression of viral replication [10, 54] Cohort studies with patients with HBV-associated cirrhosis reported that ETV treatment significantly reduced the risk of HCC (45%-63%) compared to the untreated patient group, highlighting the importance of long-term treatment [55-57] Thus, patients with cirrhosis should be closely monitored for HCC even if they are in the early stages and treated with oral antivirals. Treatment of patients with HBV-associated cirrhosis using ETV is recommended due to its strong and high barrier to resistance [58, 59].

In a multicenter, retrospective, cohort study comprising

1666 patients who received ETV or tenofovir treatment, the majority of whom were noncirrhotic patients (67%), the annual incidence of HCC was 1.37%, and the cumulative risk of HCC was 3.4% and 8.7% at 3 and 5 years, respectively [60]. Another study of 1951 chronic HBV patients from 10 European centers reported that cirrhotic patients who received ETV/tenofovir treatment for at least 5 years had a significantly lower risk of HCC (1.57% and 3.22%, respectively) compared to those who received shorter treatment courses [61].

5.3. Transplant Patients

HBV infection is considered a frequent indication for liver transplantation and currently affects 10%-15% of liver transplant patients. High rates of hepatitis B relapse were observed upon liver transplantation for chronic HBV-related diseases before effective antiviral and immunoprophylactic agents were available. This is highly prevalent in patients with detectable viremia at the time of transplantation. Recurrence of HBV infection has been associated with an increased risk of graft failure and decreased long-term survival [62].

ETV and concomitant low-dose, on-demand hepatitis b immunoglobulin administration is associated with a lower rate of HBV recurrence, and thus, is considered an effective and cost-saving strategy for HBV-related liver transplant patients. HBsAg and HBV DNA should be checked periodically in liver transplant recipients during the post-transplant period to monitor reinfection or viral resistance [63].

5.4. Chronic Renal Failure

Chronic HBV infection in patients with chronic renal failure (CRF) has a distinct and challenging clinical course. The characteristics of this patient group (immunosuppressive effect of renal failure, polypharmacy, susceptibility to nosocomial infections, and immunosuppressive therapy after kidney transplantation) and changes in the clinical prognosis of liver disease influence treatment. The main goal in patients with CRF is to achieve proteinuria remission by preserving renal function and to suppress viral replication, thus preventing viral complications such as cirrhosis and hepatocellular carcinoma [64].

Typically, indications for treatment of chronic HBV are the same for those with and without renal impairment. The choice of antiviral depends partially on creatinine clearance and whether the patient is on hemodialysis or if patient has chronic HBV and reduced renal function. ETV is the recommended first-line oral treatment for previously untreated CRF patients. The dose can be adjusted based on creatinine clearance. Given its high efficacy in above patients and its genetic barrier, ETV is considered the most promising oral antiviral for patients, who are on hemodialysis and/or candidates for renal transplant [13].

5.5. HBV/HCV Coinfection

Treatment of chronic HBV/hepatitis C virus (HCV) coinfection is the same as in monoinfected patients. Typically, the dominant virus must be determined first. Direct-acting antivirals are used in the treatment as HCV is often the predominant virus. However, patients treated with direct-acting antivirals are at risk of HBV reactivation. Therefore, it is recommended that all patients with chronic HCV infection, who are HBsAg positive and have no indication for treatment for chronic HBV infection, receive prophylaxis for HBV during and for 12 weeks following the direct-acting antiviral therapy. Although cases with dominant HBV are less rare, it is recommended that patients treated with NA should be monitored for HCV reactivation and treated with direct-acting antivirals in case of reactivation [65].

5.6. HIV/HBV Coinfection

Several studies on the natural prognosis of HIV/HBV coinfection reported a worse prognosis in terms of higher HBV replication levels, more rapid and frequent progression to cirrhosis, hepatic decompensation, HCC development, and liver-related mortality compared to patients with HBV monoinfection. National and international guidelines recommend treating all HIV-positive individuals with chronic HBV infection with the aim to prevent progression and complications of liver disease, thereby improving survival and quality of life [66-68].

5.7. HBV and Hepatosteatosis

There are relatively few numbers of studies on the effects of NAs used in chronic HBV on hepatosteatosis and serum lipid profile. In a retrospective cohort study of 348 patients with chronic HBV in North America (72% received TDF and 28% received ETV), patients treated with TDF were more likely to have hypercholesterolemia and a reduction in low-density lipoprotein compared to patients on ETV [69]. In the treatment of chronic HBV, it was reported that TAF significantly increased serum lipid levels at the end of 48 weeks of treatment compared to ETV treatment, although there was no increase in the incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) [70]. Paradoxically, certain studies suggested that patients treated with TAF did not have elevated lipid levels compared to HBV-uninfected controls [71].

5.8. Advanced Age

The use of ETV in older adults is considered an important issue given the special pharmacokinetic and pharmacodynamic characteristics of this population. There are several potential causes, which may induce renal dysfunction in older patients, including the aging process, underlying comorbid conditions such as hypertension and diabetes, and

the use of therapeutic agents with possible nephrotoxic potential. ETV may prove to be a better choice as older adults are at high risk for renal and metabolic bone disease. ETV may be preferred in patients over 60 years of age, with bone disease (chronic steroid use or use of other drugs that reduce bone density, history of fragility fractures, osteoporosis), impaired renal function (eGFR < 60 ml/min/1.73 m^2, albuminuria > 30 mg/24 h or moderate proteinuria), low phosphate levels (<2.5 mg/dl), and in patients who undergo hemodialysis. The dose of ETV should be adjusted accordingly in patients with eGFR of <50 mL/min [13].

6. Resistance Development

Antiviral therapies are used to prevent the clinical and histological progression of the disease. This is achieved by long-term suppression of HBV replication. Thus, NA is often the treatment of choice. Nevertheless, the efficacy of antiviral therapy for chronic HBV is reduced due to emerging viral resistance [13]. The requirement of three substitutions for ETV resistance combined with strong suppression of HBV replication, creates a high genetic barrier (due to complete suppression of viral replication) to virologic progression in patients infected with wild-type virus [27]. Therefore, ETV is a potent NA against HBV and drug resistance is rare in patients that have not been exposed to NA. However, previous studies have reported ETV resistance cases in patients that were not previously exposed to NA [27, 72].

Long-term ETV monotherapy is effective for suppressing serum HBV DNA levels in chronic HBV patients with partial virologic response. A multicenter cohort study reported that in patients with partial virologic response with detectable HBV DNA level at week 48 under ETV treatment, virologic response was achieved in 81% of patients in approximately 3 years with ETV treatment without changing the treatment regimen, and neither patient cohort developed ETV resistance [73]. Another clinical study of 142 naive chronic HBV patients indicated that 73.4% of 64 patients with partial virologic response achieved virologic response within 4 years with long-term ETV treatment, and only 2.1% developed viral resistance during 7 years of follow-up [74].

Medication compliance is important for achieving permanent viral suppression and preventing HBV-related complications in chronic HBV treatment. A 10-year, longitudinal, observational study of 894 naive chronic HBV patients, who received ETV treatment, reported that patients with higher medication compliance of 90% or above had lower mortality and less risk of hepatic complications, including cirrhosis and HCC. However, the risk of viral breakage was higher in patients with lower medication compliance of below 90% compared to patients with higher compliance. It was also reported that the risk of liver-related mortality, HCC, and cirrhotic complications significantly increased in the patient group with lower medication compliance. It was also emphasized that complications increased especially in cirrhotic patients, as the rate of medication compliance decreased [75].

7. End of Treatment

End of treatment criteria in patients with chronic HBV infection who have been started on ETV treatment are similar to those treated with other potent oral antiviral agents. In patients who have achieved sustained viral suppression and are eligible for close follow-up after treatment discontinuation, the decision of drug discontinuation can be based on certain variables, including duration of HBV DNA suppression, baseline HBeAg status, liver cirrhosis status, spontaneous HBsAg loss, or reduction in HBsAg titration [9, 13, 76].

As with other oral antiviral agents, spontaneous HBsAg loss under ETV treatment is not expected and is rare (0%-2%) [13]. Guidelines recommend discontinuation of oral antiviral treatment in patients with HBsAg loss. Discontinuation of treatment is rarely recommended and is considered a debated issue in the relevant literature in regard to HBV-associated cirrhotic patients. The Asian Pacific Association for the Study of the Liver (APASL) clinical practice guidelines advise that oral antiviral therapy can be discontinued in certain cases of compensated cirrhosis under close monitoring. Nevertheless, the typical approach is to continue antiviral therapy for life, as this is believed to be crucial for halting the progression of cirrhosis, reducing the risk of hepatocellular cancer development, and increasing life expectancy [9, 12, 13, 76].

Practices are variable and the decision to discontinue ETV should be made for patients, who are eligible for close follow-up, as regards the noncirrhotic patients. If this is the case, the guidelines recommend that treatment can be discontinued for HBeAg-positive patients provided that HBV DNA levels are negative for at least 12 months upon HBeAg seroconversion (preferably 3 years in APASL); for HBeAg-negative patients, treatment can be discontinued provided that long-term persistent viral suppression is achieved (three times at 6-month intervals in APASL, >3 years of HBV DNA negativity in the European Association for the Study of the Liver) while under consolidation therapy for at least 2-3 years [9, 13, 76].

Close monitoring of HBV DNA and ALT levels is necessary, especially in the first 12 months considering that the complications associated with HBV exacerbation may develop in all patients who discontinue ETV treatment. It was reported that viral recurrence is seen in more than 50% of the patients and clinical recurrence in more than 35% of patients, regardless of HBeAg status, although varied viral and clinical recurrence rates in the first year after oral antiviral therapy has been discontinued [76].

8. Real-life Data

Clinical studies reported that ETV is well tolerated, virologic responses (SV) of over 90% were achieved in patients

upon 5 years of treatment, approximately 5% of patients developed HBsAg seroconversion, and 31% lost HBeAg [77-79]. Furthermore, large histologic improvements were reported upon ETV treatment [10]. Nevertheless, clinical trials are conducted under standardized conditions and often exclude elderly patients, patients with co-infections, or those with comorbidities. Therefore, data from real-life studies are important to support and validate the results reported by the clinical trials [79].

Treatment response in chronic HBV is evaluated by permanent suppression of HBV DNA level, seroconversion of HBsAg and HBeAg, improvement in ALT values, and improvement in liver histology [77]. The risk of HCC is considered significantly reduced when these goals are achieved [85]. Accordingly, data from ETV-related real-life studies reported results that supportive of clinical trials with high rates of consistency.

8.1. Viral Response (VR) Rates in Real-life Studies

Real-life studies have suggested that the likelihood of HBV DNA loss increases by an average of 5% each month after the onset of ETV treatment, and VR rate was over 75% after a 4-year treatment [75, 79]. It was reported that VR was higher in NA-naive and HBeAg-negative patients. VIRGIL study [75], one of the largest real-life studies conducted in Europe, reported that responses in NA-naive and NA-experienced patients were 86% and 61%, respectively, and in another study, it was 51% and 17%, respectively [80, 81].

In one of China's largest real-life studies on ETV [82], the VR rates in NA-naive and NA-experienced patients were 69% and 53%, respectively. In this study, VR was 54% in HBeAg-positive patients and 88% in HBeAg-negative patients. In other studies, VR rates of 88% vs. 98% [83], 65% vs. 95% [75], 61% vs. 92% [84] were reported in HBeAg-positive and -negative patients, respectively. In the ENUMERATE study [85], one of the largest real-life studies with the largest number of patients conducted in the USA, VR rates were 84% vs 96%, respectively. It was reported that the VR rate in cirrhotic patients (68%) was comparable to noncirrhotic patients [82]. In a multicenter, prospective study [86], which included NA-naive patients with decompensated cirrhosis, VR upon ETV treatment was 92% after 120 weeks of follow-up, and another study [87] reported a very high rate (89%) after 24 months of follow-up.

8.2. Serologic Response Rates in Real-life Studies

Similar to VR, serologic response rates differ in patients exposed or not exposed to NA. In a study, HBeAg seroconversion rates were 17.4% and 25.3%, respectively, whereas HBsAg seroconversion rates were 5.8% and 6.3% in NA-naive patients and patients previously exposed to NA, respectively [80]. In the ENUMERATE study, 1- and 5-year HBeAg loss was 10.6% vs. 46% and HBeAg seroconversion was 8.9% vs. 33.7%, whereas HBsAg seroconversion rate was 5.2% in HBeAg-positive patients and 4.6% in HBeAg-negative patients at year 5 [85].

8.3. Biochemical Response Rates in Real-life Studies

ALT normalization is one of the treatment goals. In the ENUMERATE study [89], ALT normalization rates of 72.8%, 78.1%, and 80.4% were achieved at years 1, 3, and 5, respectively. In the VIRGIL study [75], ALT normalization rates were 74% in NA-naive patients and 66% in patients previously exposed to NA. In two other studies, these rates were 76% vs. 78% (84) and 87% vs. 83% [82], respectively.

Another study reported similar biochemical response rates in HBeAg-positive patients (78%) and HBeAg-negative patients (83%), with 82% of patients achieving a biochemical response upon 48 weeks of treatment [84]. A study, which investigated ETV response in adolescents, showed that ALT normalization rate of 87.5% after 2 years of follow-up was at least as high as in adults [75]. Similarly, it was reported that biochemical response was over 70% in cirrhotic patients [82].

8.4. Histological Response and HCC Data in Real-life Studies

Clinical trials reported that up to 90% histological improvements and regression in fibrosis scores were achieved in patients upon ETV treatment [10, 56]. Accordingly, a number of real-life studies, which confirmed the results of clinical trials, reported that the efficacy of ETV treatment in cirrhotic patients was comparable to that in noncirrhotic patients, and that the risk of HCC was significantly reduced in the long term [75, 82].

In a real-life study of the Chinese population, ETV treatment was associated with histologic improvements as high as 89.5% in NA-naive patients with compensated or decompensated cirrhosis [88]. Referring to the risk of HCC, Hosaka et al. reported the 5-year cumulative HCC incidence rates of 3.7% in the group, which received ETV, and 13.7% in the control group [55]. Although the efficacy of ETV in reducing the risk of HCC was demonstrated, there is an ongoing debate between studies, which compare its efficacy with that of TDF. Certain studies reported that there was no difference between ETV and TDF [89-92], while others asserted that TDF was superior to ETV [93-95].

9. Future Research and Perspectives

Antiviral agents used for chronic HBV treatment are orally administered as a single daily dose. Since treatment compli-

ance is important for viral suppression and can be permanent, there is ongoing research on different formulations of these long-acting drugs, including parenteral injection or subcutaneous implant [96]. It was reported by an experimental study, which investigated polymer-based subcutaneous implant formulations containing ETV, that drug release continued in rat tissues for up to 180 days, but ETV-induced localized toxicity developed [97].

In another study, Ho et al. synthesized a new ETV precursor lipid ester molecule (entecavir-3-palmitate) and aqueous microparticles formed from this molecule were subcutaneously administered to rats; authors reported a steady drug release of up to 4 weeks with a single dose injection [98]. In a study by Zhang et al., ETV-integrated extended-release multiple microspherical particles were developed and administered intramuscularly to rats; accordingly, stable plasma concentrations up to 42 days were achieved with a single dose injection. The authors suggested that this new formulation was promising for alternative treatment of HBV [99].

Furthermore, it was reported that ETV also had potential oncologic antitumor activity in addition to its potent antiviral activity. ETV is a safe drug that has been successfully used in combination with chemotherapeutic drugs for decades to prevent HBV reactivation in patients with cancer. Moreover, recent studies suggested that ETV inhibited the enzyme lysine specific demethylase 5B (KDM5B), which is expressed in breast, lung, skin, liver, and prostate tumors, and PARP-1, which plays an important role in DNA repair in tumor cells. KDM5B is a transcriptional repressor of tumor suppressor genes, and it is well-established that overexpression of this enzyme can lead to drug resistance in some types of tumors. Inhibition as induced by ETV on KDM5B may prevent the proliferation and apoptosis of tumor cells and may contribute to tumor cell death through PARP-1 inhibition. These properties suggest that ETV may have additional potential for use in oncology in combination with chemotherapeutic drugs in the treatment of cancer, as inhibition of both enzymes is associated with reduced occurrence of tumor resistance [100-102].

10. Conclusions

ETV was the first molecule used in the treatment of chronic HBV with had a high barrier to resistance and given its safe profile and low drug-drug interaction, it is still a widely used nucleoside analog. ETV use in compensated and decompensated cirrhotic patients seems highly effective in terms of tolerability and viral suppression [86, 101]. The decrease in the number of new chronic HBV cases upon effective vaccination, and the effectiveness of elimination efforts support the expectation that HBV infection could be brought under control in the near future. Nevertheless, the phenomenon of an aging population should not be ignored in the treatment of chronic HBV. Therefore, there is ever-increasing importance of comorbidity management and medication compliance in chronic HBV treatment [103, 104].

ETV has been used as a treatment for chronic HBV for many years, and thus, there is a wealth of real-life data regarding its usage. Patient drug compliance, low bone and renal side effects, weight gain, low risk of MASLD, and metabolic dysfunction-associated steatohepatitis (MASH) are indicative of the fact that ETV can be used safely in the future.

Abbreviations

HBV	Hepatitis B virus
ETV	Entecavir
NA	Nucleos(t)ide Analogs
LAM	Lamivudine
ADV	Adefovir
LdT	Telbivudine
TDF	Tenofovir Disoproxil Fumarate
TAF	Tenofovir Alafenamide
ALT	Alanine Aminotransferase
GFR	Glomerular Filtration
AASLD	American Association for the Study of Liver Diseases
FDA	Food and Drug Administration
ULN	Upper Limit of Normal
cccDNA	Covalently Closed Circular DNA
peg-IFN	Pegylated Interferon
HCC	Hepatocellular Carcinoma
CHB	Chronic Hepatitis B
CRF	Chronic Renal Failure
HCV	Hepatitis C Virus
MASLD	Metabolic Dysfunction-associated Steatotic Liver Disease
APASL	Asian Pacific Association for the Study of the Liver
VR	Viral Response

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Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

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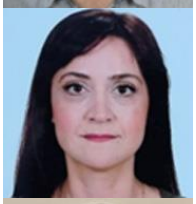
Biography

Cigdem Mermutluoglu is an Assistant Professor in the Department of Infectious Diseases and Clinical Microbiology at Dicle University Faculty of Medicine, Diyarbakır, Türkiye. I am an Assistant Professor in the Department of Infectious Diseases and Clinical Microbiology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye. I have been working in the field of infectious diseases since 2009. Dr. Mermutluoğlu is actively involved in national multicenter studies and academic collaborations on liver disease and infection-related metabolic outcomes.

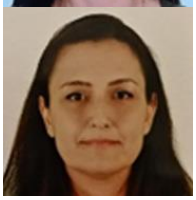
Halim Bayram works as an Infectious Diseases and Clinical Microbiology Specialist at Gaziantep City Hospital. He graduated from Çukurova University Faculty of Medicine in 2004. After completing his specialist training in the Department of Infectious Diseases and Clinical Microbiology at Celal Bayar University Faculty of Medicine, he completed his compulsory service at Kilis State Hospital in 2010 and worked at Gaziantep Dr. Ersin Arslan Training and Research Hospital from 2013 to 2023. He has been working at Gaziantep City Hospital since October 2023.

Tugce Bozok Simsek is an assistant professor in the Department of Infectious Diseases and Clinical Microbiology at Mersin University Faculty of Medicine. She graduated from Cukurova University Faculty of Medicine in 2012 and completed her specialist training in the Department of Infectious Diseases and Clinical Microbiology at Cukurova University Faculty of Medicine in 2019.

Abdullah Golbol is a specialist in infectious diseases. He graduated from Ankara University Faculty of Medicine in 2011 and received his specialty training in 2017 at İzmir Katip Çelebi University Atatürk Training and Research Hospital.

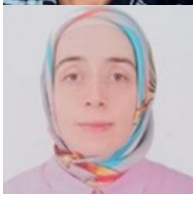


Evrim Gulderen Kuscu is an assistant professor at the Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Kahramanmaras University. She graduated from Ankara University Faculty of Medicine in 2001 and completed her specialist training at the Department of Infectious Diseases and Clinical Microbiology at Ankara Numune Education and Research Hospital in 2008.



Hande Berk Cam currently serves as a specialist physician in the Department of Infectious Diseases and Clinical Microbiology at Antalya Training and Research Hospital. She graduated from Marmara University School of Medicine (English Program) in 1998 and completed her specialty training in Infectious Diseases and Clinical Microbiology at Istanbul University, Istanbul Faculty of Medicine, in 2005. Since 2013, she has been providing regular infectious disease consultation services to the Hematology and Bone Marrow Transplantation Unit of the same hospital, where she is responsible for managing infectious complications in this patient population.

Yusuf Arslan has been working as a specialist in Infectious Diseases and Clinical Microbiology at Batman Training and Research Hospital for the past five years.



Rukkiye Bulut Assistant professor, MD, was born in Konya in 1988. She completed her primary and high school education in Konya. She graduated from Selcuk University Faculty of Medicine in 2012. She completed her residency training in Infectious Diseases and Clinical Microbiology in Necmettin Erbakan University Meram Faculty of Medicine between 2013-2019. She worked as an attending physician at Gumushane State Hospital for approximately 3 years. She has been working as an academician at Necmettin Erbakan University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology since 2022.

Hakan Celik graduated from Cumhuriyet University Faculty of Medicine in 2012. Between 2012 and 2018, he served as a physician under the Turkish Ministry of Health, gaining broad clinical experience. From 2019 to 2020, he worked at Yeni Yuzyıl University Gaziosmanpasa Hospital Emergency Department, followed by a position as Medical Manager at Abdi İbrahim Pharmaceuticals between 2020 and 2024. Dr. Celik was known for his dedication to medicine and patient care. He is fondly remembered by his colleagues and students for his professionalism, kindness, and commitment to improving human health.

Mustafa Kemal Celen is a professor senior faculty member. He has over two decades of clinical and academic experience in viral hepatitis, HIV infection, and related co-infections. Professor Celen has participated in numerous national and international multicenter studies and clinical trials, contributing to evidence-based improvements in infectious disease management. He is actively involved in collaborative research projects and public health initiatives aiming to enhance prevention and treatment outcomes both in Turkiye and worldwide.

Research Field

Cigdem Mermutluoglu: viral hepatitis (HBV, HDV, HCV), metabolic-associated fatty liver disease (MASLD/MASH), HIV infection,

and antimicrobial resistance in Gram-negative bacteria.

Halim Bayram: Resistant healthcare-associated infections, community-acquired infections, viral hepatitis, bacteriological and viral diseases.

Tugce Bozok SimSek: Viral hepatitis, HIV, sepsis, healthcare-associated infections.

Abdullah Golbol: Viral hepatitis, healthcare-associated infections.

Evrim Gulderen Kuscu: Viral hepatitis, HIV, invasive fungal infections, healthcare-associated infections.

Hande Berk Cam: Infectious complications in immunosuppressed patients (including HIV), febrile neutropenia, antifungal therapies, antiviral prophylaxis and vaccination strategies, nosocomial bacteremia, and antibiotic resistance.

Yusuf Arslan: Hepatitis, HIV, and brucellosis infections.

Rukkiye Bulut: Viral hepatitis, health care-associated infections, infections in immunocompromised host.

Hakan Celik: Viral hepatitis.

Mustafa Kemal Celen: Hepatitis B and D management, HIV treatment optimization, and infection control.