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Hepatitis B Virus Treatment and Hepatocellular Carcinoma: Controversies and Approaches to Consensus

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Keywords
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Abstract
Background: Long-term therapy with nucleos(t)ide analogs (NAs) such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF) favorably affects the incidence of hepatocellular carcinoma (HCC) on the basis of data from randomized or matched control studies. Recent data suggest a lower HCC incidence after 5 years of ETV or TDF therapy in chronic hepatitis B (CHB) patients, especially those with baseline cirrhosis. ***Summary:*** Three controversial issues remain to be resolved regarding hepatitis B virus (HBV) treatment and HCC. (1) The efficacy of antiviral treatment for the prevention of HCC is not established. The guidelines of the American Association for the Study of Liver Diseases (AASLD), the Asian Pacific Association for the Study of the Liver (APASL), and the European Association for the Study of the Liver (EASL) for the management of HBV infection state that antiviral treatment of HBV with interferon and NAs prevents the development of HCC. Among experts in CHB treatment, however, there is disagreement on the HCC prevention effects of antiviral treatment. (2) The rationale for antiviral management in patients with high HBV DNA and normal levels of alanine aminotransferase is unclear. The AASLD, EASL, and APASL guidelines do not recommend antiviral treatment for immune-tolerant CHB patients, and the terms and methods of treating such patients remain to be clarified. (3) The efficacy of first-line treatment with NAs, including ETV, TDF, and tenofovir alafenamide fumarate (TAF), to prevent HCC in CHB patients remains unknown. Several studies have produced controversial results regarding the effects of NAs on the risk and prevention of HCC. In the present review, we discuss these 3 issues, citing recent studies and clinical management guidelines from major international associations. ***Key Messages:*** Suggested approaches for reaching a consensus including applying the propensity score matching method, performing randomized controlled studies, and performing clinical studies with larger numbers of subjects and longer follow-up.

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Introduction

Chronic hepatitis B (CHB) is the most common cause of hepatocellular carcinoma (HCC) and the second leading cause of cancer-related mortality worldwide [1, 2]. Global deaths from HCC attributed to hepatitis B virus (HBV) are projected to double by 2040 [1–3]. Analysis of randomized or matched control studies indicates that long-term therapy with nucleos(t)ide analogs (NAs), such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF), reduces the incidence of HCC [4–6].

Recent data suggest that 5 years of ETV or TDF therapy reduces the incidence of HCC in CHB patients, especially those with baseline cirrhosis [4, 6]. Nonetheless, the following 3 controversial issues regarding HBV treatment and the incidence of HCC remain to be resolved.

1. The efficacy of antiviral treatment for the prevention of HCC is not established.

Guidelines of the American Association for the Study of Liver Diseases (AASLD) [7], the Asian Pacific Association for the Study of the Liver (APASL) [8], and the European Association for the Study of the Liver (EASL) [4] for the management of HBV infection recommend antiviral treatment for HBV with interferon (IFN) and NAs for the prevention of HCC. Among experts in CHB treatment, however, there is disagreement on the HCC prevention effects of antiviral treatment.

2. The rationale for antiviral treatment of patients harboring high HBV DNA and normal alanine aminotransferase levels is not yet clear.

AASLD, EASL, and APASL guidelines have not reached a consensus regarding the efficacy of treatment during the immune-tolerant phase. Although positive hepatitis B e antigen (HBeAg), high serum HBV DNA, and normal alanine aminotransferase (ALT) levels are 3 key features of this phase, the guidelines do not currently recommend antiviral treatment for immune-tolerant CHB patients.

Further, the correlation between very high HBV DNA levels (especially >6 $\log_{10}$ IU/mL) and risk of HCC remains unclear, especially in middle-aged and older HBeAg-positive patients with normal ALT levels [1, 9]. Thus, the terms and methods of treating CHB patients with high levels of HBV DNA and normal levels of ALT in the immune-tolerant phase must be clarified.

3. The efficacy of first-line NAs, including ETV, TDF, and tenofovir alafenamide fumarate, for CHB patients to prevent HCC remains unclear.

ETV, TDF, and tenofovir alafenamide fumarate (TAF) in the AASLD and EASL clinical practice guidelines [4, 7], and ETV and TDF in the APASL clinical practice guidelines are recommended as first-line NAs for CHB because of their comparable high antiviral efficacy and low rate of resistance [8]. The results of several studies of ETV, TDF and TAF administration, however, have raised questions regarding the risk of HCC. To date, no studies have provided clear evidence regarding the potential HCC prevention effects of ETV, TDF, and TAF administration [10–16]. In the present review, we address these 3 issues and cite recent studies on HBV treatment and HCC prevention with reference to AASLD, EASL, and APASL guidelines for the management of HBV infection and suggest approaches for reaching a consensus.

Efficacy of Antiviral Treatment for HCC Prevention

Regarding the efficacy of antiviral treatment for HBV with IFN and NAs, the AASLD 2018 guidelines for the management of HBV infection state that, as for any patient with CHB, the treatment goals are to reduce the risk of progression to cirrhosis- and liver-related complications, including HCC. The APASL 2016 guidelines for the management of HBV infection state that the risk of CHB progressing to HCC may be reduced by antiviral therapy and recommend liver biopsy for noncirrhotic patients with a family history of HCC as well as treatment for moderate to severe inflammation or significant fibrosis.

The EASL guidelines for the management of HBV infection recommend treatment with NAs for the prevention of HCC in CHB patients [4, 6] on the basis of a European study (Table 1). A European 10-center cohort study of 1,951 adult Caucasian CHB patients (cirrhosis 201, 27%) without HCC at baseline received ETV/TDF for ≥1 year; 1,205 (62%) patients without HCC within the first 5 years of therapy were followed up for 5–10 (median, 6.8) years. HCC was diagnosed in 101/1,951 (5.2%) patients within the first 5 years and 17/1,205 (1.4%) patients within 5–10 years, demonstrating that the HCC risk decreases with ETV/TDF therapy beyond year 5, particularly in those with compensated cirrhosis, older age (especially ≥50 years), lower platelet counts, and liver stiffness ≥12 kPa [6] (Table 2).

The AASLD [17], EASL [18], and APASL [19] guidelines for the management of HCC all recommend antiviral therapy for HBV patients to reduce the risk of HCC. Among experts in the treatment of CHB, however, there

is controversy regarding antiviral HBV treatment for the prevention of HCC.

The achievement of HBsAg seroclearance during NA treatment is closely associated with improved clinical outcomes and is a criterion for the safe discontinuation of therapy [20]. HBsAg seroclearance is rarely, if ever, achievable, however, and necessitates long-term (almost indefinite) NA therapy for most patients with CHB. In the absence of HBsAg seroclearance, HCC can occur even during long-term continuous treatment with highly potent NAs [21–24].

A virologic response is defined as serum HBV DNA <15 IU/mL at 1 year of treatment for CHB or the achievement of a sustained virologic response for chronic hepatitis C (CHC). Kim et al. [23] reported that a virologic response was achieved in 1,520 patients with CHB (76.0%) and 475 patients with CHC (64.8%). During the median follow-up period of 6 years, 228 patients with CHB (11.4%) and 59 patients with CHC (8.0%) developed HCC. Among patients with virologic response, CHB was independently associated with a significantly higher incidence of HCC (hazard ratio [HR] 2.17; 95% confidence interval [CI] 1.30–3.63; $p = 0.003$) compared with CHC.

This does not mean cure, however, and does not address the reason for the persistent risk of HCC in CHB patients with a virologic response [23]. A positive outcome of antiviral treatment with NAs for the prevention of HCC was described in 651 randomly assigned patients having CHB with histologically confirmed cirrhosis or advanced fibrosis (98% Asian and 85% male) receiving lamivudine (LAM) or placebo. HCC occurred in 3.9% of the LAM group ($n = 436$) and 7.4% of the placebo group ($n = 215$; HR 0.49, $p = 0.047$; Table 2) [25].

A comparison between 482 ETV-treated and 69 untreated (control group) HBV-related cirrhosis patients (total of 551) revealed that ETV treatment reduced the risk of HCC (propensity score matching: HR 0.55, 95% CI: 0.31–0.99, $p = 0.049$; Table 2) [26]. In a comparison of the incidence of HCC in 472 ETV-treated (cirrhosis 311, 19.2%) and 1,143 untreated HBV patients (cirrhosis 195, 12.1%), propensity score matching eliminated baseline differences, resulting in a sample size of 316 patients per cohort. The cumulative HCC incidence rate at 5 years was 3.7% and 13.7% in the ETV and control groups, respectively ($p < 0.001$). Cox proportional hazard regression analysis adjusted for a number of known HCC risk factors showed that patients in the ETV group were less likely to develop HCC than those in the control group (HR 0.37, 95% CI: 0.15–0.91, $p < 0.001$; Table 2), leading to the conclusion that long-

Table 1. Comparison of major international guidelines for the management of HBV

	AASLD, 2018	EASL, 2017	APASL, 2015
1 Prevention of HCC with IFN and NAs in HBV	Positive	Positive	Positive
2 Definition of immune-tolerant phase	ALT <35 U/L in men, <19 U/L in women, HBeAg (+), HBV DNA >10^6 IU/mL	Phase 1 HBeAg (+), Chronic HBV infection	ALT <30 U/L in men, <19 U/L in women, HBeAg (+), HBV DNA >20,000 IU/mL, >30 years old
3 Antiviral treatment for immune-tolerant phase	Not recommended	Not recommended	Not recommended
4 First-line treatment for CHB	ETV, TDF, and TAF	ETV, TDF, and TAF	ETV and TDF

AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of Liver; APASL, Asian Pacific Association for the Study of the Liver; HCC, hepatocellular carcinoma; IFN, interferon; NAs, nucleos(t)ide analogs; HBV, hepatitis B virus; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; CHB, chronic hepatitis B; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide fumarate.

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Table 2. Representative remarks on the prevention of HCC with NAs

Author/year	Cirrhosis patients' population	NAs	Outcome	Prevention of HCC under NAs positive or suspected
Liaw et al. [25] 2004	Cirrhosis or advanced fibrosis, LAM-treated: 436; placebo group: 215	LAM	HCC in 3.9% patients in LAM group (n = 436) and 7.4% of those in placebo group (n = 215) (HR 0.49, p = 0.047)	Positive
Wong et al. [26] 2013	Cirrhosis, ETV-treated: 482; control group: 69	ETV	ETV-treated patients (n = 482) showed reduced risk of HCC compared with controls (n = 69). (HR 0.55, 95% CI: 0.31–0.99, p = 0.049)	Positive
Hosaka et al. [27] 2013	Cirrhosis, ETV-treated: 116 (25%); control group: 195 (17%)	ETV	The cumulative HCC incidence rates at 5 years 3.7% and 13.7% in ETV (n = 472) and control group (n = 1143), respectively (p < 0.001)	Positive
Wu et al. [28] 2014	Cirrhosis, NAs-treated: 2,847 (13.2%); controls: 3,016 (14.0%)	ETV, LAM, and telbivudine	The NAs-treated cohort (n = 21,595) showed a significantly lower 7-year incidence of HCC (7.32%; 95% CI: 6.77–7.87%) than controls (n = 21,595) (22.7%; 95% CI: 22.1–23.3%; p < 0.001)	Positive
Papatheodoridis et al. [6] 2017	Cirrhosis, ETV/TDF-treated: 201	ETV and TDF	HCCs diagnosed in 101/1,951 (5.2%) patients within first 5 years and 17/1,205 (1.4%) patients within 5–10 years in Caucasian CHB patients	Positive
Su et al. [29] 2016	Cirrhosis, ETV-treated: 1,315; untreated group: 503	ETV	Compared with the untreated cohort (n = 503), treated patients (n = 1,315) were associated with a 60% HCC risk reduction (HR 0.40, 95% CI: 0.28–0.57)	Positive
Choi et al. [21] 2017	Population-based cohort No description regarding the percentage of cirrhosis	LAM, ADV, telbivudine, clevudine, ETV, and TAF	Annual deaths from liver cancer increased by 17.8% (95% CI: 17.6–18.0), while the annual number of patients receiving oral antiviral agents against HBV increased from 1,716 to 187,226 between 1999 and 2013	Suspected

HCC, hepatocellular carcinoma; NAs, nucleos(t)ide analogs; LAM, lamivudine; ETV, entecavir; TDF, tenofovir disoproxil fumarate; ADV, adefovir; HR, hazard ratio; CI, confidence interval.

term ETV treatment reduces the incidence of HCC in HBV-infected patients [27].

A comparison by propensity score matching between 21,595 ETV-treated (cirrhosis 2,847, 13.2%) and 21,595 untreated CHB patients (cirrhosis 3,016, 14.0%) demonstrated that the incidence of HCC was significantly lower in the treated cohort over a 7-year follow-up (7.32%, 95% CI: 6.77–7.87) than in the control (22.7%, 95% CI: 22.1–23.3, $p < 0.001$; Table 2) [28]. Another study comparing between 1,315 ETV-treated cirrhosis patients and 503 untreated HBV-related cirrhosis patients concluded that ETV therapy was associated with a 60% lower risk of HCC incidence (HR 0.40, 95% CI: 0.28–0.57; Table 2) [29]. Even with successful treatment using antivirals, the risk of HCC is not eliminated and surveillance for HCC should continue in persons who are at risk.

To evaluate whether NA therapy prevents HCC in HBV patients, a population-based analysis of mortality from liver disease and liver cancer from 1999 to 2013 was implemented using data obtained from the national death certificate database of Korea, an HBV-endemic country. In terms of liver disease, the number of annual deaths decreased by 62.3% (95% CI: 62.0–62.6) and the crude death rate decreased by 64.6% (95% CI: 64.3–64.9) from 21.2 to 7.5 per 100,000 population; the age-standardized death rate also declined by 75.0% (95% CI: 74.7–75.3). In contrast, the number of annual deaths from liver cancer increased by 17.8% (95% CI: 17.6–18.0) and the crude death rate increased by 10.2% (95% CI: 10.0–10.4) from 20.5 to 22.6, although the age-standardized death rate decreased by 26.9% (95% CI: 26.6–27.2). The annual number of patients receiving oral antiviral agents against HBV increased from 1,716 to 187,226 during the study period [21] (Table 2).

The age-standardized mortality rate of liver cancer and incidence rate greatly decreased from 24.7 and 33.8, respectively, in 1999, to 16.4 and 19.9, respectively, in 2014. The dissociation between crude rates and age-standardized rates for liver cancer mortality and incidence may be explained by the rapidly aging population in Korea. The crude rates and absolute number of liver cancer mortality and incidence rates continue to increase. These data suggest that liver cancer is currently the most important cancer to overcome in Korea [30].

Previous studies reported a dissociation between trends in total death (increased) and age-standardized death rate (decreased) in the global burden of the disease [31]. These findings were attributed to changes in population growth and shifts in global age structures. In addition, the competing nature between liver disease mortality and liver cancer mortality should be carefully considered [21]. For example, in terms of the absolute death number, the wide use of antiviral drugs for hepatitis B and C may cause a rapid decline in liver disease mortality. Expanding the number of the at-risk population, however, may inadvertently lead to an increase in the absolute liver cancer incidence and mortality.

To observe prevention of HCC, a randomized controlled trial involving patients given ETV, TDF, or TAF and untreated patients would not be realistic. To reach a consensus, a comparison should be conducted between the incidence of HCC in ETV- or TDF-treated and untreated HBV patients (control group) using the propensity scored matching method adjusted for a number of HCC risk factors, as described previously [26, 27] (Table 2).

Rational for Antiviral Treatment of Patients Harboring High HBV DNA and Normal ALT Levels

The immune-tolerant phase, representing the early phase of the CHB, is not well understood. The concept of true immune-tolerance has been underestimated from the viewpoint of immunology and major international guidelines from AASLD, EASL, and APASL have not yet reached a consensus on the definition of the immune-tolerant phase [32]. While positive HBeAg, high serum HBV DNA levels, and normal serum ALT levels are the 3 key features of this phase, the APASL guidelines also take age into consideration [8] (Table 1). No consensus has been reached, however, regarding the lower cutoff level of HBV DNA for defining the immune-tolerant phase, which varies between 6 $\log_{10}$ IU/mL and 2 × 7 $\log_{10}$ IU/mL in clinical practice guidelines [4, 7, 8, 33]. A new nomenclature, Phase 1 or HBeAg-positive chronic HBV infection, is given by the latest version of the EASL guidelines published in April 2017 [4]. Although current major international guidelines advise against starting antiviral treatment for immune-tolerant CHB patients [4, 7, 8] (Table 1), some new data suggest that treating such patients may reduce the risk of liver fibrosis and the progression to HCC.

Current practice guidelines recommend delaying therapy until patients show significantly increased ALT levels or evidence of inflammation and/or fibrosis on biopsy [4, 7, 8, 33] (Table 1). These recommendations are based on the notion that disease progression to hepatic fibrosis and cirrhosis begins with an immune-active phase.

In a natural cohort study of CHB patients (REVEAL-HBV study), the HCC risk was highest at HBV titers >10^6 copies/mL (~5 $\log_{10}$ IU/mL) regardless of serum ALT levels or HBeAg [34]. In previous studies, patients with HBV DNA levels at 10^6–10^7 copies/mL had a significantly higher risk of HCC compared with those having persistent HBV DNA levels >10^7 copies/mL or <10^6 copies/mL [34].

A cohort study in Korea was conducted with 6,949 noncirrhotic, treatment-naïve CHB patients (mean age 45 years) having ALT levels <2 times the upper limit of normal for 1 year. During 8.0 years of median follow-up, 363 patients (5.2%) developed HCC. By multivariate Cox regression analysis, the HCC risk was highest with a baseline HBV DNA level of 6–7 $\log_{10}$ IU/mL (HR 4.98, p < 0.001) and lowest with a baseline HBV DNA level of >8 $\log_{10}$ IU/mL (HR 0.90, p = 0.71) and ≤4 $\log_{10}$ IU/mL (HR 1.00, reference), independent of other predictive factors. The HCC risk was highest with a moderate serum HBV DNA level of 6–7 $\log_{10}$ IU/mL in CHB patients without significant ALT elevation [1].

Untreated patients in the immune-tolerant phase have a significantly higher risk of HCC than immune-active phase patients treated with NAs [9]. The presence of significant hepatic necroinflammation/fibrosis is a significant risk factor for HCC and liver disease progression. Few patients, however, undergo repeat liver biopsy because of its invasive nature. The use of noninvasive tests for hepatic fibrosis is also limited because of their inaccuracy in identifying a significant fibrosis (i.e., F2 fibrosis). Those with a positive family history of HCC and African ethnicity may harbor a greater risk of HCC [17–19].

Untreated HBeAg-negative CHB patients with a high viral load but no significant increase in ALT levels display a higher risk of clinical events than treated patients in an active phase with elevated ALT [35]. The relation between the occurrence of HCC and high HBV DNA levels without ALT elevation is viewed as follows.

Selection and expansion of clonal hepatocytes are major risk factors for HCC and are observed without increased ALT levels or hepatic fibrosis [36–39]. Therefore, reduction of HBV DNA levels to <8 $\log_{10}$ IU/mL, despite its persistence at >4 $\log_{10}$ IU/mL in HBeAg-positive CHB patients, suggests clonal hepatocyte expansion and an increased risk of HCC, even with persistently normal ALT levels. HBV DNA integration into human host chromosomes may further increase chromosomal instability [36].

Progressive integration of the HBV genome into human host chromosomes may increase serum HBV DNA levels to >4 $\log_{10}$ IU/mL in HBeAg-negative patients [40, 41]. A recent study demonstrated that increasing levels of viremia above 20,000 IU/mL indicate a higher frequency of HBV-host genome integration in HBeAg-negative patients currently not indicated for treatment [40]. Random integration of the viral genome into host chromosomes may result in the loss of tumor suppressor gene functions, and/or the activation of tumor-promoting genes that are specifically involved in hepatocarcinogenesis [38, 40].

A recent study demonstrated that inhibition of HBV replication by TDF reduces the number of transcriptionally active distinct HBV-host DNA integrations in patients with HBV viremia above 2,000 IU/mL and minimally elevated ALT levels [42]. Thus, the findings mentioned above [35] may explain the high HCC risk in individuals with increased HBV DNA levels (>4 $\log_{10}$ IU/mL) among HBeAg-negative CHB patients. It is well known that HBV-associated hepatocarcinogenesis occurs without signs of significant hepatic inflammation and/or fibrosis [35].

Several studies have consistently shown that the application of current guideline recommendations may be too late to considerably prevent HCC, although the progression of fibrosis may be blocked [9, 21, 35]. If the goal of antiviral treatment is more the prevention of HCC than the prevention of hepatic inflammation and/or fibrosis progression, the recommendations may have to be considered with caution [43].

Early treatment intervention should therefore be considered to prevent HCC before ALT levels increase in patients with moderate viral loads of between 4 and 8 $\log_{10}$ IU/mL, especially those older than 40 years of age. Accumulating data on the long-term efficacy and safety of anti-HBV drugs such as ETV, TDF, and TAF offer a potent high genetic barrier to resistance, and decreasing their cost may facilitate initiation of early treatment [44–46]. With these considerations in mind, recent findings may help provide appropriate treatment options to obviate HCC in CHB patients [1].

Given the poor prognosis of patients with HCC, these findings may have considerable clinical implications toward preventing cancer in patients with CHB. Current treatment guidelines for CHB should be interpreted with caution given that HBV-associated hepatocarcinogenesis could be underway in patients who are not eligible for antiviral therapies by current guidelines. Therefore, efforts to reconcile treatment guidelines with recent clinical evidence should be made to further reduce the development of HCC [47].

Additional studies are needed to refine HCC risk prediction models by incorporating a broad range of HBV DNA levels. Randomized controlled trials based on those accurate models may be warranted to determine whether antiviral treatment reduces the risk of HCC in noncirrhotic CHB patients with moderate levels of HBV DNA and no significant ALT increase [1].

Efficacy of First-Line Treatment with NAs, ETV, TDF, and TAF, for CHB to Prevent HCC

ETV, TDF, and TAF in the AASLD and EASL guidelines, and ETV and TDF in the APASL guidelines are equally recommended as first-line NAs for CHB in clinical settings because of their similarly high antiviral efficacy and low rate of resistance [4, 7, 8] (Table 1). Regarding the reduction of HCC with NAs such as ETV and TDF, however, the results are controversial and inconsistent in a number of studies demonstrating more favorable outcomes with TDF than with ETV treatment. A study comparing ETV and TAF showed no difference between the 2 groups in reducing the HCC risk [48]. Another recent real-world data study indicates that TAF has comparable efficacies to TDF in terms of the risk of HCC [49].

In Korea, one of the most HB-endemic nations, a nationwide cohort study, validated by a hospital cohort for the first time demonstrated that CHB patients treated with TDF were at significantly lower risk of developing HCC than those treated with ETV [24]. In the national cohort, the annual incidence rate of HCC was significantly lower in the TDF group (n = 12,692, 0.89 per 100 PY) than in the ETV group (n = 11,464, 1.19 per 100 PY). By multivariate-adjusted analysis, TDF therapy was associated with a significantly lower risk of HCC (HR 0.68, 95% CI: 0.59–0.77). Compared with the ETV group (n = 1,560), the TDF group also showed a significantly lower risk of HCC in the 10,923-pair propensity score-matched national cohort (HR 0.68, 95% CI: 0.60–0.78) and 869-pair propensity score-matched hospital cohort (HR 0.68, 95% CI: 0.46–0.99, Table 3) [24].

Furthermore, HCC recurrence was compared between patients treated with TDF or ETV after surgical resection of HBV-related HCC. A cohort study conducted between 2010 and 2018 included 1,695 consecutive patients treated with ETV (n = 813) or TDF (n = 882) after curative-intent hepatectomy for HBV-related HCC of Barcelona Clinic Liver Cancer stage 0 or A. Posthepatectomy, HCC recurrence and overall survival were compared between the ETV- and TDF-treated groups by propensity score matching and multivariate-adjusted Cox regression analyses (Tables 4, 5).

During the median follow-up of 37.6 months with continued ETV or TDF therapy, HCC recurred in 561 (33.1%) patients. By multivariate-adjusted analysis, the TDF group demonstrated significantly lower rates of HCC recurrence (HR 0.82; 95% CI: 0.68–0.98; p = 0.03) and death or transplantation (HR 0.62; 95% CI: 0.44–0.88; p = 0.01; Table 3) [10].

The mechanisms of TDF and ETV, with the former imparting a significantly lower risk of HCC than the latter, might be explained, in part, by the better virologic response profiles of the TDF group, as shown in the hospital cohort, and in other studies [50–52]. Nevertheless, considering that a virologic response is not an independent risk factor for HCC, the difference in the HCC risk after TDF or ETV treatment cannot be fully explained by their antiviral potency. A recent study demonstrated that higher serum IFN-λ3 levels are induced in patients treated with the nucleotide analogs adefovir dipivoxil and TDF, but not in those treated with the nucleoside analogs LAM and ETV [53]. IFN-λ exhibits potent antitumor activity in murine models of cancer, including hepatoma [54, 55]; this antitumor activity is assumed to contribute to the difference in the HCC risk. Moreover, ETV is carcinogenic in mice and rats when administered at doses higher than those used in humans [24]. Also, ETV is known to potentially incorporate into the human genome and to contribute to a putative mechanism of carcinogenicity, especially when the embedded genome has higher error rates during subsequent rounds of replication [56–58]. These data raise concerns about the carcinogenic potential of ETV, even at clinical doses during long-term treatment, especially in patients with cirrhosis and increased chromosomal instability of hepatocytes [59, 60].

Several reports from Korea, however, have questioned the conclusions reached in other studies. A total of 7,015 consecutive patients diagnosed with CHB were treated with TDF or ETV between February 2007 and January 2018 at the liver unit of the Catholic University of Korea and screened for study eligibility: finally, 3,022 patients (ETV: 1,583, TDF: 1,439) were analyzed. No difference in the incidence rate of HCC between TDF and ETV therapy was detected in the entire cohort (HR 1.030, 95% CI: 0.703–1.509, p = 0.880; Table 3) or in subgroups with chronic hepatitis and cirrhosis [15].

In a study of 404 CHB patients (ETV n = 180, TDF n = 224), TDF was associated with a lower incidence of HCC (HR 0.31, 95% CI: 0.12–0.79; p = 0.014), but no statistical significance was detected after adjusting for sus-

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Table 3. Comparison of ETV, TDF, and TAF on reduction of HCC

Study area	Patients	Outcome	Superiority or equality	Reference	Year
Korea					
National Cohort	ETV: 11,464, TDF: 12,692`	ETV: 1.19/100 PY, TDF: 0.89/100 PY	TDF > ETV	Choi et al. [24]	2019
Hospital Cohort	ETV: 1,560, TDF: 1,141	HR 0.68, 95% CI: 0.60–0.78, HR 0.68, 95% CI: 0.46–0.99			
Korea	ETV: 1,484, TDF: 1,413	ETV: 1.92/100 PY, TDF: 1.69/100 PY, HR 0.975, $p = 0.852$	ETV = TDF	Kim et al. [16]	2019
Korea	ETV: 1,583, TDF: 1,439	HR 1.030, 95% CI: 0.703–1.509 $p = 0.880$	TDF = ETV	Lee et al. [15]	2020
Korea	ETV: 180, TDF: 224	HR 0.36, 95% CI: 0.12–1.14 $p = 0.08$	ETV = TDF	Ha et al. [61]	2020
Korea	ETV: 813, TDF: 882	HR 0.82, 95% CI: 0.68–0.98 $p = 0.03$ (after surgical resection)	TDF > ETV	Choi et al. [10]	2021
Korea	ETV: 1,525, TAF: 286	ETV: 1.67/100 PY, TAF: 1.19/100 PY, HR 0.681, 95% CI: 0.351–1.320, $p = 0.255$	ETV = TAF	Lee et al. [48]	2021
Korea	TDF: 2,245, TAF: 502	TDF: 0.90/100PY, TAF: 0.82/100PY, $p = 0.60$	TDF = TAF	Lim et al. [49]	2022
China	ETV: 2,124, TDF: 1,574	RR 0.66, 95% CI: 0.49–0.89, $p = 0.008$	TDF > ETV	Zhang et al. [12]	2019
China	ETV: 28,041, TDF: 1,309	ETV: 0.49/100 PY, TDF: 0.06/100 PY, HR 0.36, 95% CI: 0.16–0.80, $p = 0.013$	TDF > ETV	Yip et al. [11]	2020
Taiwan and Asia-Pacific	ETV: 4,837, TDF: 700	HR 0.89; 95% CI: 0.41–1.92, $p = 0.77$	TDF = ETV	Hsu et al. [14]	2020
Taiwan and Asia-Pacific	ETV: 19,702, TDF: 16,266	ETV: 3.44%/5Y, TDF: 3.39%/5Y, HR 0.88, 95% CI: 0.73–1.07 $p = 0.20$	TDF = ETV	Tseng et al. [71]	2020
Hong Kong and China	ETV: 56,346, TDF: 28,662	HR 0.73, 95% CI: 0.62–0.85 $p < 0.001$	TDF > ETV	Cheung et al. [70]	2020
Europe	ETV: 772, TDF: 1,163	ETV: 1.08/100 PY, TDF: 1.2/100 PY, $p = 0.321$	ETV = TDF	Papatheodoridis et al. [72]	2020
USA	ETV: 2,193, TDF: 1,094	HR 1.00, 95% CI: 0.76–1.32	ETV = TDF	Su et al. [73]	2021

ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide fumarate; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; PY, person-years; RR, rate ratio – HR combined with incidence rate ratios; Y, year.

Table 4. Experts' opinions regarding prevention of HCC with NAs and approaches to solve these controversies

Author	Year	Opinion	Prevention of HCC under NAs positive or suspected
Liaw et al. [25]	2004	Continuous treatment with lamivudine delays clinical progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation and the risk of HCC	Positive
Wong et al. [26]	2013	Entecavir therapy reduces the risks of hepatic events, HCC, liver-related, and all-cause mortality of CHB patients with liver cirrhosis in 5 years, particularly among those who had maintained viral suppression	Positive
Hosaka et al. [27]	2013	Long-term ETV treatment may reduce the incidence of HCC in HBV-infected patients. The treatment effect was greater in patients at higher risk of HCC	Positive
Wu et al. [28]	2014	Nucleoside analog therapy use is associated with reduced risk of HCC in patients with chronic HBV infection	Positive
Papatheodoridis et al. [6]	2017	The HCC risk decreases beyond year 5 of ETV/TDF therapy in Caucasian chronic hepatitis B patients, particularly in those with compensated cirrhosis; older age (especially ≥50 years), lower platelets, and liver stiffness ≥12 kPa	Positive
Su et al. [29]	2016	Four-year ETV therapy significantly reduces the risk of HCC, cirrhotic events and mortality in patients with CHB-related cirrhosis	Positive
Choi et al. [21]	2017	Marked reduction in liver disease mortality by widespread use of antiviral treatments against HBV may increase the life expectancy and number of patients at risk of developing liver cancer, inadvertently leading to increased burden of liver cancer in an HBV-endemic population	Suspected

Approach to solve the controversy: comparisons should be conducted between the incidence of HCC in ETV- or TDF-treated and untreated HBV patients (control group) using the propensity score matching method adjusted for a number of HCC risk factors.

tained virologic suppression through propensity score matching (HR 0.36, 95% CI: 0.12–1.14; $p = 0.08$; Table 3) [61]. Regarding the mechanism underlying the equivalent effects of ETV and TDF on the reduction of HCC, a Korean study observed that the hypothesis of the induction of IFN-λ3 production by TDF and the carcinogenic potential of ETV is problematic [48].

First, the level of serum IFN-λ3 imparts higher anticarcinogenic and antiviral effects to patients treated with TDF than to those treated with ETV, but conflicting data are also reported [17, 62–65]. Moreover, because IFN-λ assays are not standardized, the causality of the relation between higher IFN-λ3 levels and a lower incidence of HCC requires further investigation.

Second, in mice, ETV at 4 mg/kg increases the incidence of lung adenoma and carcinoma, HCC, and vascular tumors, and at 1.4–2.6 mg/kg increases the incidence of HCC, brain microglial tumors, and skin fibroma [66]. These doses, however, are at least 100-fold higher than those used in humans. In contrast, 2 recent large-scale real-life studies demonstrated that long-term ETV therapy does not increase the risk of cancer [67, 68]. Moreover, in a long-term follow-up study [69], the incidence of HCC did not differ statistically during or after the first 5 years of ETV treatment (2.29% vs. 1.66%, $p = 0.22$); should long-term ETV administration induce a significant procarcinogenic effect in humans, the HCC incidence would progress rapidly over time.

A recent Korean study comparing the impact of ETV and TAF on the reduction of HCC [48] demonstrated no statistical difference in the annual incidence of HCC in ETV ($n = 1,525$) and TAF ($n = 286$) patients (1.67 vs. 1.19 per 100 PY, respectively) with HR 0.681, 95% CI: 0.351–1.320, $p = 0.255$, as determined by propensity score matching methods, suggesting that ETV- and TAF-treated CHB patients face a similar risk of developing HCC [48]. Studies from China, Taiwan, and Hong Kong as well as from Korea report conflicting results regarding the efficacy of ETV and TDF for obviating HCC [11, 14–16, 24].

In a large nationwide cohort study in Hong Kong, 29,350 treatment-naive CHB patients were started on ETV ($n = 28,041$) and TDF ($n = 1,309$) as first-line therapy. After propensity score weighting and 1:5 matching, TDF was associated with a lower risk of HCC than ETV (HR 0.36, 95% CI: 0.16–0.80, $p = 0.013$; Table 3) [11].

In a meta-analysis from Hong Kong, 85,008 CHB patients received ETV ($n = 56,346$) and TDF ($n = 28,662$); TDF was associated with a lower HCC risk than ETV, particularly in cirrhotic patients (HR 0.73, 95% CI: 0.62–

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Table 5. Experts' opinions regarding comparison of ETV, TDF, and TAF on reduction of HCC and approaches to solve these controversies

Author	Year	Opinion	Superiority or equality
Choi et al. [24]	2019	Tenofovir treatment was associated with a significantly lower risk of HCC compared with ETV treatment	TDF > ETV
Kim et al. [16]	2019	HCC and death or OLT was not statistically different between the ETV and TDF groups	ETV = TDF
Lee et al. [15]	2020	The clinical outcomes in patients with CHB who received TDF or ETV treatment. There was no difference in the intermediate-term risk of HCC and mortality or LT between the two drugs	TDF = ETV
Ha et al. [61]	2020	TDF was associated with lower HCC (HR 0.31, 95% CI, 0.12–0.79; $p = 0.014$); however, statistical significance was not reached	ETV = TDF
Choi et al. [10]	2021	Among patients who underwent curative hepatectomy for HBV-related HCC, TDF therapy was associated with a significantly lower risk of HCC recurrence and better overall patient survival compared with ETV therapy	TDF > ETV
Lee et al. [48]	2021	ETV- and TAF-treated CHB patients have similar risk of developing HCC	ETV = TAF
Zhang et al. [12]	2019	There is a better effect of tenofovir in reducing HCC incidence than ETV, which indicates tenofovir should be used more widely while treating chronic hepatitis B patients	TDF > ETV
Yip et al. [11]	2020	TDF was associated with a lower risk of HCC than treatment with ETV	TDF > ETV
Hsu et al. [14]	2020	TDF and ETV did not significantly differ in the prevention of HCC in patients with CHB	TDF = ETV
Tseng et al. [71]	2020	No significant difference was detected between TDF and ETV in their association with incident HCC	TDF = ETV
Cheung et al. [70]	2020	TDF was associated with a lower HCC risk compared with ETV among patients with CHB, particularly cirrhotic patients	TDF > ETV
Papatheodoridis et al. [72]	2020	In Caucasian patients with CHB, with or without cirrhosis, long-term ETV or TDF monotherapy is associated with similar HCC risk	ETV = TDF
Su et al. [73]	2021	No difference in the risk of HCC between patients with CHB treated with ETV versus TDF	ETV = TDF

Approach to solve the controversy: further clinical studies or trials with a larger number of patients and longer follow-up are needed to resolve these controversial issues and to reach a consensus.

0.85, $p < 0.001$; Table 3) [70]. Taiwan and Asia-Pacific study showed no association between TDF ($n = 700$) and ETV ($n = 4,837$) regimens with HCC risk in a multivariable-adjusted analysis (HR 0.89, 95% CI: 0.41–1.92, $p = 0.77$; Table 3) [14].

Another Taiwan and Asia-Pacific study reported that the risk of HCC with TDF (16,266) and ETV (19,702) treatment was similar (primary outcome, TDF: 3.39%/5Y, ETV: 3.44%/5Y; adjusted HR 0.88, 95% CI: 0.73–1.07; $p = 0.20$) by analysis of 14 comparative studies with covariate adjustment. No significant difference between TDF and ETV in their association with incident HCC was observed [71].

In a total of 3,698 patients (1,574 under TDF therapy, and 2,124 under ETV therapy) in China, TDF was more efficacious than ETV in mitigating the HCC incidence (rate ratio [RR-HR combined with incidence rate ratios] 0.66, 95% CI: 0.49–0.89, $p = 0.008$; Table 3), indicating that TDF should be used more widely in treating CHB patients [12].

In contrast to the above conflicting Korean and Asian data, European and American studies have concluded that ETV and TDF provide similar efficacy. A European study in 1935 Caucasians with CHB treated with ETV ($n = 772$) and TDF ($n = 1,163$) demonstrated similar HCC risk in the 2 groups (ETV: 1.08% PY, TDF: 1.2% PY, $p = 0.321$; Table 3) [72].

In the USA, no difference in the risk of HCC was detected between veteran-affairs patients treated with ETV ($n = 2,193$) and TDF ($n = 1,094$) before and after propensity score matching (HR 1.00, 95% CI: 0.76–1.32; Table 3) [73]. The controversial results can be partly attributed to the arbitrary nature of significance levels, leading to contradictory conclusions from very similar datasets. The use of observational data, however, which is prone to both within- and between-study heterogeneity of patient characteristics, also lends additional uncertainty. The synchronous introduction of ETV and TDF in East Asia, where the majority of these studies were conducted, further complicates analyses, as does the difference in the follow-up times between ETV and TDF cohorts. Researchers conducting meta-analyses in this area must make many methodologic decisions to mitigate bias but are ultimately limited to the methodologies of the included studies. It is therefore important for researchers, as well as the audience of published meta-analyses, to be aware of the quality of observational studies and meta-analyses in terms of patient characteristics, study design, and statistical methodologies [74].

It is important to note that all the studies comparing the risk of HCC between TDF and ETV therapies have indicated one direction favoring TDF or no direction. No high-quality studies have provided evidence favoring ETV over TDF [13]. Further clinical studies or trials with a larger number of patients and longer follow-up are needed to resolve these controversial issues and to reach a consensus.

Conclusion

Serum levels of HBV DNA are closely associated with the risk of HCC in CHB patients independent of HBeAg and ALT levels. Treatment with NAs, including ETV, TDF, and TAF, may lower the risk of HCC incidence and recurrence in such patients. Three issues have constrained the resolution of CHB treatment and the obviation of subsequent HCC.

1. The AASLD [7], APASL [8], and EASL [4] guidelines for the management of HBV infection recommend antiviral treatment for HBV with IFN and NAs for the prevention of HCC. Among experts in CHB treatment, however, continuing controversy exists regarding antiviral treatment for the optimal prevention of HCC. A growing evidence from large-scale cohort studies suggests that early initiation of antiviral treatment even with persistently normal ALT levels may be necessary to minimize the risk of HCC.
2. The AASLD, EASL, and APASL guidelines make no recommendations for antiviral treatment in patients in the immune-tolerant phase of CHB, especially patients younger than 30 years of age. Nonetheless, the cutoff level of lower serum HBV DNA levels for the definition of the immune-tolerant phase CHB is not consistent across the guidelines. Even if we have the consensus for the definition of immune-tolerant phase CHB, many patients remain in the gray zone with no treatment recommendations.
3. Whether ETV, TDF, and TAF treatments have different effects on the prevention of HCC is not clear yet. To resolve this issue, we suggest a meta-analysis by using individual patient data from the cohort studies or randomized trials with a larger number of subjects and longer follow-up.

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Conflict of Interest Statement

Young-Suk Lim is an advisory board member of Bayer Healthcare and Gilead Sciences and receives investigator-initiated research funding from Bayer Healthcare and Gilead Sciences. Masatoshi Kudo reports receiving lecture fees from Eisai, Bayer, MSD, Bristol-Myers Squibb, Lilly, and EA Pharma; receiving grants from Gilead Sciences, Taiho, Sumitomo Dainippon Pharma, Takeda, Otsuka, EA Pharma, AbbVie, and Eisai; and having advisory roles at Eisai, Ono, MSD, Bristol-Myers Squibb, and Roche. The other authors have no conflicts of interest to disclose.

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Author Contributions

Kim S.K., Fujii T., Kim S.R., Nakai A., and Hagiwara S. wrote the manuscript; Lim Y.-S. and Kudo M. approved the final version.

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