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REVIEW ARTICLE

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# Hepatitis B virus long-term impact of antiviral therapy nucleot(s)ide analogues (NUCs)

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## Abstract

The goal of antiviral therapy is to improve the quality of life and survival of patients with chronic hepatitis B (CHB) by halting the progression to cirrhosis, end-stage liver disease or hepatocellular carcinoma (HCC), thus preventing anticipated liver-related death. Oral administration of potent and less resistance-prone nucleot(s)ide analogues (NUCs), such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF) has become the most popular treatment strategy worldwide because of their excellent efficacy and safety profile as well as easy management confirmed in both registration trials and in clinical practice studies. Long-term administration of ETV or TDF suppresses HBV replication in >95% of patients, resulting in biochemical remission, histological improvement including the regression of cirrhosis and prevention or reversal of clinical decompensation but not the development of HCC, particularly in patients with cirrhosis. Moreover, NUCs can be administered to all patients including those with severe liver disease, the elderly and in those who do not respond, are unwilling to take or have contraindications to interferon. The need for long-term, perhaps indefinite, treatment is the main limitation of NUCs therapy with the associated costs, unknown long-term safety and the low rates of hepatitis B surface antigen (HBsAg) seroclearance, which is still the best stopping rule for NUCs-treated patients with cirrhosis.

**KEYWORDS**
cirrhosis, hepatitis B, hepatocellular carcinoma, nucleot(s)ides analogues

## 1 | INTRODUCTION

Chronic infection with the hepatitis B virus (HBV) is a major health problem worldwide, with roughly 240 million people with chronic infection.[1] If left untreated, patients with HBV infection are at high risk of progression to cirrhosis, clinical decompensation, HCC and liver-related death.[2–4] To stop the progression of liver disease, international guidelines recommend either a short course of pegylated interferon (Peg-IFN) or the long-term administration of third-generation nucleot(s)ide analogues (NUCs), such as entecavir (ETV) or tenofovir disoproxil fumarate (TDF). Phase III registration trials of a new tenofovir, tenofovir alafenamide (TAF), have recently been published.

We review the evidence of the long-term benefits of third-generation NUCs therapy in patients with chronic hepatitis B (CHB) infection.

**Abbreviations:** ADV, adefovir; CHB, chronic hepatitis B; ETV, entecavir; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LMV, lamivudine; MELD, model for end-stage liver disease; NUCs, nucleot(s)ide analogues; PCR, polymerase chain reaction; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

## 2 | VIROLOGICAL, BIOCHEMICAL AND SEROLOGICAL RESPONSES

### 2.1 | ETV and TDF registration trials in NUC-naïve patients: virological response of 98-99% at 8 years

ETV administration for up to 5 years in 183 HBeAg-positive patients (0.5 mg/day the first year, then 1 mg/day) resulted in a virological

(HBV DNA <300 copies/mL) and biochemical response in 94% (88/94) and 80% (78/98) of patients, respectively, with HBeAg seroconversion and HBsAg seroclearance in 23% (33/141) and 1.4% (2/145) of patients.[5] ETV-resistance (R) emerged in one patient (1.2%) only.[6]

High antiviral efficacy was also reported in the long-term follow-up of the TDF registration trial.[7] After 8 years, 98% of the 146 HBeAg-positive patients and 99% of the 264 HBeAg-negative patients achieved a virological response (HBV DNA <400 copies/mL), without evidence of TDF-R. HBeAg seroclearance was achieved in approximately 30% of patients, while HBsAg loss occurred in 12% and 1% of the non-Asian HBeAg-positive and -negative patients respectively. Interestingly enough, no TDF-R was detected through to year 8.[8]

A double-blind study in 126 NUC-naïve HBeAg-positive CHB patients with high viral loads who were randomly assigned to receive TDF plus placebo (n = 64) or TDF plus emtricitabine (FTC) (n = 62) for 192 weeks showed that the TDF and FTC combination provided better viral suppression (HBV DNA <69 IU/mL) than TDF alone (76% vs 55%, $P = .016$). While three cases seroconverted to anti-HBe, none achieved HBsAg seroclearance.[9]

Overall, therapy with ETV or TDF resulted in rapid and profound suppression of HBV replication in both HBeAg-positive and -negative patients, although the PCR-negative rates in high viral load patients is still suboptimal.

**Key points**

- Maintained suppression of hepatitis B virus (HBV) prevents progression of chronic hepatitis B (CHB) to cirrhosis and end-stage liver disease, thus preventing anticipated liver-related death.
- This goal can be pursued through long-term administration of the nucleot(s)ide analogs (NUCs) entecavir (ETV) and tenofovir (TDF), that are now the most popular antiviral strategy worldwide.
- NUCs result in marginal hepatitis B surface antigen (HBsAg) clearance, but are associated with almost universal virological and biochemical remission, histological improvement and the prevention or reversal of liver decompensation.
- Despite the suppression of HBV, the risk of hepatocellular carcinoma (HCC) still remains in both patients with and without cirrhosis.

## 2.2 | ETV and TDF in field practice studies in NUC-naïve patients: virological response of 97-99% at 5 years

In two European field practice studies including 1162 CHB patients (mean age 51 years old, 76% HBeAg negative, 36% with cirrhosis) treated with ETV, the 5-year cumulative probability of a virological response was 97% and 99% respectively.[10,11] Only one patient developed ETV-R (L180M, M204V, S202G) at year 3, and was successfully rescued by TDF.[11] The same efficacy was also reported in Asian studies including 1126 NUC-naïve patients. At year 5, 98% and 95% of patients, respectively, achieved undetectable serum HBV DNA and normal ALT, while two patients developed ETV-R within the fourth year of treatment[12–15] (Figure 1).

Four European field practice studies including 1597 CHB patients (mean age 47 years, 75% HBeAg negative, 26% with cirrhosis) reported that a 3-4 year course of TDF treatment achieved virological response rates ranging from 92% to 100% without emergence of TDF-R[16–19] (Figure 2).

Although long-term ETV or TDF treatment achieves a virological response in all patients, the rates of HBsAg seroclearance remain very low, ranging from 0.2% to 5.7%. Moreover, this endpoint is rarely achieved (~1%) in HBeAg-negative patients or in HBeAg-positive patients infected at birth. On the other hand, in NUC-treated HBeAg-positive patients with good predictors of response, such as short duration of infection, genotype A, elevated ALT levels and moderate levels of HBV DNA, this endpoint can be achieved in up to 20% of the patients after 5 years of treatment.[10–19] This is important because the best stopping rule for NUC-treated patients is HBsAg loss and anti-HBs seroconversion, and the latter is the only safe stopping rule in patients with cirrhosis. However, the possibility of safe discontinuation of NUCs before HBsAg seroconversion remains controversial. A recent review including 1716 patients from 25 studies reported that a durable virological remission, HBV DNA <20 000 IU/mL, was only observed in 51% of initially HBeAg-positive patients and 30% in HBeAg-negative patients after 3 years after NUCs discontinuation.[20]

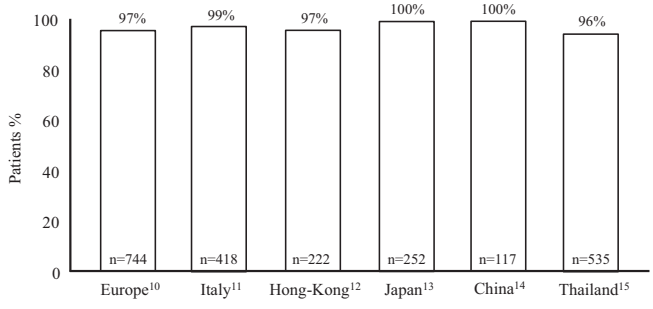


**FIGURE 1** Five-year virological response rates in NUC-naïve CHB patients treated with ETV in clinical practice

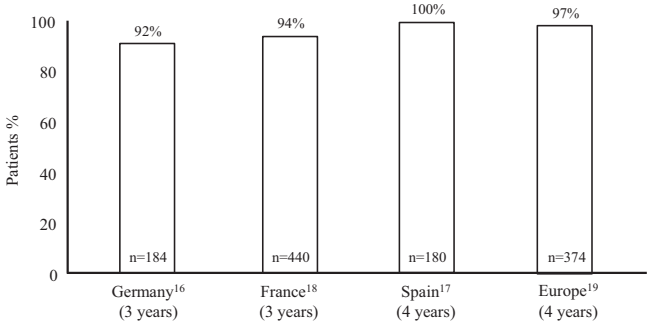


**FIGURE 2** Virological response rates of 3-4 years in NUC-naïve CHB patients treated with TDF in clinical practice

### 2.3 | ETV and TDF in NUC-resistant patients

Although lamivudine (LMV) is no longer recommended by international societies as the first-line therapy for CHB patients because of its suboptimal efficacy and high rates of LMV-R,[2–4] this drug is still a widely prescribed antiviral agent in low-resource countries because it is inexpensive. Switching LMV-R patients to ETV monotherapy has not proven to be effective because of the high rate (43%) of ETV-R associated with a breakthrough after 5 years of treatment.[6] On the other hand, a recent study in 280 LMV-R CHB patients randomized to receive TDF (n = 141) or TDF plus FTC (n = 139) reported similar rates (83%) of virological response (HBV DNA <69 IU/mL) at week 240 of treatment in both arms as well as rates of HBeAg loss and seroconversion, with no emergence of TDF-R.[21] In a recent multicentre Korean trial,[22] Adefovir-resistant (ADV-R) patients (rtA181V/T and/or rtN236T) were randomized to TDF monotherapy (n = 50) or TDF+ETV (1 mg/day) combination therapy (n = 52) for 48 weeks. After week 48, all patients received an additional 48-week course of TDF monotherapy (96 weeks in total). Virological response rates (HBV DNA <15 IU/mL) were similar in the two arms at week 48 (62% vs 63%; $P = .88$) as well as at week 96 (64% vs 63%; $P = .96$). Virological breakthroughs because of poor drug adherence occurred in one and two patients respectively. Additional resistance mutations did not accumulate during treatment.[22]

Overall, TDF monotherapy suppresses viral replication in most patients with previous resistance to nucleoside analogues, whereas ETV is effective in ADV-resistant patients not resistant to LMV. In a few selected cases, the two drugs combined can be used to achieve viral suppression.

### 2.4 | TAF in NUC-naïve patients

In a 48-week phase III RCT comparing the efficacy and safety of TAF vs TDF in HBeAg-negative patients, 94% of patients who received TAF and 93% of those who received TDF achieved complete suppression of viral replication ($P = .47$).[23] In the HBeAg-positive study, 64% of patients who received TAF and 67% of those treated with TDF achieved this endpoint ($P = .25$).[24] HBeAg-negative CHB patients receiving TAF had significantly smaller mean percentage declines in bone mineral density than those receiving TDF (hip −0.29% vs −2.16%; spine −0.88% vs −2.51%, $P < .0001$) and lower mean changes in creatinine clearance (−1.8 mL/min vs −4.8 mL/min; $P = .004$).[23] HBeAg-positive patients receiving TAF also had significantly smaller mean decreases in bone mineral density (hip −0.10% vs −1.72%; spine −0.42% vs −2.29%; $P < .0001$) and smaller mean increases in serum creatinine (0.01 vs 0.03 mg/dL; $P = .02$).[24] Tubular toxicity was demonstrated in HBeAg-positive and negative-patients treated with TDF, but not in those treated with TAF.

Overall, although the virological suppression rates were similar between TAF and TDF, the renal and bone safety profile of the former were better in NUC-naïve patients with eGFR >50 mL/min (by the Cockcroft-Gault method).

## 3 | REGRESSION OF FIBROSIS

In 57 patients receiving long-term ETV treatment, a second liver biopsy performed after a median of 6 years showed significant improvement in the Ishak fibrosis score in 88% of patients, including all 10 patients with advanced fibrosis or cirrhosis at baseline.[25,26] Histological improvement in the 348 patients treated with TDF for 5 years, 304 (87%) was substantial (≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis) and fibrosis regressed with ≥1 unit decrease in the Ishak scoring system in 176 (51%).[27] Seventy-one of the 96 patients with cirrhosis (74%) had a histological reversal of cirrhosis while three (1.2%) of the 252 patients without cirrhosis at baseline progressed to cirrhosis during treatment. Low BMI, absence of diabetes mellitus, normal ALT and mild or absent necroinflammation at year 5 were associated with a higher probability of the regression of cirrhosis and on multivariate analysis, BMI<25 kg/m² was an independent predictor of the regression of cirrhosis (OR 7.4, 95%CI 1.87-29.41, $P = .0044$).[27]

Overall, long-term effective treatment with ETV or TDF prevents the histological progression to cirrhosis and results in the regression of fibrosis or cirrhosis in 80% of the patients included in registration trials. Comorbidities play a major role in perpetuating liver damage, while viral replication is suppressed by oral therapy.

## 4 | REVERSAL OF DECOMPENSATION

Reversal of clinical decompensation has been a clue to confirming the effectiveness of NUCs in preventing HBV-related mortality.[2] In a randomized, open-label study in 195 patients with decompensated cirrhosis (Child-Turcotte-Pugh score ≥7), ETV 1 mg/daily caused greater viral suppression (57% vs 20%; $P < .0001$) and decrease in the MELD score decline (2.6 vs 1.7 points) than ADV 10 mg/day. Cumulative death rates were 23% vs 33% in ETV and ADV-treated patients respectively.[28] The virological efficacy of one year of TDF in patients with decompensated liver disease was evaluated in a double-blind study that randomized 112 patients to receive either TDF (n = 45), combination therapy with FTC plus TDF (n = 45) or ETV (n = 22). After 48 weeks of treatment, similar response rates (HBV DNA <400 copies/mL) were observed in the three treatment arms (71%, 88% and 73% respectively) while ALT normalized in 57%, 76% and 55% of patients respectively. A 2-point median MELD score reduction and a 1-point median Child-Pugh score reduction was observed in all treatment arms to confirm the similar efficacy of these regimens.[29]

## 5 | PREVENTION OF DECOMPENSATION

Clinical decompensation is prevented in ETV or TDF-treated patients with compensated cirrhosis as long as HBV is the only cause of liver damage. This has been shown in 3-5 year real-life cohort studies in Europe and Asia with ETV[30–33] and in 3-4 year real-life cohort studies in Europe with TDF.[19,33] In Hong Kong, 1446 ETV-treated Chinese

patients followed up for 36 ± 13 months and 424 treatment-naïve patients followed up for 114 ± 31 months were studied. In patients with cirrhosis (482 ETV-treated, 69 treatment-naïve), ETV-treated patients had reduced risks of hepatic events (HR, 0.51; 95% CI, 0.34-0.78; $P$ = .002).[30] In the PAGE-B cohort study, clinical decompensation only occurred in 6/446 (1.3%) patients with compensated cirrhosis treated for 5 years with ETV or TDF (G. Papatheodoridis, personal communication). In most of these cases, other cofactors of liver damage could be identified.

## 6 | IMPROVEMENT IN PORTAL HYPERTENSION

Long-term pharmacological NUCs suppression of HBV in HBeAg-negative genotype D patients with compensated cirrhosis leads to the regression of grade 1 fibrosis oesophageal varices in most of the patients (83%) treated continuously for 12 years with a negligible risk of de novo occurrence of oesophageal varices.[34] In a Chinese study including 79 patients treated with cirrhosis and 39 untreated controls, antiviral therapy delayed the progression of oesophageal varices, with lower mean increase in variceal grade per year in treated patients (1.0±1.3 vs 1.7±1.2, respectively, $P$ = .003).[35]

## 7 | PREVENTION OR REDUCTION OF HCC

Chemoprevention of HCC by long-term administration of ETV or TDF, is still a matter of debate. The annual incidence of HCC in NUC-naïve CHB patients without cirrhosis ranged from 0.6% to 1.4% and 0.8% to 1.4% in Asian and European patients treated with ETV respectively[10,11,32,33,36–39], while the annual HCC risk in TDF-treated patients without cirrhosis ranged from 0.4 to 1%.[19,33,39] In ETV-treated patients with cirrhosis, the annual incidence of HCC ranged from 2% to 4.1% in Asian studies[31,36,37,39] and is 2.6% in European studies while data from European studies in TDF-treated patients with cirrhosis revealed that the risk ranged from 3.7% to 4%.[19,33,39] These HCC rates are very similar to estimates in natural history studies in untreated patients (Figures 3 and 4).

However, the HCC rates tended to decline compared to both the natural history studies and internal controls after 3-4 years of successful therapy.[36,37,40] A Japanese study did not confirm these results, showing a rapid and profound protective effect of ETV, although the number of enrolled patients was limited, there was no matching for the relevant predictors of HCC, the patients with early tumours were excluded and the rates of diagnosis of HCC were unexpectedly high in the control group.[36] HCC chemoprevention by ETV was not evaluated in a long-term multicentre study in Italy,

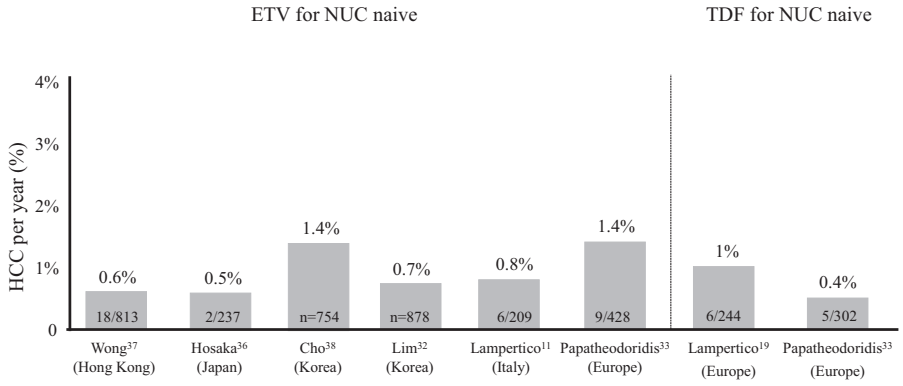


**FIGURE 3** HCC rates per year among NUC-naïve CHB patients without cirrhosis treated with ETV or TDF monotherapy for 4-6 years

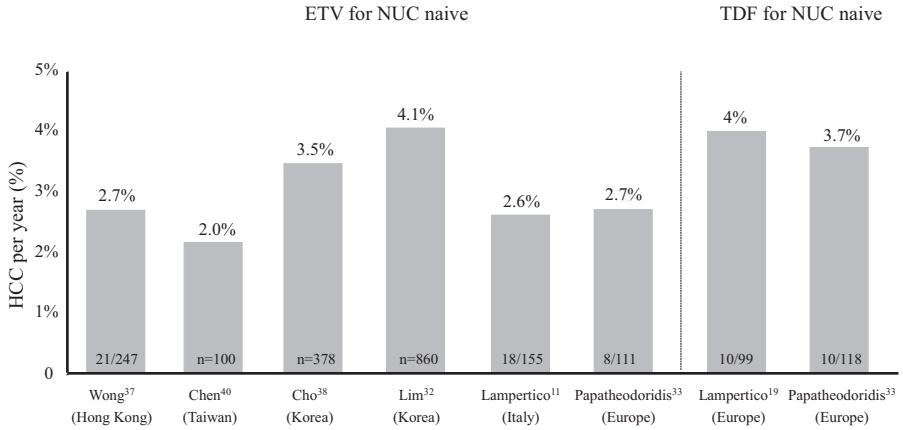


**FIGURE 4** HCC rates per year among NUC-naïve patients with compensated cirrhosis treated with ETV or TDF monotherapy for 4-6 years

where the yearly tumour rate in patients with compensated cirrhosis was 2.7%, that is, similar to that of the untreated population.[11] This was also the outcome in a Greek study in the rate of HCC (3.4%) in HBeAg-negative patients with cirrhosis (80% NUC-naïve) who were treated with ETV.[41]

In a recent review assessing the incidence of HCC in patients treated with modern antiviral drugs, the mean incidence of HCC in NUC-treated patients were 0.72 and 0.58 per 100 person years in patients without cirrhosis and 3.44 and 3.71 per 100 person years in those with cirrhosis, in Asian and Caucasian studies respectively.[42]

The 6-year TDF registration study described 14 cases of HCC (nine HBeAg negative at baseline, three cirrhotics) with an estimated yearly rate of 0.4%.[43] Compared to predicted HCC rates with the REACH-B score, the HCC rates remained unaffected despite successful TDF treatment for the first 5 years. In the 4-year multicentre European NUC-naïve TDF cohort study, HCC developed more frequently (10/99) in patients with cirrhosis (yearly rate 4.2%) than in patients with CHB (6/244, yearly rate 1%).[19] These HCC rates are not only similar to those reported in ETV studies but are also similar to predictions for European patients with HBV who were left untreated. In a large, multicentre, European cohort study, 1666 adult patients with CHB treated with ETV or TDF were enrolled. The 1-, 3- and 5-year cumulative probabilities of HCC were 1.3%, 3.4% and 8.7% respectively.[33]

Because the early diagnosis of HCC increases indications for curative therapies and in certain cases the patient's prognosis, identification and close surveillance for the risk of HCC is important.[2,3] Risk scores (GAG-HCC, CU-HCC and REACH-B) for the prediction of HCC have recently been developed and validated in cohorts of untreated and treated Asian CHB patients.[37,44–46] The PAGE-B score which is only based on baseline age, gender and platelet count (c-index = 0.82, 0.81 after bootstrap validation) has been developed and validated for Caucasian patients, in whom the accuracy of these Asian scores was found to be suboptimal. Patients with a PAGE-B score ≤9, between 10-17, ≥18 had a 5-year cumulative incidence of HCC of 0%, 3% and 17%, respectively, in the derivation and 0%, 4% and 16% in the validation dataset.[39] This score may represent a simple and reliable tool to predict the 5-year risk of HCC in CHB patients treated with ETV or TDF.

## 8 | SAFETY

Although NUCs are generally well tolerated, clinical manifestations including myopathy, nephropathy, neuropathy, hepatic steatosis, pancreatitis, macrocytosis, hyperlactaemia and lactic acidosis have been described in few cases.[47]

### 8.1 | Nephrotoxicity

Ten cases of TDF-associated Fanconi syndrome, an acute and severe form of proximal tubular toxicity, have been described, while no cases have been linked to the administration of ETV.[47–49] A TDF to ETV switch is the current recommended strategy as a rescue protocol for this severe but rare complication. TAF could be also useful in these patients but more data are necessary before this strategy can be recommended.

In nine real-life studies evaluating changes in renal function in 1310 NUC-naïve patients treated with ETV and 1287 with TDF, nephrotoxicity was mainly observed with TDF.[47] In 664 NUC-experienced patients enrolled in five real-life studies, the impact of TDF on renal function varied between studies. Possible reasons for the observed discrepancies include the use of different definitions and cut-offs for reporting renal toxicity, and differences in patient populations (i.e. excluding patients with comorbidities). A significant association was found, in particular for older age, pre-existing renal insufficiency, comorbidities and prior long-term use of ADV.[47]

To prevent and/or reduce the risk of renal complications, monitoring of glomerular function and tubular function to define the optimal dose and identify the few cases with kidney impairment, respectively, is currently recommended.[2–4] TAF could represent a new therapeutic option for NUC-experienced patients with a low eGFR and/or chronic tubular damage, but these studies are still ongoing.

### 8.2 | Reduced bone mineral density (BMD)

Three studies have specifically assessed changes in BMD during NUC therapy.[47] In a US study, 106 adolescents did not reach the endpoint of a decrease of at least 6% from baseline in lumbar spine BMD over 72 weeks. An Italian study assessed BMD in 60 CHB patients who switched from LMV+ADV to TDF. The proportion of patients with reduced BMD was 53% at baseline, 73% at month 6 and 53% after 12 months of TDF treatment. In a UK cohort including 170 patients, a reduction in BMD during TDF was limited to one anatomical site. Age, smoking, a lower BMI and TDF exposure were independent predictors of low BMD in univariate and multivariate analysis. Because the real impact of NUC on BMD has not been confirmed, current guidelines and reviews do not recommend determining bone density at baseline and during NUC therapy in HBV patients.[2–4,47]

### 8.3 | Lactic acidosis

In 2009, there were five cases of lactic acidosis reported in patients with decompensated cirrhosis (all with a baseline MELD score >22 points) who were receiving ETV.[50] This risk was not confirmed in other studies including patients with severe liver disease treated with ETV for 2 years.[29,51] No major safety issues were reported in 3823 patients exposed to ETV for 12-66 months.[11,12,52–54] However, because all NUC can potentially cause lactic acidosis in patients with advanced liver disease, these patients must be carefully monitored.

## 9 | SURVIVAL

A retrospective–prospective study from Hong Kong compared 1446 ETV-treated patients and 424 untreated patients showed that there was no difference in hepatic events between treated and untreated

cohorts.[30] However, the risk of all clinical outcomes was reduced in the 482 patients with cirrhosis treated with ETV compared with to the 69 untreated patients with cirrhosis after adjustment for the MELD (model for end-stage liver disease) score, including liver-related mortality (HR 0.26; 95% CI 0.13-0.55; $P < .001$) and all-cause mortality (HR 0.34; 95% CI 0.18-0.62; $P < .001$). Interestingly, ETV-treated patients with cirrhosis who failed to achieve undetectable serum HBV DNA had a comparable risk of hepatic events as untreated patients.[30] A retrospective Korean study including 5374 patients with CHB treated with ETV (n = 2000) or LMV (n = 3374) showed that ETV therapy was associated with a significantly lower risk of death or transplantation than LMV in patients with cirrhosis (HR 0.42; 95% CI 0.31-0.57) but not in those without.[32] A nationwide, multicentre, retrospective–prospective cohort study in Taiwan in 1315 ETV-treated and 503 untreated patients with cirrhosis with a median treatment and follow-up of 4 and 6 years, respectively, reported that ETV therapy significantly reduced risks of liver-related and all-cause mortality compared with the untreated cohort.[55]

In the PAGE-B cohort study, 1815 adult Caucasians with CHB with or without compensated cirrhosis who received ETV/TDF for ≥12 months were included.[56] Five-year survival was 97% in patients without cirrhosis and 92% in those with compensated cirrhosis ($P < .001$). HCC was the only cause of liver-related death in the 1269 patients without cirrhosis while in the 503 patients with cirrhosis, 50% died of liver disease (HCC in 75% of cases) while 50% died of non-liver-related causes. In conclusion, a large cohort of Caucasian patients treated for 5 years with ETV or TDF survival was excellent, that is, >95%, with a significant proportion of deaths because of causes not related to liver disease. The development of HCC is a major factor affecting overall mortality and the only factor affecting liver-related mortality in these patients.

## 10 | CONCLUSIONS

Long-term administration of third generation NUCs such as ETV or TDF suppresses viral replication in most patients, resulting in biochemical remission, histological improvement as well as the regression of cirrhosis in two thirds of responders. The safety profile of these oral therapies is excellent, although a few selected patients on TDF may develop Fanconi syndrome or chronic tubular toxicity. TAF can represent an important new therapeutic option in these latter patients. Successful pharmacological suppression influences the natural course of CHB by improving portal hypertension, reducing/preventing clinical decompensation and extending survival. HCC is the only complication that may occur with effective oral therapy as long as there are no other causes of liver disease. Lifelong HCC monitoring is therefore essential in this population.

Overall, the current treatment algorithm for HBV infection is highly effective, safe, simple and inexpensive. This is even more so since ETV and TDF will soon become available as generics. Nevertheless, unmet medical needs do exist such as identifying new stopping rules for patients on long-term NUCs therapy, new strategies to achieve a functional cure and sensitive scores to identify responders at risk of HCC.

## CONFLICTS OF INTEREST

Pietro Lampertico: speaking bureau/advisory boards: BMS, Roche, Gilead Sciences, GSK, MSD; Mauro Viganò: speaking and teaching: Roche, Gilead Sciences, BMS; Others: nothing to disclose.

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