Research Article
Viral Hepatitis

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Hepatocellular carcinoma risk in patients with chronic hepatitis B receiving tenofovir- *vs.* entecavir-based regimens: Individual patient data meta-analysis

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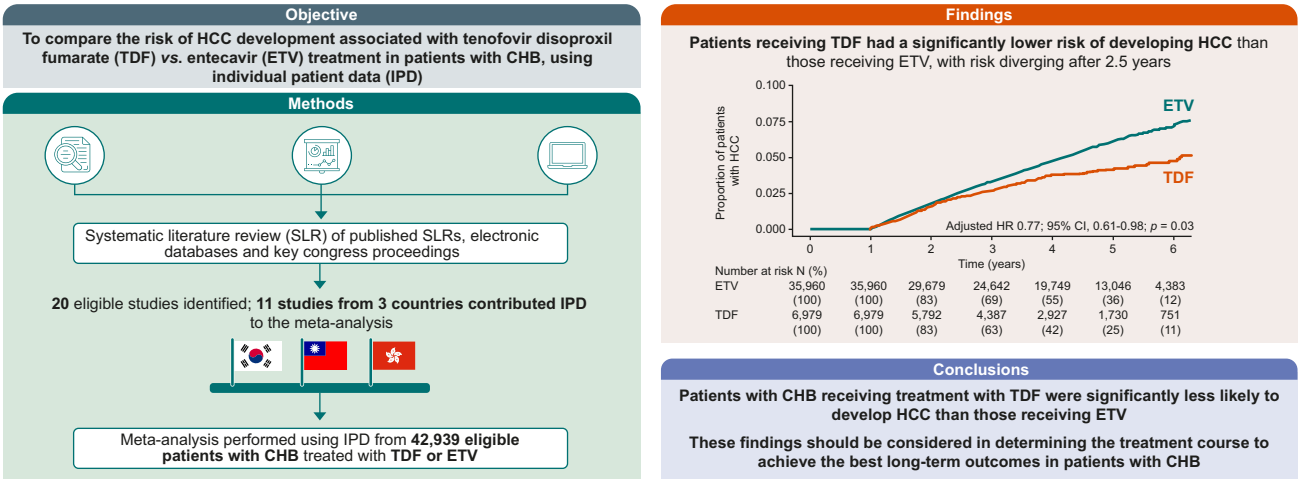
Graphical abstract



Highlights

- Relative HCC risk for TDF *vs.* ETV treatment is undetermined in patients with CHB.
- Prior meta-analyses are limited by heterogeneity of observational studies.
- Using individual patient data enables a consistent analytic approach across studies.
- TDF was consistently associated with lower HCC risk than ETV.

Impact and implications

Previous aggregate data meta-analyses have reported inconsistent conclusions on the relative effectiveness of tenofovir disoproxil fumarate and entecavir in reducing hepatocellular carcinoma risk in patients with chronic hepatitis B (CHB).
This individual patient data meta-analysis on 11 studies involving 42,939 patients from Korea, Taiwan and Hong Kong suggested that tenofovir disoproxil fumarate-treated patients have a significantly lower hepatocellular carcinoma risk than entecavir-treated patients, which was observed in all subgroups of clinical interest and by different analytical methodologies. These findings should be taken into account by healthcare providers when determining the optimal course of treatment for patients with CHB and may be considered in ensuring that treatment guidelines for CHB remain pertinent.

https://doi.org/10.1016/j.jhep.2022.12.007
 J. Hepatol. 2023, 78, 534–542

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Hepatocellular carcinoma risk in patients with chronic hepatitis B receiving tenofovir- *vs.* entecavir-based regimens: Individual patient data meta-analysis

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Journal of Hepatology **2023**. vol. 78 | 534–542

Background & Aims: The comparative risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) receiving tenofovir disoproxil fumarate (TDF) *vs.* entecavir (ETV) remains controversial. In this individual patient data (IPD) meta-analysis, we aimed to compare HCC risk between the two drugs and identify subgroups who may benefit more from one treatment than the other.

Methods: Published meta-analyses, electronic databases and congress proceedings were searched to identify eligible studies through January 2021. We compared HCC risk between the two drugs using a multivariable Cox proportional hazards model with anonymised IPD from treatment-naïve patients with CHB receiving TDF or ETV for ≥1 year. Treatment effect consistency was explored in propensity score matching (PSM), weighting (PSW) and subgroup analyses for age, sex, hepatitis B e-antigen (HBeAg) positivity, cirrhosis and diabetes status.

Results: We included 11 studies from Korea, Taiwan and Hong Kong involving 42,939 patients receiving TDF (n = 6,979) or ETV (n = 35,960) monotherapy. Patients receiving TDF had significantly lower HCC risk (adjusted hazard ratio [HR] 0.77; 95% CI 0.61–0.98; $p = 0.03$). Lower HCC risk with TDF was consistently observed in PSM (HR 0.73; 95% CI 0.59–0.88; $p < 0.01$) and PSW (HR 0.83; 95% CI 0.67–1.03; $p = 0.10$) analyses and in all subgroups, with statistical significance in the ≥50 years of age (HR 0.76; 95% CI 0.58–1.00; $p < 0.05$), male (HR 0.74; 95% CI 0.58–0.96; $p = 0.02$), HBeAg-positive (HR 0.69; 95% CI 0.49–0.97; $p = 0.03$) and non-diabetic (HR 0.79; 95% CI 0.63–1.00; $p < 0.05$) subgroups.

Conclusion: TDF was associated with significantly lower HCC risk than ETV in patients with CHB, particularly those with HBeAg positivity. Longer follow-up may be needed to better define incidence differences between the treatments in various subgroups.

Introduction

Chronic hepatitis B (CHB), a hepatotropic infection affecting over 250 million people worldwide,[1,2] is associated with a long-term risk of hepatocellular carcinoma (HCC), the most common primary cancer of the liver. HCC incidence is increasing; it is the fifth most common cause of cancer worldwide, and the third leading cause of cancer-related death.[3,4] As CHB is a major risk factor for HCC, effective treatment with nucleo(s)tide analogue (NA) therapies is critical in reducing HCC risk.[5] Tenofovir-based therapies, such as tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide, and entecavir (ETV) are recommended first-line therapies for CHB.[6] However, whether these therapies differ in their ability to reduce HCC risk in patients with CHB remains undetermined.

Randomised-controlled trials (RCTs) are the gold standard of evidence for comparing treatment efficacy, yet few address this topic. Two RCTs comparing TDF and ETV have been published in the last 5 years; however, observed incidence of HCC was too low to allow for meaningful comparisons of HCC risk.[7–10] Meta-analyses have therefore relied upon data from observational studies.[11–17] Despite published meta-analyses including similar primary studies, the statistical significance of results and subsequent clinical recommendations vary.[18] While some meta-analyses suggest that TDF is associated with lower HCC risk than ETV,[12–15] others suggest there is no

Keywords: Chronic hepatitis B; hepatocellular carcinoma; tenofovir disoproxil fumarate; entecavir; individual patient data; meta-analysis.
Received 19 July 2022; received in revised form 29 November 2022; accepted 2 December 2022; available online 23 December 2022
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https://doi.org/10.1016/j.jhep.2022.12.007

difference.[16,17] It is unclear which therapy provides the greatest reduction in HCC risk.

Observational study data are often limited by heterogeneous methodologies and patient populations. Within- and between-study heterogeneity may contribute to previous meta-analyses reaching different conclusions. As such, meta-analyses conducted using individual patient data (IPD) can help address challenges faced by aggregate data meta-analyses by allowing for a consistent analytic approach across data from multiple studies.[18] We aimed to analyse a dataset of individual records of patients with CHB receiving TDF or ETV to provide a more robust estimate of HCC risk between the treatments and identify any subgroup of patients who may benefit more from one drug than the other.

Patients and methods

Study selection and data collection

To identify relevant data sources, a systematic literature review of existing meta-analyses, electronic databases and key congress proceedings was conducted in accordance with a pre-specified protocol, published on PROSPERO (ID CRD42021249314). Relevant primary studies were extracted from three recently published meta-analyses (Tseng *et al.* 2020, Choi *et al.* 2020 and Cheung *et al.* 2020).[12,13,16] An electronic database search using terms specified by Cheung *et al.* 2020 (most recent search date [9 June 2020] of the three meta-analyses; Table S1) was re-run in January 2021 to capture any relevant articles published since the aforementioned meta-analyses. Proceedings from the 2020 congresses of the Asian Pacific Association for the Study of the Liver, the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver were manually searched. Identified studies were deemed eligible as per the inclusion/exclusion criteria outlined in Table S2, for a total of 20 eligible studies conducted in East Asia (Fig. 1), of which 11 agreed to participate in the meta-analysis,[19–29] contributing data from 48,461 patients across three countries (Table S3). Where two studies involved the same study sites, data were only requested from one study, to avoid duplication. All study sites were required to have ethics approval from their institutional review boards.

Consistency checks were performed to ensure data quality and accuracy, including assessment of outlying values and missing data. Dataset variables were aligned across study sites and all IPD from each study site were merged into a single dataset.

Patient eligibility criteria

Patient-level eligibility criteria, as defined in the study protocol (PROSPERO [ID CRD42021249314]), were applied to the initial 48,461 identified patients to produce the analysis dataset of

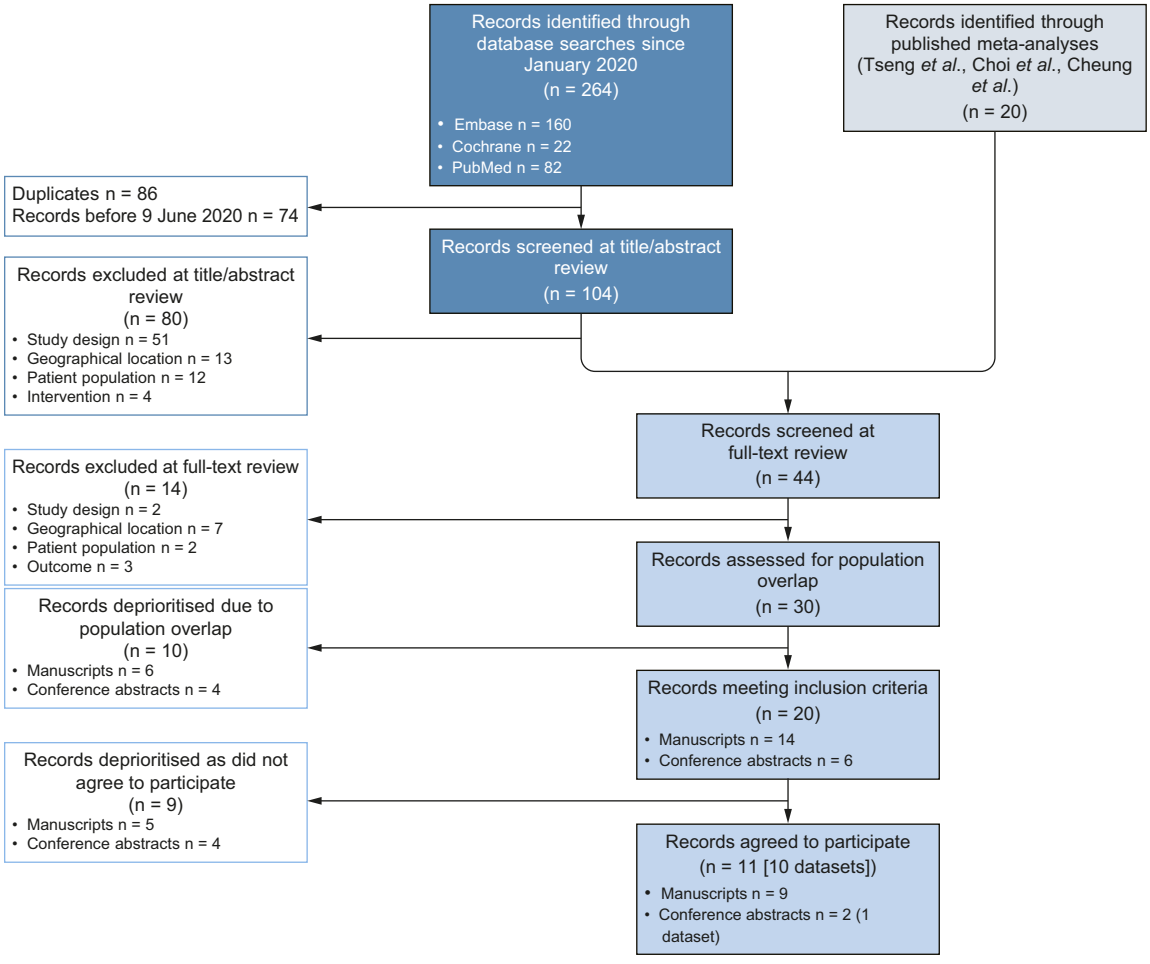

Fig. 1. PRISMA flow diagram of the literature review.

42,939 patients. Included patients were: adults with CHB (defined as hepatitis B surface antigen [HBsAg] positive for at least 6 months prior to treatment) who were treatment-naïve before initiating treatment with TDF or ETV monotherapy, and who completed at least 1 year of treatment with either regimen (Table S4).

Covariates

Covariate selection and adjustment

To account for possible unbalanced treatment arms, potential confounding variables were adjusted for. Demographic information including age and sex, and comorbidities including diabetes mellitus, hypertension, cirrhosis, decompensated cirrhosis, ascites and hepatic encephalopathy were selected as covariates. Laboratory data including viral load, hepatitis B e-antigen (HBeAg) status, alanine aminotransferase (ALT), bilirubin, creatinine, alpha-fetoprotein and albumin levels, international normalised ratio and platelet counts were also included as covariates (Table S5). Using these variables, systematic differences in patient characteristics between the treatment groups were adjusted for via multivariable analysis (primary analysis approach), propensity score matching (PSM) and propensity score weighting (PSW).

Missing data and imputation

All studies provided full information on follow-up time, HCC events, age, sex and investigator-defined cirrhosis (Table S6). Partial missingness was observed in most variables (Table S6), and aspartate aminotransferase was excluded from the analysis as missingness in this variable was substantial (40.8%). As the definition of cirrhosis potentially varied across studies, we utilised an objective, composite cirrhosis definition: patients were classified as having cirrhosis if they had site-defined cirrhosis and Child-Turcotte-Pugh score ≥6 (*i.e.* had at least compensated cirrhosis); or if they had baseline platelet count <150,000/μl (a cut-off frequently used in the original studies included in this analysis).

Multiple imputation[30] was applied to the pooled dataset (all patients) to generate 20 imputed datasets via predictive mean matching for continuous variables and a logistic regression model for binary variables (Table S5); a random intercept was included for each study in the imputation models. The primary analysis and all secondary analyses (except complete-case) were performed across all imputed datasets, with results pooled using Rubin's rules to obtain a final estimate.[31]

Statistical analyses

Primary analysis

The primary analysis was conducted using a one-stage approach, in which data from different studies were analysed simultaneously using a model which accounted for within-study clustering of patients. All eligible patients were included, and a multivariable Cox proportional hazards model was used to evaluate the risk of HCC (hazard ratio [HR]) in those receiving treatment with TDF *vs.* ETV. The HCC incidence rate (number of HCC cases per 100 person-years) for each treatment group was estimated post-censoring at 6.5 years' follow-up.

This model adjusted for all variables specified in Table S5 through inclusion of covariates as fixed effects. To account for potential between-study differences, study-specific interactions with the characteristics specified in Table S5 were also considered. Variable selection was applied to identify study-interactions for inclusion; backwards selection (using stepAIC from the MASS package[32]) was applied to each of the 20 imputed datasets, and interaction terms retained in at least 50% of imputed datasets (≥10) were kept in the final model. Separate baseline hazards were estimated for each study and cluster-robust standard errors were produced to account for within-study correlation. A treatment indicator was also included as a covariate in the model.

An unadjusted univariable analysis was performed as a point of reference for comparison *vs.* the multivariable primary analysis. The same approach was used as per the multivariable analysis, but no baseline characteristics were adjusted for.

Sensitivity analyses

Seven analyses were conducted using a one-stage approach to assess sensitivity of the primary analysis results to different methodological assumptions and approaches. A complete case analysis which excluded patients missing data for any PAGE-B variables (age, sex and platelet count) was conducted to assess robustness of the results without imputation. A second analysis excluded only patients missing data for viral load (imputation was performed for other variables). Patients missing data for additional variables (such as alpha-fetoprotein, Child-Turcotte-Pugh score and international normalised ratio etc.) were retained in these two analyses; as viral load and the variables included in PAGE-B are most influential on HCC risk, this approach allowed a balance between maintaining sample size while exploring the effect of imputation on the association between treatment and HCC risk. A treatment start date analysis excluded patients initiating treatment prior to 2011, limiting discrepancies in follow-up time due to the earlier introduction of ETV. A cirrhosis definition analysis used a different platelet count threshold (<100,000/μl) within the composite cirrhosis definition. An additional analysis only utilised the site-specific definition of cirrhosis. A PSM analysis matched patients 1:5 (TDF:ETV) to balance characteristics across treatment arms. A PSW analysis used weighting to balance observed baseline characteristics of patients in both treatment arms. Finally, using a two-stage approach (in which studies are analysed separately and then resulting study-specific estimates are combined), a PSW analysis including HRs from studies which declined to contribute IPD to the meta-analysis was performed, to assess the impact of selection bias on the primary analysis results. HRs were obtained from publications or requested directly from declining studies.

Subgroup analyses

Subgroup analyses (using a one-stage, multivariable approach) were conducted in subgroups of clinical interest: age at treatment initiation (50 years of age or over, under 50 years of age), sex (male, female), HBeAg positivity (HBeAg positive, HBeAg negative), cirrhosis status (present, absent) and diabetes status (present, absent).

Statistical analyses are discussed in detail in the supplementary methods.

Results

Patient disposition and baseline characteristics

The analysis included 42,939 patients, 6,979 receiving TDF and 35,960 receiving ETV. Both groups were similar in terms of age (48.32 *vs.* 52.26 years; TDF *vs.* ETV, respectively), sex (female: 38.64% *vs.* 34.13%) and follow-up time (3.71 *vs.* 3.97 years). At baseline, a similar percentage of patients in both groups had cirrhosis (38.01% *vs.* 39.23%). However, a greater percentage of the TDF group was HBeAg positive (49.65% *vs.* 33.69%), while a greater percentage of patients receiving ETV were diabetic (27.42% *vs.* 18.38%) and hypertensive (38.67% *vs.* 21.12%; Table 1).

Primary analysis

In the univariable analysis, patients receiving TDF were associated with significantly lower HCC risk than those receiving ETV (HR 0.64; 95% CI 0.48–0.84; p <0.01). Risk of HCC diverged between the groups after 2.5 years' follow-up. Following adjustment for potential confounding variables, patients receiving TDF showed significantly lower HCC risk than those receiving ETV (adjusted HR 0.77; 95% CI 0.61–0.98; p = 0.03; Fig. 2). At 6.5 years' follow-up, the annual HCC incidence rate for patients receiving TDF *vs.* ETV (number of HCC cases per 100 person-years) was 0.86 (95% CI 0.75–0.98) *vs.* 1.18 (95% CI 1.13–1.24), respectively; in total, 223 patients in the TDF group (3.20%) and 1,687 patients in the ETV group (4.69%) developed HCC.

Secondary analyses

Sensitivity analyses

Regardless of analytic methodology, patients receiving TDF had a consistently lower risk of HCC (HR <1.0), although statistical significance varied across analyses.

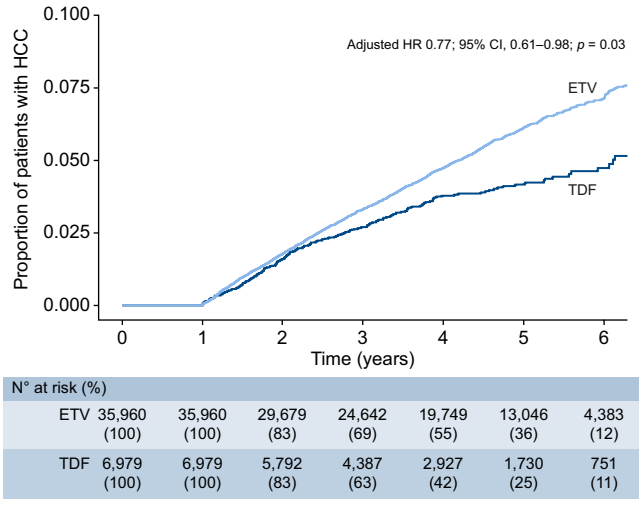

Fig. 2. Cumulative incidence of HCC in patients with CHB treated with TDF or ETV. Statistical significance testing was performed using the Wald test. ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; TDF, tenofovir disoproxil fumarate.

Baseline characteristics between the two groups were well-balanced after PSM and PSW (Table 1, Table S7 and Table S8). In the PSM (TDF: n = 6,475; ETV: n = 15,958) and PSW (TDF: n = 6,220; ETV: n = 14,488) analyses, TDF was associated with a lower HCC risk (HR 0.73; 95% CI 0.59–0.88 *vs.* HR 0.83; 95% CI 0.67–1.03, respectively). Only the PSM analysis was statistically significant (p <0.01 and p = 0.10 for PSM and PSW, respectively).

When the alternative cirrhosis definition was used (platelet count threshold <100,000/μl rather than <150,000/μl as in the primary analysis; Table S9), TDF was associated with a consistently lower risk of HCC than ETV (adjusted HR 0.77; 95% CI 0.61–0.98; p = 0.03) (TDF: n = 6,979; ETV: n = 35,960).

Table 1. Baseline characteristics of eligible patients.

Characteristic	TDF[a]	ETV[a]	Standardised mean difference		
			Original	After PSM	After PSW
Number	6,979	35,960	n.a.	n.a.	n.a.
Age, median (IQR), years	48.32 (12.21)	52.26 (12.60)	0.32	0.02	0.00
Sex, (%)	F: 38.64, M: 61.36	F: 34.13, M: 65.87	0.09	0.01	0.00
Viral load, median (IQR), log_{10} IU/ml	5.76 (2.00)	5.47 (2.04)	0.14	0.15	0.00
HBeAg positivity, (%)	49.65	33.69	0.33	0.06	0.00
Cirrhosis defined by study site, (%)	41.70	27.66	0.03	0.07	0.00
Cirrhosis defined as per analysis plan, (%)	38.01	39.23	0.00	0.18	0.00
Hepatic encephalopathy, (%)	0.16	0.32	0.03	0.02	0.00
Ascites, (%)	4.17	2.87	0.07	0.02	0.00
Diabetes, (%)	18.38	27.42	0.22	0.20	0.00
Hypertension, (%)	21.12	38.67	0.39	0.20	0.00
Albumin, median (IQR), g/dl	4.11 (0.72)	4.02 (0.64)	0.13	0.03	0.00
INR, median (IQR)	1.09 (0.23)	1.1 (0.21)	0.05	0.05	0.00
Platelet count, median (IQR), x1,000/μl	180.92 (66.51)	178.47 (70.25)	0.04	0.00	0.00
Bilirubin, median (IQR), mg/dl	1.26 (2.57)	1.32 (2.43)	0.02	0.04	0.03
ALT, median (IQR), IU/L	173.81 (333.56)	182 (354.72)	0.02	0.05	0.00
Creatinine, median (IQR), mg/dl	0.89 (1.25)	0.98 (1.16)	0.07	0.02	0.00
AFP, median (IQR), ng/ml	22.44 (141.97)	16.04 (124.50)	0.05	0.02	0.01
mPAGE-B score, median (IQR)	10.00 (5.00)	11.00 (5.00)	n.a.	n.a.	n.a.
Follow-up time, median (IQR), years	3.71 (1.58)	3.97 (1.62)	0.20	0.38	0.57

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e-antigen; INR, international normalised ratio; mPAGE-B, modified PAGE-B; PSM, propensity score matching; PSW, propensity score weighting; TDF, tenofovir disoproxil fumarate.
[a]After applying eligibility criteria; before weighting.

The analysis using the site-specific definition of cirrhosis produced a similar result (adjusted HR 0.79; 95% CI 0.63–0.99; p = 0.04) (TDF: n = 6,979; ETV: n = 35,960).

In the treatment start date analysis, which excluded patients initiating treatment prior to 2011, the difference in HCC risk between TDF- and ETV-treated patients was not significant (adjusted HR 0.83; 95% CI 0.66–1.05; p = 0.11) (TDF: n = 6,922; ETV: n = 26,498). The complete case analysis excluding patients missing data for any PAGE-B variables produced a statistically significant result (adjusted HR 0.77; 95% CI 0.61–0.98; p = 0.03) (TDF: n = 6,396; ETV: n = 32,959), while the analysis which excluded patients missing data for viral load produced a similar result (adjusted HR 0.79; 95% CI 0.62–1.01; p = 0.06) (TDF: 5,635; ETV: 22,663).

Finally, the two-stage PSW analysis which included HRs from declining studies found that TDF was associated with a lower risk of HCC than ETV, although this difference was not statistically significant (adjusted HR 0.85; 95% CI 0.72–1.01; p = 0.18).

Subgroup analyses

In all subgroup analyses, TDF was associated with a consistently lower risk of HCC compared with ETV (HR <1.0), although statistical significance again varied (Fig. 3). The risk difference was statistically significant for ≥50 of age (p <0.05), male (p = 0.02), HBeAg-positive (p = 0.03) and non-diabetic (p <0.05) subgroups and was most pronounced in the HBeAg-positive subgroup (HR 0.69; 95% CI 0.49–0.97).

Discussion

Using IPD of 42,939 patients from 11 studies conducted in Korea, Taiwan and Hong Kong, the present meta-analysis found that TDF was associated with significantly reduced HCC risk compared with ETV in patients with CHB. Sensitivity analyses supported the relationship of TDF with lower HCC risk, with consistent relationships observed in the context of different analytical methodologies. This result was also observed in all subgroups of clinical interest, although sample size differences may have precluded achievement of formal statistical significance in some subgroups.

In line with our findings, many aggregate data meta-analyses suggest that TDF reduces HCC risk more substantially than ETV for patients with CHB (Fig. 4). Not all meta-analyses have been in agreement; of ten published meta-analyses, seven concluded that TDF provides a greater reduction of HCC risk, while two observed no significant difference.[11–17,33–35] The only meta-analysis that specifically analysed a subgroup of East Asian patients reported a significant difference between the treatments in this subgroup, although no such difference was reported for the entire cohort.[35] As Asian patients with CHB tend to develop HCC at higher rates than those from Europe or the United States,[36] our meta-analysis may be of particular relevance to patients from East Asia. Previous meta-analyses used observational studies, which have inherent within- and between-study heterogeneity from lack of randomisation, with frequently unbalanced treatment arms and different patient populations resulting in

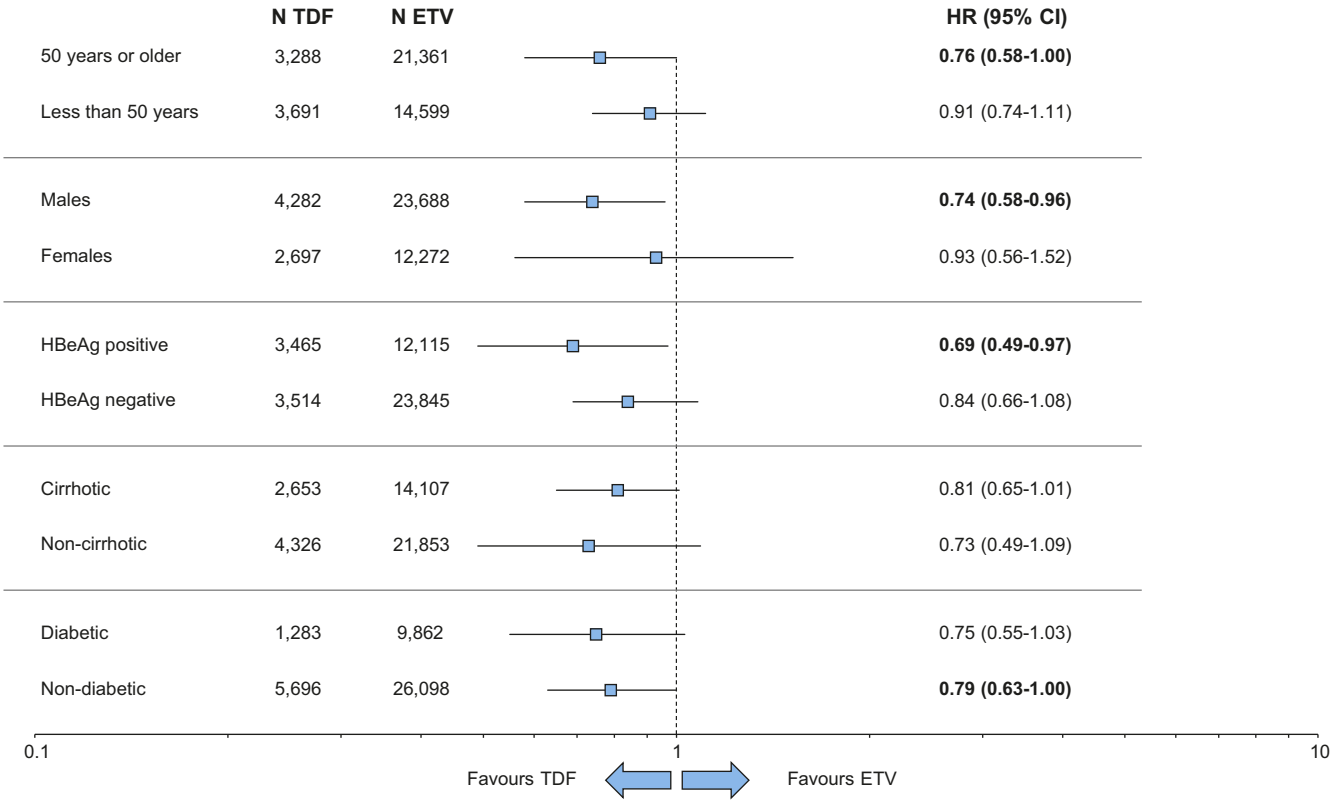

Fig. 3. Subgroup analyses for cumulative incidence of HCC in patients with CHB treated with TDF or ETV. Statistical significance testing was performed using the Wald test. Statistically significant results are in bold. For the '50 years or older' and 'non-diabetic' subgroups, the upper bound of each CI is <1.00, but each has been rounded up to 1.00 when reported to two decimal places. ETV, entecavir; HBeAg, hepatitis B e-antigen; HR, hazard ratio; TDF, tenofovir disoproxil fumarate.

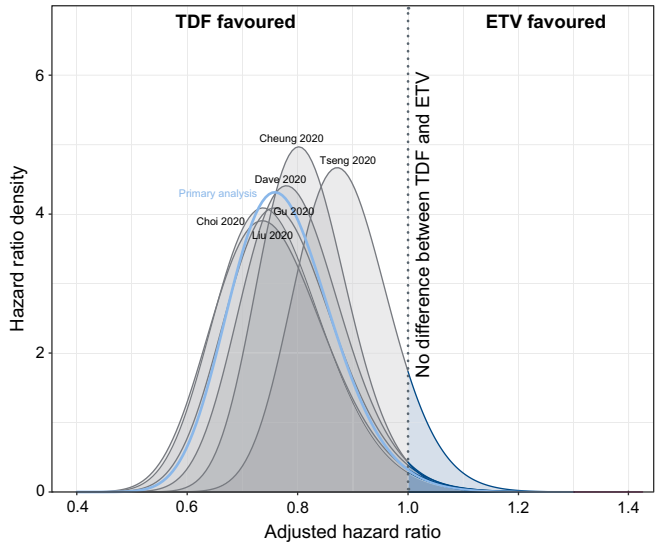

Fig. 4. Plot of estimated densities of the adjusted HRs of meta-analyses published from December 2019 onwards and our primary analysis. ETV, entecavir; TDF, tenofovir disoproxil fumarate.

differences in baseline HCC risk for each treatment group. Aggregate data meta-analyses have been unable to fully account for potential bias resulting from heterogeneity, as they are limited by methodologies of included studies. Overall HRs produced by these meta-analyses have relied on inconsistent estimates, sometimes leading to wider confidence intervals, low precision and data that are difficult to interpret,[18] which may account for their varied conclusions.

IPD meta-analysis can address many of the aforementioned challenges in a consistent way. The approach has been used previously to investigate HCC recurrence in patients with hepatitis C and evaluate the utility of hepatitis B core-related antigen as a marker for high viral load in patients with CHB.[37,38] To generate IPD, individual patients from multiple studies are combined into a master dataset, with the same inclusion criteria, methodologies and assumptions applied across all patients. Covariate adjustment, PSM and PSW, requiring IPD, were utilised in this study to address within-study heterogeneity. Our analysis further explored heterogeneity through subgroup analyses, in which TDF was associated with a consistently lower HCC risk even when patients were categorised into more homogenous groups of clinical interest. A recently published meta-analysis by Tan *et al.* used reconstructed IPD from Kaplan-Meier curves to compare HCC risk between TDF and ETV.[39] In the overall cohort, as well as in the majority of subgroup and sensitivity analyses, the authors reported a significantly lower risk of HCC in patients receiving TDF. This finding held true for the subgroup of patients who were treatment-naïve, aligning with the results of our analysis (in which all included patients were treatment-naïve). Despite the significant difference in HCC risk observed between TDF and ETV throughout many of the analyses, Tan *et al.* ultimately concluded that the difference was unlikely to be clinically significant. However, the use of synthetic IPD prevented Tan *et al.* from consistently adjusting for confounding variables and systematic differences in patient characteristics; our analysis, which used actual IPD, was better able to address potential sources of heterogeneity and apply a consistent methodology across all included data, likely resulting in a more robust estimate of HCC risk.

While our analysis demonstrated a clear difference between TDF and ETV, building on previous findings, the mechanisms behind this difference are not fully understood. The subgroup analysis suggests there may be a greater benefit with TDF over ETV in HBeAg-positive than HBeAg-negative patients, and similarly in non-cirrhotic *vs.* cirrhotic patients. In the initial phase of CHB infection, characterised by very high serum HBV DNA levels, patients are primarily HBeAg-positive and non-cirrhotic, as a substantial immune response has not yet been mounted. In this phase, oncogenesis is predominantly driven by mutations in the host genome due to viral integrations into host DNA.[40] HBV integrations are associated with chromosomal instability, activation of tumour-promoting genes and functional loss of tumour-suppressor genes, contributing to HCC development.[40] Studies have suggested that TDF may provide faster and more complete suppression of HBV DNA levels than ETV,[41–44] particularly in patients with high baseline HBV DNA levels.[41,44] An RCT also suggested that the reduction in HBsAg level was more profound with TDF treatment than ETV treatment.[42] These superior virologic and serologic responses by TDF compared to ETV may result in different levels of effectiveness in HCC prevention.

Moreover, a recent study suggested a higher interferon λ3 level in patients with CHB treated with nucleotide analogues (*e.g.*, TDF) than in those treated with nucleoside analogues (*e.g.*, ETV).[45] The potent antiviral and antitumour activity of the interferon λ pathway was demonstrated in murine models of cancer, including hepatoma, in previous studies;[46] this could provide another explanation for the results of the current study. The higher levels of interferon λ3 associated with TDF may also explain why patients discontinuing TDF have earlier virological relapse than those discontinuing ETV;[47] withdrawal of TDF and subsequent absence of the immunomodulatory effect could result in earlier and more vigorous relapse following treatment cessation.

Suppression of HBV replication may also lead to indirect suppression of oncogenesis via faster resolution of the liver inflammatory response, the other predominant driver of HCC risk in patients with CHB.[48] Chronic liver inflammation leads to fibrosis and cirrhosis; cessation or reversal of these are key goals in treating CHB.[49] While both TDF and ETV have been shown to reverse cirrhosis, a large cohort study reported the reversal rate after 5 years of treatment to be higher with TDF (73.8% *vs.* 61.5%, $p = 0.038$).[50]

Epidemiologic observations have been consistent, with all meta-analyses comparing HCC risk between the two treatments either neutral or in favour of TDF. Our IPD meta-analysis showed high internal consistency in favour of TDF over ETV across all analyses. Our results also indicate a potential advantage of TDF in suppressing the oncogenic impacts of viral replication in patients who have not yet developed cirrhosis. These findings are important to consider as there has historically been a focus on clinical intervention for patients with later stages of CHB,[6] highlighting the need for treatment guidelines to evolve as new evidence becomes available.[51] Given increasing HCC incidence worldwide, of which CHB is a major cause, early and effective treatment of CHB has the potential to provide long-term benefits for patients with CHB, reducing

HCC and mortality and decreasing the burden placed on healthcare systems by the long-term consequences of CHB infection.

Several limitations of this analysis should be mentioned. Differences in follow-up time between TDF and ETV patients could not be fully accounted for and may confound the results, although the sensitivity analysis excluding patients initiating treatment prior to 2011 reduced the discrepancy in follow-up time and produced a result similar to that of the primary analysis, albeit without statistical significance. Underlying data collection methodologies and definitions used across study sites could not be aligned; heterogeneity in these may have influenced our results. Additionally, no adjustment for multiple testing was performed. Some study sites had substantial missing data, necessitating imputation; if missingness of data was related to HCC risk, this may have biased the results. Even after extensive follow-up, only half of identified study sites agreed to participate, which may have led to selection bias. However, this limitation was mitigated by the two-stage PSW sensitivity analysis, which included the HRs of declining studies and found that patients receiving TDF had a lower risk of HCC than ETV, albeit without statistical significance. Finally, all included studies were from East Asia, so results may not be generalisable to the global CHB population.

Our analysis revealed that patients with CHB receiving treatment with TDF *vs.* ETV were significantly less likely to develop HCC. Although statistical significance varied, lower HCC risk with TDF was consistently observed throughout all sensitivity and subgroup analyses, and was particularly notable in HBeAg-positive patients. Since the incidence curve gradually diverged between the two groups after 2.5 years' follow-up, longer follow-up may be needed to better define incidence differences between TDF and ETV in some subgroups. Use of IPD rather than aggregate data produced results with less uncertainty than previous meta-analyses, providing more robust evidence that TDF conveys a benefit over ETV in reducing HCC risk in patients with CHB. These findings should be considered when determining the most appropriate treatment course for patients with CHB and have implications for healthcare systems in reducing the burden of CHB.

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Abbreviations

ALT, alanine aminotransferase; CHB, chronic hepatitis B; ETV, entecavir; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; IPD, individual patient data; NA, nucleo(s)tide analogue; PSM, propensity score matching; PSW, propensity score weighting; RCT, randomised controlled trial; TDF, tenofovir disoproxil fumarate.

Financial support

This study was sponsored by Gilead Sciences. Support for third-party writing assistance for this article, provided by Isabel Haber, BS, Costello Medical, US, was funded by Gilead Sciences in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Conflict of interest

Won-Mook Choi has no conflicts of interest to disclose. Terry Cheuk-Fung Yip has served as an advisory committee member and a speaker for Gilead Sciences. Grace Lai-Hung Wong has served as an advisory committee member for Gilead Sciences and Janssen, as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen and Roche, and has received research grants from Gilead. W Ray Kim has served as an advisory committee member for Gilead Sciences, Inovio Pharmaceuticals and Roche. Leland J Yee is an employee of, and owns stock in, Gilead Sciences. Craig Brooks-Rooney is an employee of Costello Medical, which received payment from Gilead Sciences for analytical services for this study. Tristan Curteis is an employee of Costello Medical, which received payment from Gilead Sciences for analytical services for this study. Harriet Cant was an employee of Costello Medical at the time of the study, which received payment from Gilead Sciences for analytical services for this study. Chien-Hung Chen has no conflicts of interest to disclose. Chi-Yi Chen has no conflicts of interest to disclose. Yi-Hsiang Huang received research grants from Gilead Sciences and Bristol-Meyers Squibb and honoraria from Abbvie, Gilead Sciences, Bristol-Meyers Squibb, Ono Pharmaceutical, Merck Sharp & Dohme, Eisai, Eli Lilly, Ipsen and Roche and has served in an advisory role for Abbvie, Gilead Sciences, Bristol-Meyers Squibb, Ono Pharmaceuticals, Eisai, Eli Lilly, Ipsen, Merck Sharp & Dohme and Roche. Young-Joo Jin has no conflicts of interest to disclose. Dae Won Jun has no conflicts of interest to disclose. Jin-Wook Kim has no conflicts of interest to disclose. Neung Hwa Park has no conflicts of interest to disclose. Cheng-Yuan Peng has served as an advisory committee member for Bristol-Myers Squibb and Gilead Sciences. Hyun Phil Shin has no conflicts of interest to disclose. Jung Woo Shin has no conflicts of interest to disclose. Yao-Hsu Yang has no conflicts of interest to disclose. Young-Suk Lim is an advisory board member of AbbVie, Arbutus Biopharma, Assembly Biosciences, Brii Biosciences, Bayer Healthcare, GlaxoSmithKline, Gilead Sciences, Janssen, Olix Pharmaceuticals, Roche, Vaccitech, and Vir Biotechnology; and received grant/research support from Gilead Sciences.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Substantial contributions to study conception and design: WMC, TCFY, GLHW, WRK, LJY, CBR, TC, HC, CHC, CYC, YHH, YJJ, DWJ, JWK, NHP, CYP, HPS, JWS, YHY, YSL; substantial contributions to analysis and interpretation of the data: WMC, TCFY, GLHW, WRK, LJY, CBR, TC, HC, CHC, CYC, YHH, YJJ, DWJ, JWK, NHP, CYP, HPS, JWS, YHY, YSL; drafting the article or revising it critically for important intellectual content: WMC, TCFY, GLHW, WRK, LJY, CBR, TC, HC, CHC, CYC, YHH, YJJ, DWJ, JWK, NHP, CYP, HPS, JWS, YHY, YSL; final approval of the version of the article to be published: WMC, TCFY, GLHW, WRK, LJY, CBR, TC, HC, CHC, CYC, YHH, YJJ, DWJ, JWK, NHP, CYP, HPS, JWS, YHY, YSL.

Data availability statement

Owing to protections around the sharing of private health data, individual patient data are not permitted to be shared or made publicly available. The study protocol is available on PROSPERO (ID CRD42021249314), and the statistical analysis plan is available on request from the corresponding author.

Acknowledgements

The authors thank the patients, the investigators and their teams who took part in this study. The authors also acknowledge Ben Farrar, PhD, Elliot Dryer-Beers, PhD, Laura Clark, DPhil, Radost Pencheva, MSc, and Seth Francis-Graham, PhD, from Costello Medical, UK, and Zarena Jafry, MPH, from Costello Medical, US, for statistical and data management support, and Isabel Haber, BS, from Costello Medical, US, for medical writing and editorial assistance based on the authors' input and direction. This study was funded by Gilead Sciences.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.12.007.

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