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Lower incidence of hepatocellular carcinoma with tenofovir alafenamide in chronic hepatitis B: Evidence from a large-scale cohort

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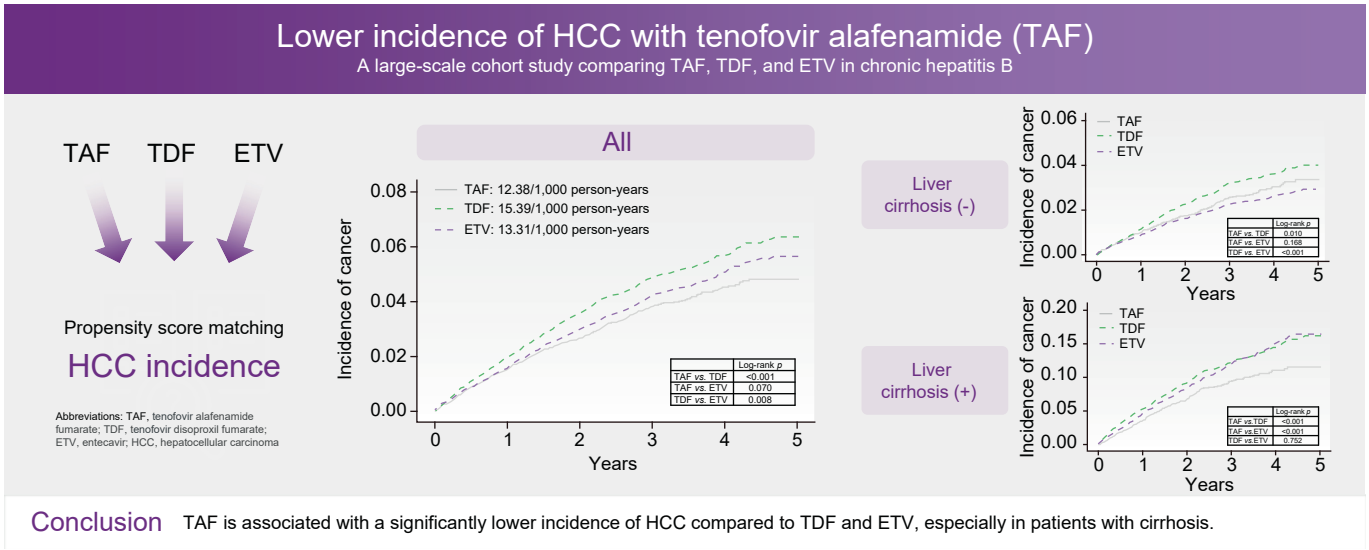
Graphical abstract



Highlights:

- TAF is associated with lower HCC incidence in patients with chronic HBV compared with TDF and ETV.
- There was significant HCC reduction with TAF in patients with and without cirrhosis.
- Propensity score matching analysis confirmed lower HCC rates with TAF *vs.* TDF and ETV.
- Cox regression showed that TAF was linked to reduced HCC risk after adjusting for key factors.

Impact and implications:

This work aimed to fill the knowledge gap regarding the comparative efficacy of tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), and entecavir (ETV) in reducing the incidence of hepatocellular carcinoma (HCC) in patients with chronic HBV. The results are particularly crucial for healthcare providers and policymakers, because they highlight the significantly lower incidence of HCC associated with TAF, especially in patients with cirrhosis. These results suggest TAF as a preferable antiviral therapy option to mitigate HCC risk, thus influencing clinical decision-making and healthcare guidelines. From a practical perspective, these findings can guide physicians in prescribing more effective treatments, assist researchers in designing further studies to explore the mechanisms behind the effectiveness of TAF, and inform policymakers to craft healthcare policies that optimize patient outcomes while considering potential limitations, such as the observational nature of the study and residual confounding factors.

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Research article

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Lower incidence of hepatocellular carcinoma with tenofovir alafenamide in chronic hepatitis B: Evidence from a large-scale cohort

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Background & Aims: Tenofovir alafenamide (TAF) lacks extensive research regarding its impact on hepatocellular carcinoma (HCC). This study evaluated and compared the effects of TAF, tenofovir disoproxil fumarate (TDF), and entecavir (ETV) on HCC incidence using nationwide claim data.

Methods: In total, 75,816 patients with treatment-naïve HBV were included in the study and divided into TAF (n = 25,680), TDF (n = 26,954), and ETV (n = 23,182) groups after exclusions. Propensity score matching (1:1:1) resulted in 17,537 patients per group. HCC incidence rates were compared among the groups.

Results: Before matching, the incidence of HCC was significantly lower in the TAF group compared with the TDF and ETV groups (11.47 *vs.* 15.04 and 14.24 per 1,000 person-years). The incidence rate ratio (IRR) for TDF was 1.31 (1.19–1.44) and for ETV was 1.24 (1.12–1.37). Before matching, the TAF group had a significantly lower HCC compared with TDF and ETV in both patients with and without cirrhosis. After matching, the TAF group had a lower HCC incidence compared with the TDF group (12.38 *vs.* 15.39, IRR 1.24, p <0.001) but not with ETV group (IRR 1.08, p = 0.219). In patients with cirrhosis, TAF had lower HCC incidence compared with TDF and ETV (30.25 *vs.* 39.56 and 38.51, respectively). In patients without cirrhosis, the TAF group had a lower HCC incidence compared with the TDF group (IRR 1.19, p = 0.030) but not the ETV group (IRR 0.85, p = 0.066). Cox regression analysis showed that the TAF group had a significantly lower HCC incidence compared with the TDF (hazard ratio 1.335, p <0.001) and ETV groups (hazard ratio 1.162, p = 0.011), after adjusting for age, gender, and cirrhosis status.

Conclusions: The TAF group consistently demonstrated a lower incidence of HCC compared with the TDF and ETV groups, especially in patients with cirrhosis.

Introduction

Contrary to the common belief that hepatocellular carcinoma (HCC) is a rare cancer, ∼1 million new cases were diagnosed worldwide in 2020 alone,[1] and the number of cases is expected to increase by 55% by 2040. In 2020, HCC was also ranked among the top three causes of cancer death in 46 countries.[2] In addition, HCC is the second leading cause of malignant deaths in Asia, with 80% of HCC cases occurring in this area, aligning with the high prevalence of chronic HBV in these regions.[3] Primary treatment for HBV is antiviral therapy, which has been well documented to effectively prevent HCC.[4] Since the 2004 report that the first-generation antiviral agent lamivudine reduces HCC incidence, current agents, such as entecavir (ETV) and tenofovir, have been shown to reduce HCC incidence by 30–40%.[5]

Research on the efficacy of primary antiviral therapies for HBV in preventing HCC is ongoing, with particular focus on comparing ETV and tenofovir disoproxil fumarate (TDF). Since the first report in 2019[6] indicating that TDF was associated with a lower incidence of HCC compared with ETV, numerous studies have been conducted.[7–14] However, these studies have yielded varying results owing to differences in study populations, duration of follow-up, and other factors.

Tenofovir alafenamide (TAF), an oral precursor of tenofovir, was created to enhance the antiviral effectiveness and safety of its active component, tenofovir diphosphate. In particular, TAF has been reported to have fewer side effects, such as renal impairment and osteoporosis, compared with TDF.[15,16] In Korea, TAF has been available for prescription as a primary treatment for chronic HBV since November 2017, and its

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prescription rate is rising more quickly than that of ETV and TDF. However, there are still limited data on whether TAF can effectively prevent the development of HCC compared with TDF or ETV. In particular, there are insufficient clinical data on TAF for patients with decompensated cirrhosis or HCC. Therefore, this study compared the incidence rate in Korea of HCC in patients with HBV treated with TAF with those treated with TDF or ETV. To obtain a higher level of evidence, we utilized a nationwide cohort from the Health Insurance Review and Assessment Service (HIRA) claim data.

Materials and methods

Data source

South Korea maintains a comprehensive healthcare system through mandatory social health insurance, covering 98% of the population. This HIRA system deals handles health insurance claims submitted by 46 million people (90% of its residents) each year. The discrepancy between the 98% of the population covered by social health insurance and the 90% of residents on the HIRA system occurs because not all insured individuals use healthcare services within a given year. The HIRA claims data are a crucial asset for healthcare service research, created when healthcare providers file claims with HIRA for reimbursement or scholarly review. The Institutional Review Board (IRB) of Soonchunhyang University Bucheon Hospital approved the current study (IRB No. SCHBC 2023-07-016-003; approval date December 11, 2023). Informed consent was waived by the IRB of Soonchunhyang University Bucheon Hospital. Our study adhered to the ethical guidelines of the World Medical Association Declaration of Helsinki.

Study population

This study used nationwide cohort data from the HIRA of South Korea. The study included patients with treatment-naïve HBV who were prescribed antiviral drugs (TAF, TDF, or ETV) for more than 90 days starting from January 2018. The exclusion criteria included subjects under the age of 18 years, patients with prior antiviral treatment experience, those who used antiviral drugs other than TAF, TDF, or ETV, individuals with a history of HCC, and those co-infected with HCV or HIV.

Study time frame

The study period spanned from January 1, 2018, to the end of the follow-up period, December 31, 2022, which was determined based on the last available claim data up to the time of analysis. The specific inclusion of treatment-naïve patients starting from 2018 was designed to ensure a homogeneous cohort, minimizing potential biases from prior treatment histories.

Minimum treatment duration

Patients were required to have been taking antiviral therapy for a minimum of 90 days to be considered part of the cohort. This criterion was established to ensure that only those who had a sustained course of treatment were included, thus providing a more accurate assessment of the impact of the antiviral drugs on HCC incidence.

Cohort selection and propensity score matching

The initial cohort comprised 105,751 patients with HBV (Fig. 1). After applying the exclusion criteria, a total of 75,816 patients were eligible for analysis. These patients were then categorized into three groups based on their treatment (TAF, TDF, or ETV). To control for potential confounders, 1:1:1 propensity score matching (PMS) was performed, adjusting for variables such as age, sex, presence of cirrhosis, and decompensation status. After PMS, each treatment group contained 17,537 patients, ensuring comparability across the groups.

Definition and study outcome

HBV was defined by using ICD-10 codes B180 or B181 and included patients who had at least two outpatient visits or at least one inpatient admission with these codes. HBV-related liver cirrhosis was defined as the concurrent presence of HBV-related codes (B180 or B181) and liver cirrhosis codes (K74, K70.2, K70.3, K76.6, or K76.7) according to the ICD-10 classification.[17–20] HBV-related decompensated cirrhosis was defined as the presence of: (1) HBV-related codes; (2) liver cirrhosis code; and (3) any of the following procedure codes, medication codes, or diagnosis codes: procedure code (abdominal paracentesis, endoscopic sclerotherapy of esophageal or gastric varices, or endoscopic ligation of esophageal or gastric varices), medication code (spironolactone, terlipressin, somatostatin, or propranolol), or diagnosis code (hepatorenal syndrome, bacterial peritonitis, hepatic failure, or esophageal varices with bleeding in diseases classified elsewhere). All exposure variables, including the presence of cirrhosis, decompensated status, and age, were evaluated at the time of antiviral treatment initiation.

The use of antiviral drugs was identified using the Korea Drug Code. TAF was coded as 665301ATB, while TDF was marked by Korea Drug Code 493901ATB [tenofovir disoproxil fumarate 0.3 g, as tenofovir disoproxil 0.245 g), 664901ATB (tenofovir disoproxil 0.245 g), 665001ATB (tenofovir disoproxil phosphate, as tenofovir disoproxil 0.245 g), 665101ATB (tenofovir disoproxil aspartate, as tenofovir disoproxil 0.245 g), 665201ATB (tenofovir disoproxil orotate, as tenofovir disoproxil 0.245 g), and 665501ATB (tenofovir disoproxil hemiedisylate, as tenofovir disoproxil 0.245 g)]. ETV was coded as 487202ATB [ETV 0.5 mg), 487202ATD (ETV 0.5-mg orally disintegrating tablet), 487203ATB (ETV 1 mg), and 487203ATD (ETV 1-mg orally disintegrating tablet)]. Comorbidity was evaluated using the Charlson Comorbidity Index, a recognized standard in clinical research for assessing comorbidity. The ICD-10 codes used to define the Charlson Comorbidity Index are provided in the supplementary material online. The primary outcome of this study was the incidence of HCC after antiviral treatment. HCC was defined as ICD-10 code C220.

Statistical analysis

To adjust for baseline characteristics as much as possible among the TAF, TDF, and ETV groups, this study used PMS. This was conducted in a 1:1:1 ratio, matching the variables known to affect the development of HCC, including age, sex, presence of liver cirrhosis, and the decompensation status. For

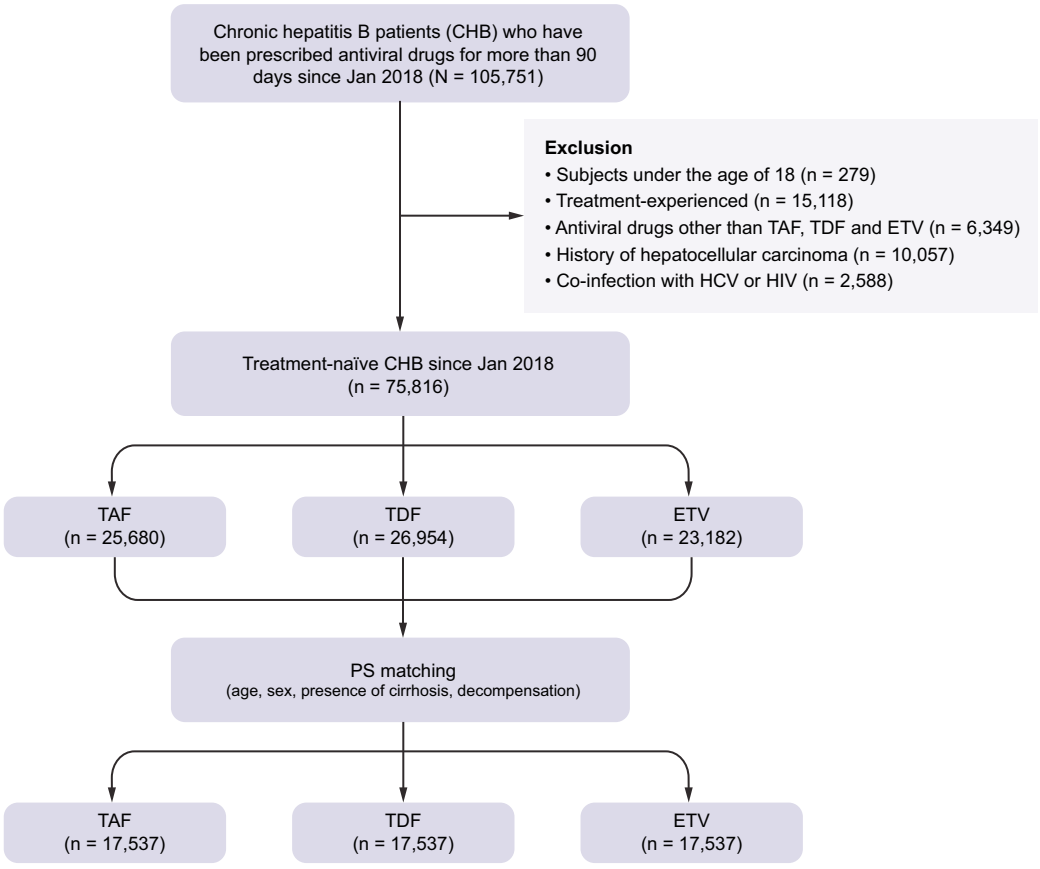


Fig. 1. Flow chart of participants enrolled in the study. ETV, entecavir; HCC, hepatocellular carcinoma; PS, propensity score; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

the sensitivity analysis, we created and analyzed an additional cohort that included follow-up time (person-year; PY) in addition to the existing matching variables, such as age, sex, cirrhosis, and decompensation state. Incidence among the groups was compared using Kaplan-Meier analysis and log-rank *p* value, with incidence rates and incidence rate ratios (IRRs) also calculated. Time at risk was defined as the period from the initiation of antiviral treatment until the occurrence of the primary outcome (HCC), death, or the end of the study period, whichever came first. Cox regression analysis was used to identify factors that influence the incidence of HCC. We tested the proportional hazards assumption for the Cox regression models using Schoenfeld residuals. The assumption was met for all variables included in the analysis. Additionally, we assessed multicollinearity among the variables, including decompensated status, cirrhosis, and the Charlson Comorbidity Index score, using the variance inflation factor. All variance inflation factor values were below the commonly accepted threshold, indicating that multicollinearity was not a concern in our models. Descriptive statistics were provided using frequencies and percentages. Group differences were evaluated using the $\chi 2$ test for categorical variables and the Student's *t* test for continuous variables. All statistical analyses were conducted using the SAS program version 9.4 (SAS Institute Inc., Cary, NC, USA), with a statistical significance threshold set at $p < 0.05$.

Results

Baseline characteristics

Table 1 details the characteristics of the patients included in the study. Before PMS, the mean age was 50.2 years, with men comprising 57.6% of the sample. The TAF group was younger on average (48.0 years) compared with the TDF and ETV groups (48.7 and 54.4 years, respectively). There were no significant differences in gender distribution among the groups. The average duration of medication use was 788.1 ± 517.3 days. At the start of antiviral therapy, 21.2% of the patients had cirrhosis, with 8.4% being decompensated. The TAF group had a higher proportion of patients with cirrhosis compared with the TDF and ETV groups (24.1% *vs.* 19.3%, 20.5%), but a lower proportion of decompensated cirrhosis (5.5% *vs.* 9.1% and 10.8%, respectively). After PMS, there were no statistically significant differences among the three groups in terms of age, gender, medication duration, cirrhosis rate, or decompensated cirrhosis rate.

The total PY of follow-up for the study population was 61,119 PY for the TAF group, 74,143 PY for the TDF group, and 62,136 PY for the ETV group before PMS. After PMS, the PY was 41,210 for the TAF group, 48,206 for the TDF group, and 48,530 for the ETV group. This was calculated based on the time at risk for each participant, from the start of antiviral therapy to the end of follow-up.

Table 1. Baseline characteristics of study groups.

Patient characteristics	Total (n = 75,816)	TAF (n = 25,680)	TDF (n = 26,954)	ETV (n = 23,182)	*p* value*
Before propensity score matching					
Age (years)	50.2 ± 12.5	48.0 ± 11.6	48.7 ± 12.2	54.4 ± 12.8	<0.001
Male, (%)	43,663 (57.6)	14,623 (56.9)	11,721 (57.8)	13,449 (58)	0.033
Duration of antiviral medication (days)	788.1 ± 517.3	826.6 ± 502.8	809.3 ± 518.3	720.9 ± 525.3	<0.001
Proportion of liver cirrhosis, n (%)	16,108 (21.2)	6,188 (24.1)	5,193 (19.3)	4,727 (20.4)	<0.001
Decompensation at start of antiviral therapy, n (%)	6,837 (8.4)	1,413 (5.5)	2,463 (9.1)	2,511 (10.8)	<0.001
Charlson Comorbidity Index score	2.8 ± 1.6	2.4 ± 0.9	2.7 ± 1.4	3.4 ± 2.2	<0.001
	Total (n = 52,611)	**TAF (n = 17,537)**	**TDF (n = 17,537)**	**ETV (n = 17,537)**	***p* value***
After propensity score matching					
Age (years)	50.6 ± 11.1	50.6 ± 11.1	50.6 ± 11.1	50.6 ± 11.1	1.0
Male, (%)	29,706 (56.5)	9,902 (56.5)	9,902 (56.5)	9,902 (56.5)	>0.999
Duration of antiviral medication (days)	800.8 ± 518.6	819.1 ± 501.2	816.6 ± 518.4	766.9 ± 533.9	<0.001
Proportion of liver cirrhosis, n (%)	10,482 (19.9)	3,494 (19.9)	3,494 (19.9)	3,494 (19.9)	>0.999
Decompensation at start of antiviral therapy, n (%)	3,459 (6.6)	1,153 (6.6)	1,153 (6.6)	1,153 (6.6)	>0.999
Charlson Comorbidity Index score	2.7 ± 1.5	2.4 ± 1.0	2.6 ± 1.4	3.2 ± 2.0	<0.001

*Group differences were evaluated using the χ^2 test for categorical variables and the Student's *t* test for continuous variables. ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Comparison of HCC incidence by antiviral agents: before propensity score matching

The incidence rates and comparisons of HCC for each antiviral therapy group are presented in Table 2 and Fig. 2. Before PMS, the incidence of HCC was significantly higher in the TDF and ETV groups compared to the TAF group (p <0.001; Fig. 2A). The incidence rate for the TAF group was 11.47 (10.65–12.35) per 1,000 PY, which was significantly lower than the incidence rate of the TDF group at 15.04 and the ETV group at 14.24. When calculating the IRR, and considering the IRR of the TAF group as 1, the IRR for the TDF group was 1.31 (1.19–1.44) and for the ETV group was 1.24 (1.12–1.37).

A stratified analysis based on the presence of cirrhosis revealed that the difference in HCC incidence rates between the TAF group and other antiviral therapy groups was statistically more significant in patients with cirrhosis (Fig. 2B). The incidence rate for the TAF group was 25.79, which was significantly lower than the 42.91 for the TDF group and 40.51 for the ETV group. The IRRs for TDF and ETV were 1.66 (1.46–1.89) and 1.57 (1.38–1.79), respectively. In the group without cirrhosis, the results were slightly different (Fig. 2C). The TAF group still had a significantly lower incidence of HCC compared with the TDF group [IRR 1.24 (1.08–1.42), p = 0.003], but the difference in incidence between the ETV and TAF groups was not statistically significant [IRR 1.06 (0.91–1.23), p = 0.480].

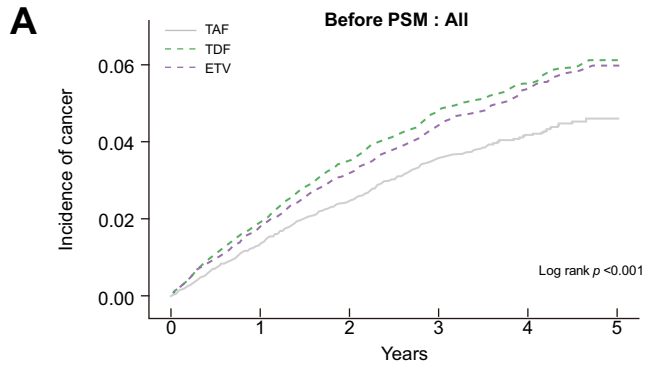
Comparison of HCC incidence by antiviral agents: after propensity score matching

After PMS, the incidence rate for the TAF group was 12.38 (11.35–13.50), which was significantly lower than that for the

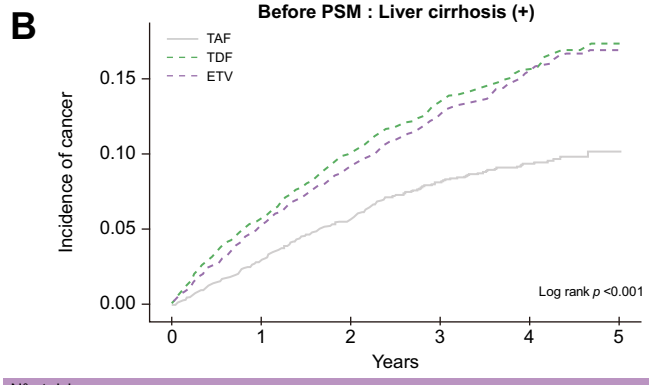
Table 2. Incidence of hepatocellular carcinoma by antiviral agents.

	Group	Total	Person-year	HCC (–)	HCC (+)	Incidence rate (95% CI)	Incidence rate ratio (95% CI)	*p* value*
All users								
Before PMS	TAF	24,979	61,119	24,979 (97.27)	701 (2.73)	11.47 (10.65–12.35)	1 (ref)	—
	TDF	25,837	74,143	25,837 (95.86)	1,115 (4.14)	15.04 (14.18–15.95)	1.31 (1.19–1.44)	<0.001
	ETV	22,294	62,136	22,294 (96.18)	885 (3.82)	14.24 (13.33–15.21)	1.24 (1.12–1.37)	<0.001
After PMS	TAF	17,537	41,210	17,027 (97.09)	510 (2.91)	12.38 (11.35–13.50)	1 (ref)	—
	TDF	17,536	48,206	16,791 (95.77)	742 (4.23)	15.39 (14.32–16.54)	1.24 (1.11–1.39)	<0.001
	ETV	17,535	48,530	16,889 (96.32)	646 (3.68)	13.31 (12.32–14.38)	1.08 (0.96–1.21)	0.219
Cirrhosis (+)								
Before PMS	TAF	6,188	14,615	5,811 (93.91)	377 (6.09)	25.79 (23.32–28.53)	1 (ref)	—
	TDF	5,192	13,890	4,596 (88.52)	596 (11.48)	42.91 (39.60–46.49)	1.66 (1.46–1.89)	<0.001
	ETV	4,726	12,910	4,203 (88.93)	885 (11.07)	40.51 (37.18–44.13)	1.57 (1.38–1.79)	<0.001
After PMS	TAF	3,249	80,98	3,249 (92.99)	245 (7.01)	30.25 (26.69–34.29)	1 (ref)	—
	TDF	3,120	9,454	3,120 (89.3)	374 (10.70)	39.56 (35.75–43.78)	1.31 (1.11–1.54)	0.001
	ETV	3,119	9,738	3,119 (89.27)	375 (10.73)	38.51 (34.80–42.61)	1.27 (1.08–1.50)	0.003
Cirrhosis (-)								
Before PMS	TAF	19,492	46,503	19,168 (98.34)	324 (6.09)	6.97 (6.25–7.77)	1 (ref)	—
	TDF	21,760	60,252	21,241 (97.61)	519 (11.48)	8.61 (7.90–9.39)	1.24 (1.08-1.42)	0.003
	ETV	18,453	49,225	18,091 (98.04)	362 (1.96)	7.35 (6.63–8.15)	1.06 (0.91-1.23)	0.480
After PMS	TAF	14,102	33,267	13,829 (98.06)	273 (1.94)	8.21 (7.29–9.24)	1 (ref)	—
	TDF	14,101	38,769	13,723 (97.32)	378 (2.68)	9.75 (8.81–10.78)	1.19 (1.02–1.39)	0.030
	ETV	14,100	38,942	13,827 (98.06)	273 (1.94)	7.01 (6.23–7.89)	0.85 (0.72–1.01)	0.066

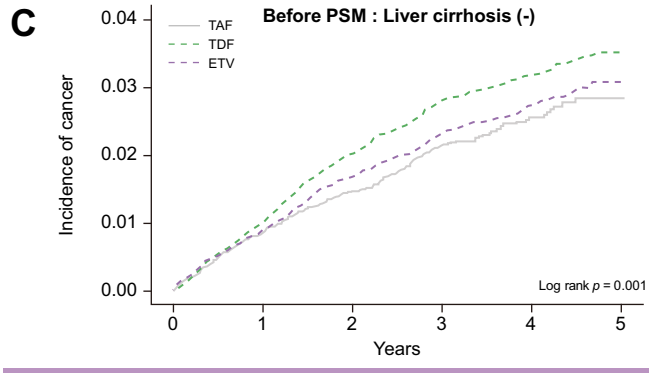
*p values were evaluated using Poisson regression analysis. ETV, entecavir; HCC, hepatocellular carcinoma; PMS, propensity score matching; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.



N° at risk						
TAF	25,680	20,386	14,488	9,513	4,201	54
TDF	26,954	23,177	18,089	12,518	6,576	214
ETV	23,182	19,566	14,929	10,448	5,498	138

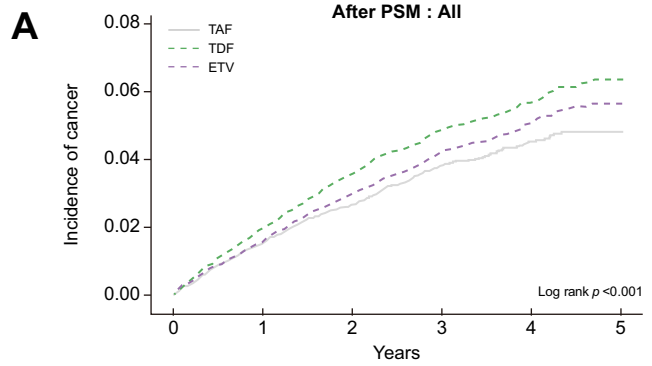


N° at risk						
TAF	6,188	4,838	3,453	2,284	1,060	14
TDF	5,193	4,340	3,347	2,327	1,224	39
ETV	4,727	3,978	3,104	2,224	1,200	32

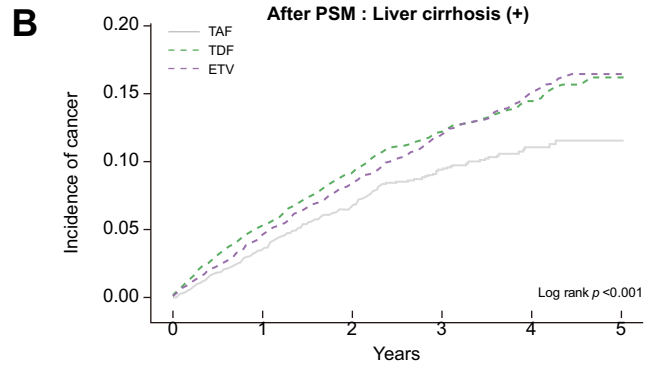


N° at risk						
TAF	19,492	15,548	11,035	7,229	3,141	40
TDF	21,761	18,837	14,742	10,191	5,352	175
ETV	18,455	15,588	11,825	8,224	4,298	106

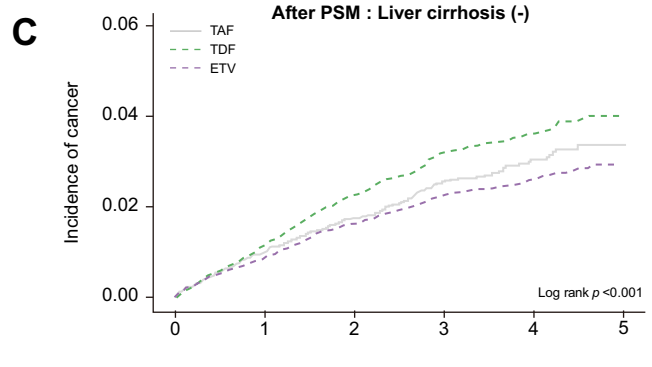
Fig. 2. Cumulative incidence of HCC (before PMS) (Kaplan-Meier analysis). (A) All patients taking ETV, TDF, or TAF. (B) Patients with liver cirrhosis. (C) Patients without liver cirrhosis. ETV, entecavir; HCC, hepatocellular carcinoma; PMS, propensity score matching; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.



N° at risk						
TAF	17,537	13,807	9,756	6,339	2,761	38
TDF	17,537	15,064	11,779	8,138	4,281	138
ETV	17,537	15,043	11,697	8,378	4,534	112



N° at risk						
TAF	3,494	2,715	1,903	1,246	572	7
TDF	3,494	2,931	2,285	1,612	851	27
ETV	3,494	2,979	2,352	1,700	929	21



N° at risk						
TAF	14,102	11,159	7,871	5,125	2,212	23
TDF	14,102	12,174	9,501	6,506	3,409	111
ETV	14,102	12,110	9,379	6,706	3,614	91

Fig. 3. Cumulative incidence of HCC (after PMS) (Kaplan-Meier analysis). (A) All patients taking ETV, TDF, or TAF. (B) Patients with liver cirrhosis. (C) Patients without liver cirrhosis. ETV, entecavir; HCC, hepatocellular carcinoma; PMS, propensity score matching; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

TDF group at 15.39 [4.32–16.54; IRR 1.24 (1.11–1.39), p <0.001; Fig. 3A]. However, there was no statistically significant difference between the TAF and ETV groups [12.38 *vs.* 13.31, IRR 1.08 (0.96–1.21), p = 0.219].

In the group with cirrhosis, the TAF group had a significantly lower incidence of HCC compared with the TDF and ETV groups after PMS (30.25 *vs.* 39.56 *vs.* 38.51, respectively; Fig. 3B). In the group without cirrhosis, the TAF group had a

Table 3. Cox regression analysis for incidence of hepatocellular carcinoma.

	Univariable		Multivariable	
Characteristics	**Hazard ratio (95% CI)**	***p* value***	**Hazard ratio (95% CI)**	***p* value***
Antiviral agents				
TAF	1 (ref)	—	1 (ref)	—
TDF	1.285 (1.148-1.439)	<0.001	1.335 (1.193-1.495)	<0.001
ETV	1.115 (0.993-1.252)	0.066	1.162 (1.034-1.306)	0.011
Age (years)	1.042 (1.037-1.046)	<0.001	1.041 (1.037-1.046)	<0.001
Male	2.239 (2.019-2.482)	<0.001	2.496 (2.247-2.773)	<0.001
Duration of antiviral medication (days)	1.000 (1.000-1.001)	<0.001	1.000 (1.000-1.001)	<0.001
Presence of liver cirrhosis	4.373 (3.997-4.785)	<0.001	3.102 (2.819-3.413)	<0.001
Decompensated cirrhosis	2.865 (2.534-3.239)	<0.001	1.627 (1.430-1.850)	<0.001
Charlson Comorbidity Index score	0.975 (0.944-1.006)	0.110	—	—

*p values were evaluated using Cox regression analysis. ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

significantly lower incidence of HCC compared with the TDF group [IRR 1.19 (1.02–1.39), p = 0.030], but there was no statistically significant difference in incidence between the TAF and ETV groups [IRR 0.85 (0.72–1.01), p = 0.066; Fig. 3C].

Sensitivity analysis including follow-up time

To address potential differences in follow-up time among the treatment groups, we conducted a sensitivity analysis by creating a new cohort. This cohort included follow-up time (PY) in addition to the original PMS variables, such as age, sex, cirrhosis, and decompensation state (Table S1 and Fig. S1). In the overall patient population, the HCC incidence rate was 9.5 per 1,000 PY for the TAF group, compared with 15.82 and 14.06 per 1,000 PY for the TDF (IRR = 1.66, p <0.001) and ETV (IRR 1.48, p <0.001) groups, respectively. In patients with liver cirrhosis, the TAF group had an incidence rate of 22.59 per 1,000 PY, while the TDF and ETV groups had higher rates of 40.2 (IRR 1.78, p <0.001) and 42.02 (IRR 1.86, p <0.001) per 1,000 PY, respectively. Among those without liver cirrhosis, the incidence rates were 6.11 for TAF, 10.77 for TDF (IRR 1.76, p <0.001), and 7.49 for ETV per 1,000 PY. The sensitivity analysis revealed that, even after accounting for follow-up time, the incidence of HCC remained lower in patients treated with TAF compared with those treated with TDF or ETV.

Cox regression analysis for the incidence of HCC

We then performed a Cox regression analysis to identify the factors related to the incidence of HCC in the PMS group (Table 3). In the multivariable analysis, even after adjusting for age, gender, presence of cirrhosis at the start of antiviral therapy, and decompensation status at the start of antiviral therapy, the TDF and ETV groups had a significantly higher incidence of HCC compared with the TAF group (TDF: adjusted hazard ratio 1.335, 95% CI 1.193–1.495, p <0.001; ETV: adjusted hazard ratio 1.162, 95% CI 1.034–1.306, p = 0.011).

When performing Cox regression analysis stratified by the presence of cirrhosis, in the group with cirrhosis, the TAF group had a significantly lower incidence of HCC compared with the TDF and ETV groups, even after adjusting for age, gender, and decompensation status at the start of antiviral therapy (TDF: adjusted hazard ratio 1.383, 95% CI 1.177–1.625, p <0.001; ETV: adjusted hazard ratio 1.329, 95% CI 1.131–1.562, p <0.001; Table S2). However, in the group without cirrhosis, the TAF group had a significantly lower incidence of HCC compared with the TDF group (adjusted hazard ratio 1.256, 95% CI 1.074–1.468, p = 0.004), but there was no significant difference compared with the ETV group in the multivariable analysis (adjusted hazard ratio 0.990, 95% CI 0.836–1.173, p = 0.911; Table S3).

Discussion

TAF, a newer drug compared with TDF or ETV, has been in use in Korea for around 4 years, but research into its association with HCC remains limited. Our study is the first extensive cohort analysis utilizing HIRA data, providing evidence that patients treated with TAF have a lower incidence rate of HCC compared with those treated with other antiviral drugs. Stratified analysis showed that the difference was more pronounced in patients with cirrhosis.

Relatively few studies have reported on how the incidence of HCC differs with TAF compared with other antiviral therapies. Lee *et al.*[21] found no significant difference in the occurrence of HCC between patients with chronic HBV treated with ETV and those treated with TAF (incidence rate: ETV *vs.* TAF: 1.67 *vs.* 1.19 per 100 PY, respectively; hazard ratio 0.681, p = 0.255). Similarly, Chon *et al.*[22] compared the risk and mortality of HCC in patients with treatment-naïve HBV treated with ETV, TDF, and TAF, and found no significant differences among the three groups (all p >0.05). Furthermore, Lim *et al.*[23] found that both TAF and TDF decreased the risk of HCC in patients with chronic HBV, particularly those without cirrhosis. However, all three studies had the limitation of relatively small TAF patient groups and shorter follow-up periods. These limitations often result in lower statistical power and potential biases that can affect the reliability of the conclusions drawn. Small sample sizes increase the margin of error and the likelihood of Type II errors, where a true effect might be overlooked. In addition, shorter follow-up periods might not adequately capture the long-term effects of antiviral therapy on HCC development, because the progression from chronic HBV to HCC can span many years or even decades. However, unlike previous studies, we provide more robust evidence with a larger sample size and longer follow-up duration.

We propose several hypotheses to explain why TAF is associated with a lower incidence of HCC compared with TDF and ETV. First, TAF might achieve more effective viral suppression because of higher intracellular concentrations of its active metabolite, tenofovir diphosphate.[24,25] This higher concentration could lead to a more sustained and potent suppression of HBV, thereby reducing the risk of liver inflammation and subsequent carcinogenesis. The potent antiviral activity of

TAF might be particularly crucial in patients with higher viral loads or more advanced liver disease, in whom effective suppression is essential to prevent progression to HCC. Second, while renal and bone toxicities associated with TDF and ETV are often asymptomatic, the improved safety profile of TAF might still contribute to better long-term adherence because of fewer clinical concerns and reduced need for monitoring.[26] Healthcare providers might prefer TAF for patients with higher risks of renal or bone complications, which could influence patient adherence through a more favorable perception of the safety of the treatment and reduced anxiety about potential long-term side effects. TDF has been associated with renal toxicity and bone mineral density loss, leading to treatment discontinuation or switching, which can compromise viral suppression. By contrast, the reduced toxicity of TAF might encourage its continuous and long-term use, ensuring sustained viral suppression and lower HCC risk. Additionally, better renal and bone health could contribute to improved overall liver function and a reduced incidence of liver-related complications, including HCC.[27,28] Third, the formulation of TAF is more convenient for patients compared with that of TDF or ETV, which we believe contributed to the higher drug compliance. We calculated the proportion of patients who continued to take the medication 1 year and 2 years after the initial prescription for the three drugs (Fig. S2). The results showed that TAF had a higher rate of adherence for over 2 years compared with either ETV or TDF. This could be due to the smaller pill size of TAF and the fact that it does not need to be taken on an empty stomach, like ETV, leading to improved compliance and potentially influencing the lower incidence of HCC.

This study has several limitations. First, despite using PMS to balance baseline characteristics, residual confounding factors might still exist. For example, factors, such as lifestyle differences, genetic predispositions, and environmental influences, were not fully accounted for and could impact HCC risk. Second, the observational nature of the study might limit the ability to establish causality. Despite concerns that the shorter follow-up period for TAF and the inclusion of patients with less severe HBV might have influenced the results, our study still found significant outcomes. However, randomized controlled trials are necessary to further validate these results and address the potential limitations identified. Third, detailed clinical data are missing from the HIRA dataset. The data lack detailed clinical stages at the initiation of the drug treatment, such as liver function tests, HBV DNA levels in the blood before the study start, HBsAg clearance, HBeAg positivity, stage of HCC at presentation, and mortality, which are crucial for a thorough analysis of treatment efficacy and patient outcomes. Furthermore, the HIRA database does not provide detailed information on the diagnostic methods used for cirrhosis. Consequently, we cannot distinguish between biopsy-based and non-invasive diagnoses, which might have led to an overestimation of cirrhosis cases. This potential confounding factor should be considered when interpreting our results. Similarly, this study could not account for metabolic dysfunction-associated steatotic liver disease (MASLD) or alcohol-related liver disease because of the absence of health examination data, including information on alcohol consumption, in the HIRA database. Instead, we performed stratified analysis according to diabetes as a surrogate for MASLD (Table S4 and Fig. S3). A lower incidence of HCC with TAF was observed in the group without diabetes, whereas no significant difference in HCC incidence was found among the three drugs in the group with diabetes. This result suggests that additional factors, such as MASLD, need to be considered, and further investigation is warranted.

In conclusion, our study demonstrates that TAF is associated with a significantly lower incidence of HCC compared with TDF and ETV, particularly in patients with cirrhosis. This suggests TAF as a preferable option for antiviral therapy in patients with chronic HBV to reduce the risk of developing HCC.

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Abbreviations

ETV, entecavir; HCC, hepatocellular carcinoma; HIRA, Health Insurance Review and Assessment Service; IRB, Institutional Review Board; IRR, incidence rate ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; PSM, propensity score matching; PY, person-years; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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Conflicts of interest

Y.S.K. previously served as an advisor for Gilead and BMS, but currently has no affiliation with either company.

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

Authors' contributions

Conceptualization: J-JY, HWL. Formal analysis: J-YK. Investigation: HWL, SGK, YSK. Writing-original draft: H-JY. Writing-review and editing: J-JY, HWL.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101268.

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