2-8-2022

Risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis B patients receiving tenofovir disoproxil fumarate versus entecavir in the United States

W. Ray Kim

Laura E. Telep

Belinda Jump

Mei Lu
Henry Ford Health, mlu1@hfhs.org

Heribert Ramroth

See next page for additional authors

Recommended Citation
Kim WR, Telep LE, Jump B, Lu M, Ramroth H, Flaherty J, Gaggar A, Chokkalingam AP, and Gordon SC. Risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis B patients receiving tenofovir disoproxil fumarate versus entecavir in the United States. Aliment Pharmacol Ther 2022.

Authors

W. Ray Kim, Laura E. Telep, Belinda Jump, Mei Lu, Heribert Ramroth, John Flaherty, Anuj Gaggar, Anand P. Chokkalingam, and Stuart C. Gordon

Received: 11 August 2021 | First decision: 2 September 2021 | Accepted: 12 January 2022

DOI: 10.1111/apt.16786

AP&T Alimentary Pharmacology & Therapeutics WILEY

Risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis B patients receiving tenofovir disoproxil fumarate versus entecavir in the United States

W. Ray Kim[1] | Laura E. Telep[2] | Belinda Jump[2] | Mei Lu[3] | Heribert Ramroth[2] | John Flaherty[2] | Anuj Gaggar[2] | Anand P. Chokkalingam[2] | Stuart C. Gordon[3]

[1]Stanford University School of Medicine, Stanford, CA, USA

[2]Gilead Sciences Inc., Foster City, CA, USA

[3]Henry Ford Health System, Detroit, MI, USA

Correspondence
W. Ray Kim, Stanford University School of Medicine, 430 Broadway, Pav C, Redwood City, CA 94063, USA.
Email: wrkim@stanford.edu

Funding information
This analysis was undertaken with the support of Gilead Sciences, Inc, which included acquisition of the data set and salary support of the epidemiologists (LET and APC). Authors unaffiliated with Gilead were not compensated in any form. The sponsor was uninvolved in other aspects of manuscript development. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Summary

Background: Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are the first-line treatment agents for chronic hepatitis B virus (HBV). Recently, whether the degree to which the risk of hepatocellular carcinoma (HCC) may be reduced by ETV vs TDF has been debated. We compared the incidence of HCC among treatment-naïve patients receiving TDF vs ETV in the United States.

Methods: From a large administrative medical claims database of commercially insured patients, we identified 166,933 adults with a diagnosis of chronic hepatitis B and a minimum of 12 months of prior enrolment, of whom 3934 and 6127 initiated ETV and TDF respectively. Fine-Gray hazard regression models incorporating treatment propensity scores (PS) were used to estimate the risk of HCC incidence associated with TDF vs ETV; variables considered for adjustment included demographic characteristics, concomitant medication use and baseline comorbidities, as well as competing events including liver transplantation and medication changes.

Results: After PS weighting, the TDF and ETV groups were well-matched. During the follow-up, 90 patients developed HCC, including 50 receiving ETV and 40 receiving TDF, giving rise to crude incidence rates of 0.62 per 100 person-years (PY) and 0.30 per 100 PY respectively. In PS-weighted, multivariable analysis, TDF was associated with a subdistribution hazard ratio for HCC of 0.58 (95% confidence interval [CI]: 0.38–0.89) compared to ETV. Results were similar when patients ≥40 years and men and women were analysed separately.

Conclusion: Among commercially insured, treatment-naïve patients with chronic hepatitis B in the United States, treatment with TDF was associated with significantly lower risk of HCC than ETV.

The Handling Editor for this article was Professor Geoffrey Dusheiko, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Hepatitis B virus (HBV) is a group 1 human carcinogen as designated by the International Agency for Research on Cancer.[1] Globally, more than 50% of hepatocellular carcinoma (HCC) is attributable to HBV infection.[2] Of the estimated 250 million individuals with chronic HBV infection, approximately 325,000 succumb to HCC each year.[3–5]

With the advent of effective oral nucleoside/nucleotide analogue polymerase reverse transcriptase inhibitors such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF) in the 2000s, effective viral suppression, achievable in the majority of patients, has been associated with reduced risk of HCC.[6–8] Although randomised clinical trial data are limited to one study which demonstrated that lamivudine, compared to placebo, was associated with lower incidence of HCC among patients with active viral replication and advanced fibrosis, a multitude of observational and modelling studies have suggested significant reductions in HCC risk in patients receiving effective anti-viral therapy.[7,9–13] Anti-viral therapy may reduce the risk of HCC by a number of mechanisms such as abrogation of inflammation-mediated signalling, prevention or regression of fibrosis altering the microenvironment in the liver and improvement in immune response.[14–19]

In most advanced healthcare settings, the majority of patients being treated for chronic HBV infection receive long-term anti-viral therapy and achieve sustained suppression of viral activity and clinical remission. Thus, in patients with compensated liver disease receiving modern anti-viral therapy, HBV's impact on morbidity and mortality associated with cirrhosis and liver failure may essentially be eliminated, highlighting HCC as the key determinant of long term outcome in those patients.[20] Although ETV and TDF are thought to share similar anti-viral potency, findings from several recent reports suggest that patients receiving TDF may experience lower HCC incidence than those receiving ETV.[7,21–24] Meanwhile, other studies, notably those in Western countries, have not observed a significant difference in HCC risk.[25–29] Thus, whether the choice of HBV treatment has a clinically meaningful impact on subsequent HCC risk has been debated. In this work, using a large US administrative claims database, we sought to compare the risk of incident HCC among patients with chronic hepatitis B starting treatment with ETV vs TDF.

2 | METHODS

The data set used for this analysis is the IQVIA PharMetrics Plus™ administrative claims database. It is the largest, non-payer–owned, integrated claims database of commercial insurers (thus, exclusive of public payers, such as Medicare) in the United States, consisting of adjudicated medical and pharmacy claims for over 150 million US health plan enrolees since 2006. Designed to be representative of the US commercially insured population, it covers both inpatient and outpatient claims as well as retail and mail order pharmacy claims. Dispensed medications are recorded based on generic product identifier codes, while diagnoses are recorded based on International Classification of Diseases (ICD) codes. For this analysis, submitted claims from 1 January 2006 through 30 March 2019 were used. Because all data are de-identified, this study was considered exempt from institutional review board oversight.

This study employs a retrospective cohort design in which the exposure (ie use of anti-viral agents) was recorded before the outcome (ie occurrence of HCC). From the data set, we assembled a cohort of adults (≥18 years) with chronic hepatitis B, from which we identified patients newly initiating ETV or TDF treatment. The individual administrative codes for these and other inclusion and exclusion criteria, as well as the outcome of HCC, are listed in Table S1. To maximise the likelihood that patients were treatment naïve and were at risk for incident HCC, we required a minimum of 1 year of enrolment prior to the index diagnosis. This look back period was used to ascertain the absence of prior HCC, comorbidities and of prior anti-HBV medications use. Exclusion criteria included: evidence of co-infection with HIV, hepatitis C virus (HCV) or hepatitis D virus (HDV); absence of treatment with ETV or TDF; simultaneous exposure to ETV and TDF; and prior exposure to pegylated interferon alpha, lamivudine, adefovir dipivoxil or telbivudine. In addition, to exclude potential prevalent HCC at baseline, patients with a diagnosis of HCC, receipt of chemotherapy or liver transplant prior to or within 6 months after treatment initiation were excluded from the study. We employed a broad definition of HCC in order to capture all cases based on an assumption that malignant liver lesions occurring in patients being treated with anti-HBV medications are highly likely to be HCC. In addition, we assessed the validity of this assumption by a sensitivity analysis using a narrower case definition.

Included patients were followed from initiation of ETV or TDF to the first of the following events: (1) HCC diagnosis, (2) end of insurance enrolment or (3) 30 March 2019, the last day covered by the data set. Initiation of a new anti-viral therapy, breaks in anti-viral treatment >90 days, and liver transplantation were recognised as potential competing events. Figure 1 summarises the cohort definition and determination of person-time. Unadjusted incidence rates of HCC in each treatment group were calculated as number of events per 100 person-years with exact Poisson 95% confidence intervals (CIs). Graphic representation of the time to HCC development was generated using Kaplan–Meier methods. The risk of HCC development associated with TDF vs ETV was estimated using Fine-Gray subdistribution hazard competing risks methods. An array of covariates was considered for adjustment including age, sex, calendar year of TDF or ETV initiation, and health conditions and medications claimed on or before baseline. Inverse probability of treatment weighing (IPTW) with stabilised propensity score (PS) weights was used to balance the baseline covariates between the TDF and ETV cohorts. Liver disease variables and variables associated with HCC risk at $P < 0.10$ in univariate logistic regression models were included in the PS estimation (Table S2). Effectiveness of the IPTW procedure in balancing baseline characteristics was assessed by examining the standardised differences of covariates between the cohorts[30]; no standardised differences over 10% were observed.

Although the approved indications for ETV are TDF are similar, only TDF is used for treatment of HBV-infected pregnant women to reduce mother-to-child transmission. This subgroup of TDF-treated patients is expected to be at low absolute risk of HCC and thus may potentially skew the results of the analysis. To address this potential concern, and because pregnancy is not captured reliably in administrative claims data, we performed sensitivity analyses restricting to the following subgroups: (1) patients over 40 years of age and (2) men and women separately. Lastly, to check for residual bias resulting from unmeasured confounding, we repeated the analysis using two negative control outcomes, namely acute myocardial infarction (AMI) and emphysema, outcome states implausibly related to treatment using ETV or TDF.

3 | RESULTS

In the data set, we identified 166 933 patients with evidence of HBV infection, of whom 10 061 met the eligibility criteria, including 3934 receiving ETV and 6127 TDF (Figure 2). In Table 1, patients were most commonly in their 40s and men. The vast majority (~90%) lacked evidence of advanced liver disease. Before PS weighting

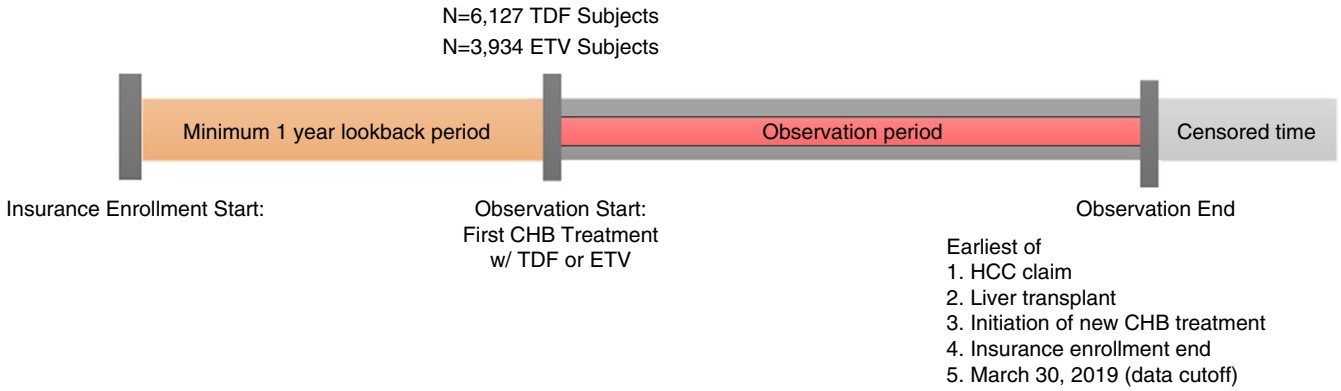

FIGURE 1 Overall study scheme. A treatment-naïve chronic hepatitis B patient was identified by lack of anti-viral prescriptions for a minimum of a year preceding the first prescription of ETV or TDF. The patient was then followed forward until one of the end points was reached. Please note that liver transplantation and medication events including switching to a new anti-viral treatment were considered in the analysis as competing events. CHB (chronic hepatitis B)

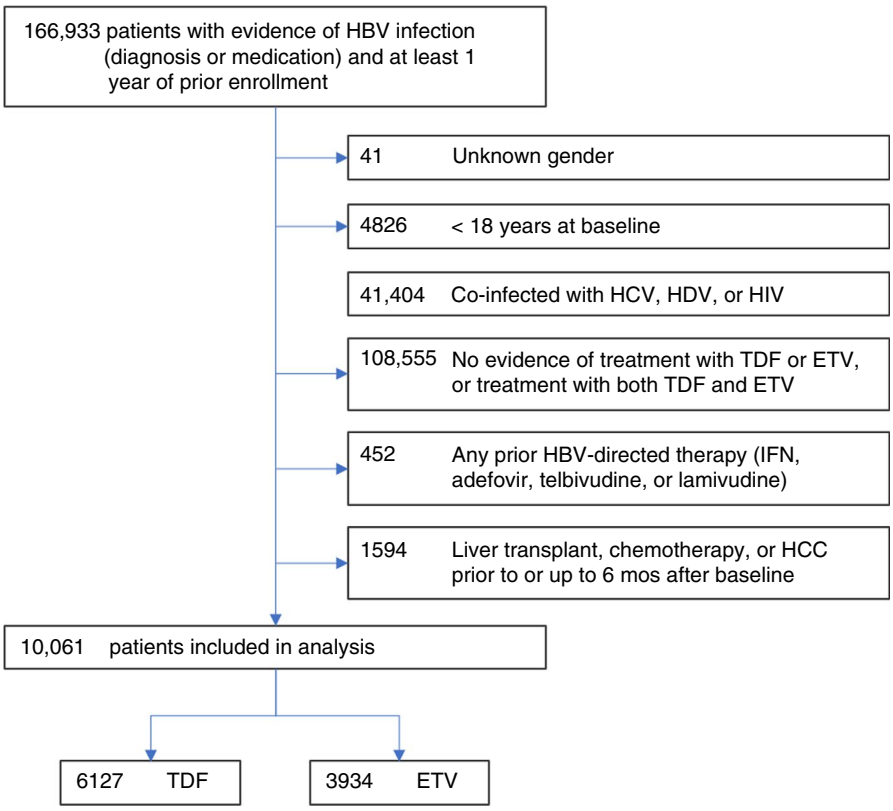

FIGURE 2 Patient disposition. A total of 10 061 adult patients with HBV monoinfection without any prior HBV therapy or evidence of prevalent HCC who were newly treated with ETV (N = 3934) or TDF (N = 6127) were included in the study

TABLE 1 Characteristics of patients with HBV infection receiving TDF and ETV, unweighted and inverse probability of treatment weighted frequencies

	n		Unweighted data			Weighted data			
Variable	**TDF (N = 6127)**	**ETV (N = 3934)**	**TDF %**	**ETV %**	***P***	**TDF %**	**ETV %**	***P***	**SMD (%)[a]**
Demographics									
Age group (years)									
18-29	845	299	13.8	7.6	<0.01	11.3	11.2	1.00	2.5
30-39	1468	747	24.0	19.0		22.0	21.8		
40-49	1684	1160	27.5	29.5		28.3	28.4		
50-59	1391	1074	22.7	27.3		24.5	24.6		
60-69	639	561	10.4	14.3		12.0	12.1		
70+	100	93	1.6	2.4		1.9	1.9		
Sex									
Female	2685	1441	43.8	36.6	<0.01	40.8	40.3	0.63	1.0
Liver disease at baseline									
Cirrhosis/Fibrosis	487	384	8.0	9.8	<0.01	8.8	8.9	0.87	0.3
Portal hypertension	108	60	1.8	1.5	0.36	1.7	1.7	0.94	0.1
Ascites	107	107	1.8	2.7	<0.01	2.1	2.1	0.98	0.0
Hepatic encephalopathy	40	17	0.7	0.4	0.15	0.6	0.6	0.96	0.1
Bleeding oesophageal varices	16	8	0.3	0.2	0.56	0.2	0.3	0.91	0.2
Any liver disease at baseline[b]	558	453	9.1	11.5	<0.01	10.0	10.4	0.54	0.2

[a]Standardised mean difference (<10% is considered well-balanced).

[b]Includes any of: cirrhosis/fibrosis, portal hypertension, ascites, hepatic encephalopathy and bleeding oesophageal varices (see ICD code listing in Table S3).

(left panel of Table 1), patients receiving TDF were more likely to be younger (≤39 years) and female. The proportion with advanced liver disease at baseline was higher among patients receiving ETV—attributable to those with a diagnosis of cirrhosis/fibrosis and ascites. In contrast, hepatic encephalopathy and portal hypertension tended to be more common among TDF-treated patients. After PS weighting (right panel of Table 1), the two groups were well-balanced in these variables.

The duration of follow-up was comparable between the two treatment groups with a mean of 752 days and 791 days for ETV and TDF respectively. During the follow-up, a total of 2155 patients experienced competing risk events, including 13 liver transplantation events, 405 anti-viral regimen changes and 1737 anti-viral treatment breaks >90 days. A total of 90 patients developed HCC, including 40 patients receiving TDF and 50 receiving ETV, giving rise to a crude HCC incidence rate of 0.62 per 100 person-years (95% CI: 0.46–0.81 per 100 person-years; total person-years = 8098) for ETV and 0.30 per 100 person-years (95% CI: 0.22–0.41 per 100 person-years; total person-years = 13 261) for TDF (Figure 3).

Table 2 summarises the results of the Fine-Gray regression analysis using treatment as an exposure variable and including covariates significant in the multivariable model at $P < 0.10$, while taking into account competing events as described above. Before adjustment or weighting, TDF was associated with a reduction in risk of HCC (unadjusted sHR = 0.52, 95% CI: 0.34-0.79). The association of TDF with a reduced risk of HCC relative to ETV persisted after adjustment in the unweighted multivariable model (sHR = 0.58, 95% CI: 0.38-0.87).

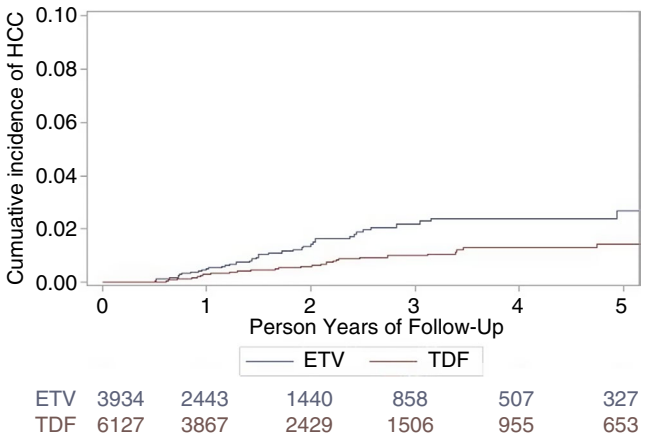

FIGURE 3 Occurrence of HCC. The incidence of HCC was higher among patients receiving ETV than in those receiving TDF ($P < 0.01$)

TABLE 2 Risk of HCC associated with TDF vs ETV: results of Fine-Gray subdistribution hazards regression

	Univariate[a]	Multivariable[a]	Multivariable with IPTW[a]	
Variable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	***P***
TDF vs ETV	0.52 (0.34-0.79)	0.58 (0.38-0.87)	0.58 (0.38-0.89)	0.01
Age (reference 18–29)				
30–39	8.27 (1.10-62.14)	7.56 (1.01-56.53)	9.71 (1.03-91.52)	0.05
40–49	8.98 (1.22-66.35)	7.84 (1.07-57.26)	10.15 (1.10-94.19)	0.04
50–59	11.25 (1.53-83.08)	9.77 (1.34-71.50)	12.79 (1.38-118.71)	0.03
60–69	22.10 (2.97-164.68)	18.50 (2.49-137.35)	25.49 (2.71-239.65)	< 0.01
70+	21.20 (2.20-204.21)	17.40 (1.82-166.75)	22.03 (1.80-269.20)	0.02
Sex (reference female)				
Male	1.20 (0.78-1.84)	1.10 (0.71-1.69)	1.11 (0.72-1.73)	0.63
Portal hypertension[b]	3.56 (1.32-9.64)	2.96 (1.06-8.25)	2.87 (1.04-7.94)	0.04

[a]Univariate risk estimates are unadjusted for other risk factors; multivariable risk estimates are mutually adjusted for all other presented risk factors; multivariable with IPTW risk estimates are mutually adjusted and weighted with inverse probability of treatment weights.
[b]Significant in the multivariable model at $P < 0.10$.

In the final IPTW-weighted, multivariable-adjusted model, TDF was associated with a statistically significant reduction in risk of HCC relative to ETV (sHR = 0.58; 95% CI: 0.38-0.89, p = 0.01).

Supplementary analyses were conducted to further assess the validity of our analysis. In sensitivity analyses to assess whether the results above were potentially influenced by the use of TDF in young, pregnant women, we repeated the multivariable weighted analyses limited to patients ≥40 years of age. The resulting sHR was 0.47 (95% CI: 0.29-0.75). We also repeated the analysis separately for each sex. The sHR was slightly higher in men (sHR = 0.62, 95% CI: 0.36-1.06) and lower in women (sHR = 0.54, 95% CI: 0.27-1.08) than in the combined analysis. A third sensitivity analysis was conducted using a narrower definition of HCC (codes 155.0 and C22.0 only, n = 79), which yielded a consistent result (sHR = 0.60, 95% CI: 0.39–0.93).

Finally, in consideration of potential unmeasured confounding in our study, we analysed our cohorts with negative control outcomes, namely, acute myocardial infarction (AMI) and emphysema (Table S4). In univariate, unweighted multivariable, and weighted multivariable analyses, TDF vs ETV had no impact on either negative control outcome.

4 | DISCUSSION

In this work, we utilised a large US administrative claims database to examine the impact of initiating therapy with two first-line anti-HBV agents, ETV and TDF, on future occurrence of HCC. After adjusting for multiple covariates and applying PS weighting methods to ensure comparability of the two treatment groups, TDF was associated with a 42% lower risk of HCC compared to ETV. In contrast to prior reports, our work makes a unique contribution to the literature for being a Western study incorporating a sample which is generalisable to a large section of the population with robust statistical power, although given the nature of administrative claims data, only limited clinical data were available with which to characterise patient phenotypes.

Published studies on HBV treatment regimens and long-term outcomes of HCC to date have reported disparate results, making this one of the more debated topics in viral hepatitis research.[7,21,23–29,31–33] These studies are predominantly derived from Asia, where the high prevalence of HBV and the high burden of HCC generate large amounts of observational data to enable such studies. Clearly, prospective randomised trials yield stronger evidence than observational studies; however, a prospective randomised trial to address this topic is unlikely to be forthcoming. For example, to demonstrate the difference in HCC incidence rates comparable to those observed in this study (0.3-0.8 per 100 person-years), a study would require thousands of patients randomised and followed for several years. A case in point may be our sex-stratified analysis, in which the difference between ETV and TDF lost statistical significance when the sample size decreased from 10 061 (combined total) to 4126 (women only) and 5935 (men only).

We designed this observational study to ensure its scientific validity by maximising comparability between the two treatment groups. First, prior Asian studies were affected by the significant gap in approval dates for the two regimens throughout Asia which resulted in imbalance in study subjects with regard to prior anti-viral exposure and proportions of advanced liver disease and cirrhosis.[34] In the United States, the ETV and TDF FDA approval dates are much closer together: ETV was approved in 2005 and TDF in 2008 for chronic hepatitis B, although "off-label" use of TDF was not uncommon for HBV-monoinfected patients since TDF was approved for use in HIV-1 infection in 2001.[35,36] In this study, the earliest baseline date for patients included was 1 January 2007, owing to the requirement of 12 months of look-back, which resulted in the similar duration of follow up.

Second, we employed PS weighting to address the potential effects of baseline differences between the two groups. Before matching, there were small yet statistically significant differences—in part due to the large sample size—in the demographic and clinical characteristics between the subjects receiving TDF vs ETV. This was driven by the larger proportion of younger and female patients in the former, which likely reflects the use of TDF during pregnancy. For that particular concern, in addition to propensity weighting, we conducted sensitivity analyses restricted to older patients and stratified for sex; results from these analyses were consistent with our overall findings with hazards of HCC for TDF vs ETV being lower by 38% (HR = 0.62, in men) to 53% (HR = 0.47, for age ≥40 years), statistical significance notwithstanding. Lastly, competing risk analyses were used to exclude potential impact of changes in the anti-viral regimen as well as other competing events such as liver transplantation.

Third, we focused on treatment-naïve patients by excluding individuals receiving any HBV therapy at any point during the year prior to cohort entry, since choice of anti-viral regimens in patients who have been exposed to multiple prior agents confound the current fibrosis status and future HCC risk. This study design resulted in the low (~10%) proportion of patients with a diagnosis indicative of cirrhosis or advanced liver disease at baseline. Although it is likely that cirrhosis is under-diagnosed and -reported in administrative data, our study results in treatment-naïve patients among predominantly non-cirrhotic patients enrich the literature to date.

Anti-viral therapy may reduce the incidence of HCC via at least three mechanisms including (1) direct effects on inflammation in response to viral activities, (2) impact on fibrosis regression, found after long-term (>5 years) therapy, and (3) possibly interference with integration of viral DNA into the host genome.[37] In our study, we observed a significant reduction in HCC incidence over a relatively short term in patients without advanced fibrosis. We interpret this to indicate that the risk reduction in our study may be driven by the direct effects on viral replication and liver inflammation. In contrast, for example, fibrosis regression would take much longer and there are no data to suggest differences in fibrosis regression between ETV- and TDF-treated patients.

Although limited in number, studies from Europe and the United States to date have tended to report no difference in HCC incidence between TDF- and ETV-treated patients.[26–29,31,38] In addition to the timing of introduction of the agents,[34] there may be biological differences between Asian and non-Asian populations. First, although head-to-head comparisons are limited, prior data have indicated that TDF may provide more potent viral suppression than ETV,[39] whereas incomplete viral control may eventually translate to higher carcinogenesis. Non-Asian patients tend to have lower serum HBV DNA, which may render TDF's relative advantage over ETV less apparent than among Asians.[40] Second, TDF has been associated with preservation of telomere length which has been proposed as a potential mechanism for protection against HCC.[41,42] Such an effect may be expected to be more pronounced in younger patients, with whom Asian cohorts tend to be enriched. Finally, ETV and TDF may elicit innate immune responses differently and this effect may differ by race. For example, compared to nucleoside analogues such as ETV, nucleotide analogues including TDF have been shown to induce interferon λ3 better, which may augment the anti-viral effect and possibly provide anti-tumour activity against HCC.[14–17] It has been reported in the HCV literature that non-Asian subjects had higher prevalence of IL-28B variant alleles associated with a lower interferon λ3 response.[43,44] Unfortunately, the claims data used in this analysis did not include race of the subject, preventing us from being able to make a direct comparison between Asians and non-Asians in the study. However, a large proportion, if not the majority, of HBV patients in the US are of Asian ancestry.

We acknowledge further limitations for the study. First, administrative claims data lack information that might provide more detailed biological or clinical insights. In addition to race and ethnicity, laboratory data such as histology, liver fibrosis, and serum ALT and virological features such as HBV DNA were not available. Due to lack of granularity in the claims codes, the distinction between fibrosis, cirrhosis and decompensated cirrhosis may not be made definitively. Death, a potential competing risk for HCC, was not reliably captured. These limitations may have led to some misclassification between the two treatment groups; however, it is unlikely that this misclassification is differential, which would, if anything, tend to bias results towards the null, contrary to the observed significant risk estimate. Second, a patient's enrolment in US commercial health insurance coverage may change over time, often because insurance is typically linked to employment; these short enrolment periods result in short follow-up periods within the data set. However, due to the study's sample size, sufficient numbers of events were observed in order to detect an effect. Finally, it is possible that the observed results may have been influenced by unmeasured, residual confounding. We conducted two unrelated, negative control outcome analyses which suggest that such influences are unlikely to be responsible for the observed association of TDF with reduced risk of HCC.

In summary, in this analysis of a large US administrative claims database, we demonstrate that the incidence rate of HCC among chronic hepatitis B patients treated with TDF was lower than that among those with ETV. The difference held up after adjusting for demographic characteristics, baseline conditions and PS weighting. To the degree that our analysis was limited to treatment-naïve patients, our data may not support altering treatment strategies in patients who are doing well on an anti-viral medication. In patients who are being prescribed ETV or TDF for the first time, our findings may be helpful when considering future risks of HCC. In patients who are thought to be at a greater risk of HCC (eg HBeAg+, high serum HBV DNA, high serum ALT, male),[45] any reduction (eg 11%-62%, complements of lower and upper bounds of the 95% confidence interval shown in Table 2) in HCC risk may be meaningful. This difference, however, would be less pronounced among lower risk patients. In light of the increasing consensus among published studies, at least among Asian patients, we propose that clinicians take into account this information for patients starting anti-viral therapy who are considered to be at a heightened risk of HCC.

ACKNOWLEDGEMENT

Bibliography management support was provided by Shalini Sethi, Gilead Sciences, Foster City, CA, USA.

Declaration of personal interests: Dr. Kim has served as a consultant and an advisory board member for Gilead Sciences. Drs. Lu and Gordon have received research funding from Gilead Sciences. Drs. Telep, Jump, Ramroth, Flaherty, and Chokkalingam are employees and stockholders of Gilead Sciences. Dr. Gaggar was an employee at Gilead Sciences and is now an employee of Arrive Bio.

AUTHORSHIP

Guarantor of the article: W. Ray Kim

Author contributions: Kim, Chokkalingam, Telep, Ramroth, Jump: Conception and design; Chokkalingam, Telep: Collection and assembly of data; Kim, Chokkalingam, Telep, Lu, Gordon: Analysis and interpretation of data; Kim, Telep, Chokkalingam: Drafting of manuscript; Kim, Telep, Ramroth, Flaherty, Gaggar, Chokkalingam, Gordon: Critical revision of manuscript for important intellectual content; Kim, Telep, Jump, Ramroth, Flaherty, Gaggar, Chokkalingam, Lu, Gordon: Final approval of manuscript; Kim, Telep, Chokkalingam, Lu: Statistical expertise. All authors have approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data subject to third party restrictions The data that support the findings of this study are proprietary and available for purchase from IQVIA PharMetrics. Restrictions apply to the availability of these data, which were used under license for this study.

ORCID

W. Ray Kim https://orcid.org/0000-0002-3030-860X

Anand P. Chokkalingam https://orcid.org/0000-0001-5200-3033

REFERENCES

1. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—part B: biological agents. *Lancet Oncol*. 2009;10:321-322.
2. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006;118:3030-3044.
3. *Global Hepatitis Report 2017*. Geneva: World Health Organization; 2017.
4. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet*. 2015;386:1546-1555.
5. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1736-1788.
6. Wong GL, Chan HL, Mak CW, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology*. 2013;58:1537-1547.
7. Choi J, Kim HJ, Lee J, Cho S, Ko MJ, Lim YS. Risk of hepatocellular carcinoma in patients treated with entecavir vs tenofovir for chronic hepatitis B: a Korean Nationwide Cohort Study. *JAMA Oncol*. 2019;5:30-36.
8. Kim JH, Sinn DH, Kang W, et al. Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment. *Hepatology*. 2017;66:335-343.
9. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004;351:1521-1531.
10. Kim WR, Loomba R, Berg T, et al. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. *Cancer*. 2015;121:3631-3638.
11. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology*. 2013;58:98-107.
12. Nguyen MH, Yang HI, Le A, et al. Reduced incidence of hepatocellular carcinoma in cirrhotic and noncirrhotic patients with chronic hepatitis B treated with tenofovir–a propensity score-matched study. *J Infect Dis*. 2019;219:10-18.
13. Gordon SC, Lamerato LE, Rupp LB, et al. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. *Clin Gastroenterol Hepatol*. 2014;12:885-893.
14. Murata K, Asano M, Matsumoto A, et al. Induction of IFN-lambda3 as an additional effect of nucleotide, not nucleoside, analogues: a new potential target for HBV infection. *Gut*. 2018;67:362-371.
15. Murata K, Tsukuda S, Suizu F, et al. Immunomodulatory mechanism of acyclic nucleoside phosphates in treatment of hepatitis B virus infection. *Hepatology*. 2020;71:1533-1545.
16. Abushahba W, Balan M, Castaneda I, et al. Antitumor activity of type I and type III interferons in BNL hepatoma model. *Cancer Immunol Immunother*. 2010;59:1059-1071.
17. Sato A, Ohtsuki M, Hata M, Kobayashi E, Murakami T. Antitumor activity of IFN-lambda in murine tumor models. *J Immunol*. 2006;176:7686-7694.
18. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013;381:468-475.
19. Arzumanyan A, Reis HM, Feitelson MA. Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma. *Nat Rev Cancer*. 2013;13:123-135.
20. Papatheodoridis GV, Sypsa V, Dalekos G, et al. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. *J Hepatol*. 2018;68:1129-1136.
21. Yip TC, Wong VW, Chan HL, Tse YK, Lui GC, Wong GL. Tenofovir is associated with lower risk of hepatocellular carcinoma than entecavir in patients with chronic HBV infection in China. *Gastroenterology*. 2020;158:215-225 e216.
22. Zhang Z, Zhou Y, Yang J, Hu K, Huang Y. The effectiveness of TDF versus ETV on incidence of HCC in CHB patients: a meta analysis. *BMC Cancer*. 2019;19:511.
23. Chang K-C, Hu T-H, Wang J-H, Chen CH, Hung C-H, Tsai M-C. Tenofovir reduce risk of hepatocellular carcinoma development higher than entecavir in chronic B hepatitis patients with liver cirrhosis. *Hepatology*. 2019;70:313a.
24. Lee C-J, Su C-W, Lin H-C, Hou M-C, Huang Y-H. Occurrence of hepatocellular carcinoma in chronic hepatitis B patients undergoing entecavir or tenofovir treatment. *Hepatology*. 2019;70:578a.
25. Kim SU, Seo YS, Lee HA, et al. A multicenter study of entecavir vs. tenofovir on prognosis of treatment-naive chronic hepatitis B in South Korea. *J Hepatol*. 2019;71:456-464.
26. Hsu YC, Wong GL, Chen CH, et al. Tenofovir versus entecavir for hepatocellular carcinoma prevention in an international consortium of chronic hepatitis B. *Am J Gastroenterol*. 2020;115:271-280.
27. Lee SW, Kwon JH, Lee HL, et al. Comparison of tenofovir and entecavir on the risk of hepatocellular carcinoma and mortality in treatment-naive patients with chronic hepatitis B in Korea: a large-scale, propensity score analysis. *Gut*. 2019;69:1301-1308.
28. Papatheodoridis GV, Dalekos GN, Yurdaydin C, et al. Similar risk of hepatocellular carcinoma (HCC) development during long-term entecavir

(ETV) or tenofovir disoproxil fumarate (TDF) therapy in Caucasian chronic hepatitis B (CHB) patients. *Hepatology*. 2019;70:286a.
29. Pol S. Tenofovir versus entecavir in HBV chronic infection: impact on HCC and other liver-related complications occurrences. *Hepatology*. 2019;70:128a.
30. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661-3679.
31. Su F, Berry K, Ioannou GN. No difference in hepatocellular carcinoma risk between chronic hepatitis B patients treated with entecavir versus tenofovir. *Gut*. 2021;70(2):370-378.
32. Wang X, Liu X, Dang Z, et al. Nucleos(t)ide analogues for reducing hepatocellular carcinoma in chronic hepatitis B patients: a systematic review and meta-analysis. *Gut Liver*. 2020;14:232-247.
33. Teng YX, Li MJ, Xiang BD, Zhong JH. Tenofovir may be superior to entecavir for preventing hepatocellular carcinoma and mortality in individuals chronically infected with HBV: a meta-analysis. *Gut*. 2019;69:1900-1902.
34. Wong GL, Lampertico P. Residual risk of HCC during long-term oral nucleos(t)ide analogues (NUCs) in patients with CHB – is one NUC better than the other? *J Hepatol*. 2019;71:453-455.
35. *Viread® (tenofovir disoproxil fumarate). Gilead Sciences, Inc*. Foster City, CA, USA; 2019.
36. *Baraclude® (entecavir) Package Insert*. Princeton, NJ, USA: Bristol-Myers Squibb Company; 2019.
37. Udompap P, Kim WR. Development of hepatocellular carcinoma in patients with suppressed viral replication: changes in risk over time. *Clin Liver Dis (Hoboken)*. 2020;15:85-90.
38. Gordon SC, Zhou Y, Li J, et al. Effect of treatment of hepatitis B patients with tenofovir disoproxil or entecavir on risk of hepatocellular cancer death in a U.S Cohort. *J Hepatol*. 2019;70:e147.
39. Gao L, Trinh HN, Li J, Nguyen MH. Tenofovir is superior to entecavir for achieving complete viral suppression in HBeAg-positive chronic hepatitis B patients with high HBV DNA. *Aliment Pharmacol Ther*. 2014;39:629-637.
40. Nguyen LH, Hoang J, Nguyen NH, et al. Ethnic differences in incidence of hepatitis B surface antigen seroclearance in a real-life multicenter clinical cohort of 4737 patients with chronic hepatitis B infection. *Aliment Pharmacol Ther*. 2016;44:390-399.
41. Leeansyah E, Cameron PU, Solomon A, et al. Inhibition of telomerase activity by human immunodeficiency virus (HIV) nucleos(t)ide reverse transcriptase inhibitors: a potential factor contributing to HIV-associated accelerated aging. *J Infect Dis*. 2013;207:1157-1165.
42. Arslan F, Vahaboglu H. Tenofovir for the prevention of HCC in patients with cirrhosis. *Am J Gastroenterol*. 2020;115:302.
43. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009;461:798-801.
44. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature*. 2009;461:399-401.
45. Lin C-L, Kao J-H. Risk stratification for hepatitis B virus related hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2013;28:10-17.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Kim WR, Telep LE, Jump B, et al. Risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis B patients receiving tenofovir disoproxil fumarate versus entecavir in the United States. *Aliment Pharmacol Ther*. 2022;00:1–8. doi: 10.1111/apt.16786