GILEAD | Medical Information

Vemlidy® (tenofovir alafenamide) Incidence and Risk of Hepatocellular Carcinoma

This document is in response to your request for information regarding the impact of Vemlidy® (tenofovir alafenamide [TAF]) on the incidence and risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB).

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Summary

Clinical Data: Incidence and Risk of HCC With TAF

Through Week 384, in TAF pivotal studies (Studies 108 and 110; global and Chinese cohorts), rates of HCC were 1.3% (14/1093) in the TAF group and 2.2% (12/539) in the TDF→TAF group (*P*=0.1515), and there was a significant reduction in HCC incidence vs predicted rates by reREACH-B in the combined TAF and TDF→TAF groups (SIR, 0.14; *P*<0.001).[1]

In the 4-year interim analysis of the phase 4 ATTENTION study in non-cirrhotic participants without notable ALT elevations, the TAF group had a significant decrease in the cumulative incidence of the primary composite endpoint of deaths and serious liver-related events (including HCC) compared with the observation (no treatment) group (HR, 0.21; 95% CI: 0.05–0.97; *P*=0.027). The number of HCC cases was lower in the TAF group (n=2) compared with the observation group (n=7).[2,3]

Real-World Data: Incidence and Risk of HCC With TAF

In a review of data from the Korean National Insurance Service Claims database that compared TAF and TDF (n=19,013 each), TAF was associated with an overall significantly lower incidence of HCC (*P*<0.0001).[4]

In a review of data from the Korean Health Insurance Review and Assessment Services, TAF (n=11,537) in comparison with TDF (n=11,537) was associated with an overall lower incidence of HCC (*P*=0.003) and a lower risk of HCC in patients without cirrhosis (*P*=0.012); no significant difference in HCC risk between groups was seen in patients with cirrhosis (*P*=0.063).[5]

The rates of HCC were evaluated in TN patients with CHB who were treated with TAF, TDF, or ETV. Over a median of 18.9 months, 39 patients (1.9%) developed HCC (TAF, n=2 [5.1%]; TDF, n=12 [30.8%]; ETV, n=25 [64.1%]), and there was no significant difference in the risk of HCC development with any of the antivirals (*P*=0.214; univariate analysis).[6]

A cohort study evaluated the risk of HCC in TN patients with CHB who received TAF or TDF. The risk of HCC was 66% lower with TAF treatment than TDF treatment (HR, 0.34; *P*<0.01).[7]

A retrospective cohort study that assessed the cumulative incidence of HCC over 24 months among patients with low- or high-risk mPAGE-B scores (<9 or ≥9, respectively) found no statistically significant difference in the incidence of HCC in the high-risk group compared with the low-risk group (2.3% vs 0%, respectively; *P*=0.173).[8]

Clinical Data: Incidence and Risk of HCC With TAF

Studies 108 and 110: Analysis of HCC Incidence

Overall study designs

Studies 108 and 110 were randomized, double-blind, phase 3 clinical trials that compared the safety, efficacy, and tolerability of TAF (pooled n=1093) with TDF (pooled n=539) in predominantly nucleos(t)ide-naive participants with CHB and included global and Chinese cohorts. Monoinfected adults with CHB with compensated liver function were randomly assigned to receive TAF 25 mg or TDF 300 mg once daily for 144 weeks in Studies 108 (HBeAg-) and 110 (HBeAg+). Upon completion of the blinded phase, eligible participants from both arms enrolled into an open-label phase and received TAF through Week 384.[1,9-11]

Global cohort

Analysis of HCC incidence and risk[9]

An analysis of the incidence of HCC and risk of HCC development through Week 384 was performed. Using the Kaplan-Meier method, the cumulative incidence of HCC by treatment group was compared using a log-rank test. Multivariate analyses were performed to determine baseline and on-treatment factors that were associated with the development of HCC. In addition, three validated models (REACH-B, aMAP, and mPAGE-B) were used to evaluate the projected risk of HCC development.

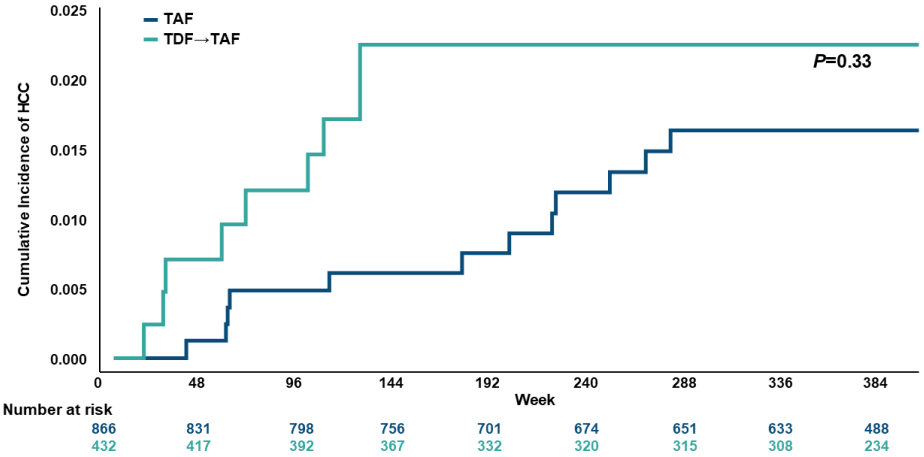
Through Week 384, 21 cases of HCC were reported. Participants who developed HCC, relative to those who did not develop HCC (n=1277), were significantly older (median, 54 vs 39 years, respectively; *P*<0.0001), were more likely to be male (86% vs 63%; *P*=0.03), had higher rates of cirrhosis at baseline (defined as FibroTest score category ≥0.75–1 [Metavir F4]; 38% vs 9%; *P*<0.0001), and had higher FibroTest scores at baseline (mean, 0.63 vs 0.37; *P*<0.0001). The overall incidence was numerically lower, and the time to onset of HCC was significantly later in the TAF group than in the TDF→TAF group (Table 1). According to the Kaplan-Meier method, the cumulative incidence of HCC was significantly lower in the TAF group than in the TDF group (*P*=0.33; Figure 1).

Table 1. Studies 108 and 110 Post Hoc Analysis: HCC Cases Through Week 384 by Treatment and Study Period[9]

	TAF (n=866)	TDF→TAF (n=432)	Overall (N=1298)
HCC cases, n (%)	12 (1.4)[a]	9 (2.1)[a]	21 (1.6)
Double-blind phase, n (%)	5 (0.6)	6 (1.4)	11 (0.7)
Open-label TAF phase, n (%)	7 (0.8)	3 (0.7)	10 (0.8)
Time to onset of HCC, median (IQR), days	1291 (397–1629)[b]	460 (180–729)[b]	729 (388–1373)

[a]*P*=0.357 for TAF vs TDF→TAF by two-sided Fisher's exact test.
[b]*P*=0.03 for TAF vs TDF→TAF by two-sided Wilcoxon rank sum test.

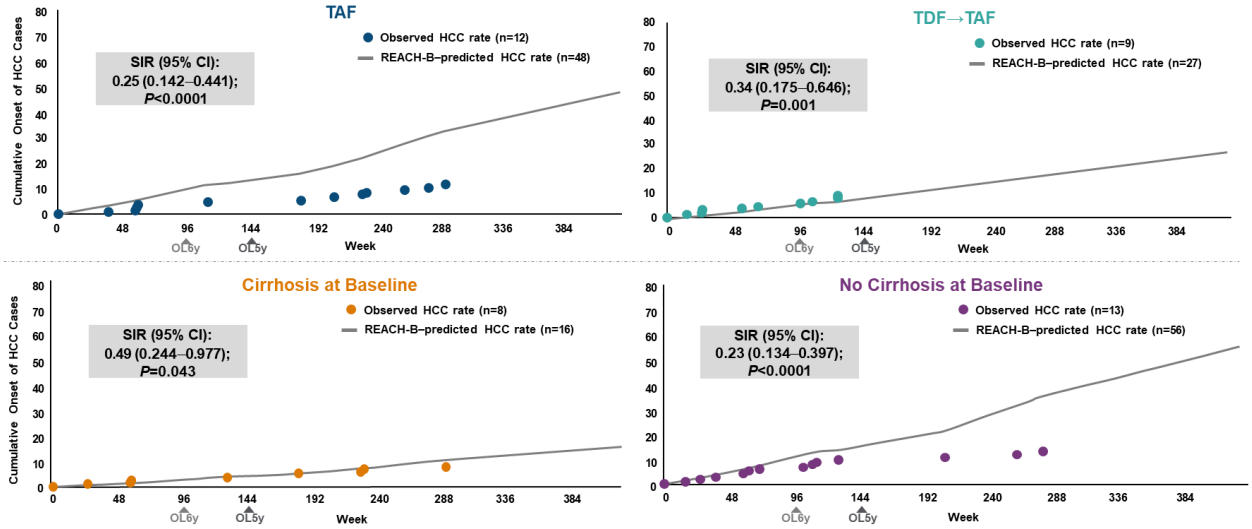
Figure 1. Studies 108 and 110 Post Hoc Analysis: Cumulative Incidence of HCC Through Week 384[9]



Multivariate analysis indicated that male sex (HR, 8.3; 95% CI: 1.88–36.73; *P*=0.005), lack of ALT normalization at Week 24 (HR, 5.22; 95% CI: 1.51–18.1; *P*=0.009), advanced age (HR, 1.11; 95% CI: 1.06–1.17; *P*<0.001), and low platelet count at baseline (HR, 0.99; 95% CI: 0.98–0.99; *P*=0.002) were predictors of HCC development.

The observed HCC cases were compared to the predicted HCC incidence as calculated by the REACH-B risk model, a validated model that used laboratory values and patient characteristics to predict the risk of HCC in CHB.[12] Through Week 384, a 72% reduction in HCC incidence vs predicted rates was observed in the pooled population (observed cases, n=21; model-predicted cases, n=75; SIR, 0.28; 95% CI: 0.183–0.431; *P*<0.0001). Both treatments were associated with a reduction in HCC incidence compared to the predicted rate, and the overall observed HCC incidence was significantly lower than the predicted incidence in participants with and those without cirrhosis at baseline (Figure 2).

Figure 2. Studies 108 and 110 Post Hoc Analysis: Observed vs Predicted Cases of HCC by Treatment and by Presence of Cirrhosis Through Week 384[9]



Abbreviations: OL5y=participants who entered the open-label phase at Week 144 (OL5y) and either continued TAF treatment or were switched from TDF to TAF at that time; OL6y=participants who entered the open-label phase at Week 96 (OL6y) and either continued TAF treatment or were switched from TDF to TAF at that time.
Note: SIR is the ratio of observed cases to predicted cases as determined by the REACH-B risk model.

The aMAP and mPAGE-B prediction tools used scores to categorize participants as being at low, medium, or high risk of HCC at baseline and over the course of the study. Within this framework, of the participants who were classified as being at low risk of developing HCC at baseline, 98% and 97% remained at that risk level at Week 384 using the aMAP and mPAGE-B models, respectively. Moderate proportions of participants who were at medium risk at baseline improved to being low risk at Week 384 (aMAP, 45%; mPAGE-B, 27%), and 1% (each model) shifted to being high risk at Week 384. Of those who were at high risk at baseline, many improved to being medium risk at Week 384 (aMAP, 68%; mPAGE-B, 49%), and smaller proportions shifted to being low risk (aMAP, 4%; mPAGE-B, 1%).

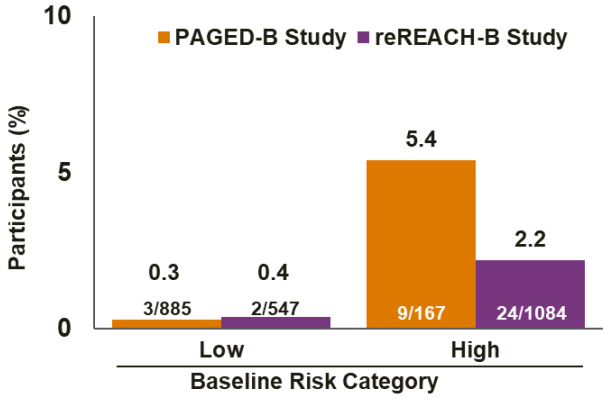
Pooled global and Chinese cohorts

Analysis of HCC incidence and risk

An analysis of the incidence of HCC and risk of HCC development through Week 384 was performed. Two validated models (PAGED-B [Study 108] and reREACH-B [Studies 108 and 110]) were used to evaluate the projected risk of HCC development.[1,13]

Through Week 384, 26 cases of HCC (1.6%; TAF, n=14 [1.3%]; TDF→TAF, n=12 [2.2%]) were reported (Figure 3). Participants who developed HCC, relative to those who did not develop HCC (n=1606), were significantly older (median, 52 vs 40 years, respectively; *P*<0.0001), were more likely to be male (88% vs 65%; *P*=0.0119), had lower albumin levels (mean, 40.1 vs 43.0; *P*=0.0003), had higher rates of cirrhosis at baseline (defined as FibroTest score category ≥0.75–1 [Metavir F4]; 35% vs 9%; *P*<0.0001), and had higher FibroTest scores at baseline (mean, 0.61 vs 0.38; *P*<0.0001).[1]

Figure 3. Studies 108 and 110 Post Hoc Analysis: Incidence of HCC Through Week 384[1,13]



The PAGED-B and reREACH-B prediction tools used scores to categorize participants as being at low or high risk of HCC at baseline and over the course of the study. Within this framework, 1% and 8% of participants who were low risk at baseline shifted to high risk at Week 384 using the PAGED-B and reREACH-B tools, respectively (Figure 4).[1,13]

Using the PAGED-B tool, <1% of participants in the low-risk group and 5% in the high-risk group developed HCC by Week 384. When stratified by treatment group, 99% of participants who were low risk in both the TAF (n=595) and TDF→TAF (n=290) groups remained at that risk level at Week 384, and 69% and 68% of participants who were in the high-risk group in the TAF (n=108) and TDF→TAF (n=59) groups, respectively, shifted to low risk. The greatest reduction in PAGED-B score occurred from baseline to Week 48, and participants who were in the high-risk group at Week 48 were significantly more likely to develop HCC than those in low-risk group (12% vs 0.5%; *P*<0.0001).[13]

Using the reREACH-B tool, there was an 86% reduction in HCC incidence vs predicted rates at Week 384 in the pooled population (observed cases, n=26; model-predicted cases, n=180; SIR, 0.14; 95% CI: 0.1–0.21; *P*<0.001). The overall observed HCC incidence was significantly lower than the predicted incidence in participants with and those without cirrhosis at baseline (SIR, 0.19; 95% CI: 0.1–0.37 and 0.14; 95% CI: 0.09–0.23, respectively; *P*<0.001 for both).[1]

Figure 4. Studies 108 and 110 Post Hoc Analysis: Risk Category Shifts at Week 384[1,13]

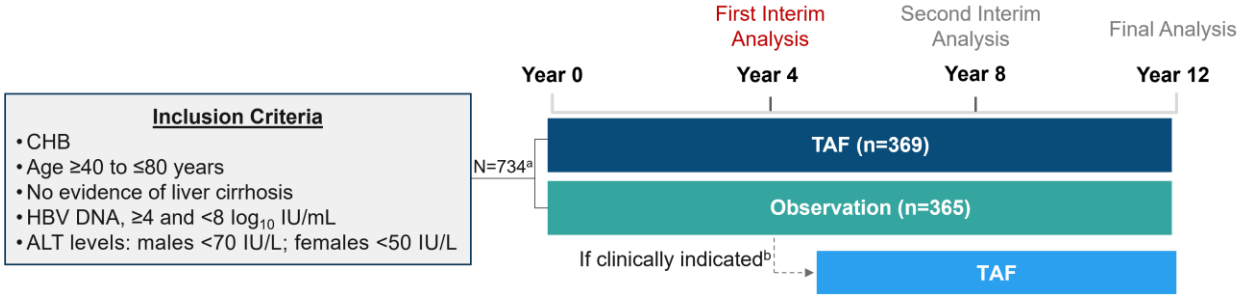
		Baseline			
		PAGED-B Study		reREACH-B Study	
	n (%)	Low Risk (n=885)	High Risk (n=167)	Low Risk (n=547)	High Risk (n=1084)
Week 384	Low Risk	569 (99)	79 (69)	307 (92)	391 (52)
	High Risk	6 (1)	36 (31)	28 (8)	368 (48)
	Missing, n	310	52	212	325

ATTENTION Study: TAF Beyond Treatment Indications

Study design and demographics[2,3]

The ATTENTION study (NCT03753074) is an ongoing, multinational, multicenter, open-label, randomized, phase 4 clinical trial. The study is evaluating the efficacy of TAF treatment in reducing the risk of serious adverse outcomes compared with no treatment (observation group) in participants with non-cirrhotic CHB with moderate serum HBV DNA levels (4–8 $\log_{10}$ IU/mL) and without significant ALT elevations. The primary endpoint is composite clinical events that included death, HCC, liver transplantation, or decompensation (Child-Pugh score ≥7, ascites, varices).

Figure 5. ATTENTION Study: Study Design[3]



[a]Randomized N=734 as of the interim analysis data cutoff; the planned overall N=780.
[b]Participants in the observation arm were allowed to transition to TAF treatment if they showed evidence of cirrhosis (Fibroscan ≥12 kPa or biopsy) or ALT ≥70 IU/L for males or ≥50 IU/L for females.

Table 2. ATTENTION Study: Baseline Demographics and Disease Characteristics[3]

Key Demographics and Characteristics	TAF (n=369)	Observation (n=365)
Age, median (IQR), years	52 (46–60)	54 (47–60)
Male, n (%)	169 (45.8)	172 (47.1)
Family history of HCC, n (%)	81 (22)	88 (24.1)
AFP, median (IQR), ng/mL	2.8 (2–4)	2.9 (2–4.1)
HBeAg-, n (%)	305 (82.7)	302 (82.7)
HBV DNA, median (IQR), $\log_{10}$ IU/mL	4.8 (4.3–5.4)	5 (4.4–5.7)
ALT, median (IQR), IU/L	31 (22–40)	31 (23–40)
LSM by Fibroscan, median (IQR), kPa	5.5 (4.5–6.8)	5.2 (4.3–6.4)
Total bilirubin, median (IQR), mg/dL	0.7 (0.5–0.9)	0.7 (0.5–0.9)
Serum albumin, median (IQR), g/dL	4.4 (4.1–4.6)	4.3 (4.1–4.5)
Platelet count, median (IQR), × 10^3/mm^3	208 (177–243)	211 (178–246)
eGFR, median (IQR),mL/min	93 (85–104)	92.5 (84–102)

Abbreviations: AFP=α-fetoprotein; LSM=liver stiffness measurement.

Results[3]

The median duration of follow-up was 17.7 months in both study arms at the Year 4 interim analysis. There were 2 primary outcome events in the TAF group (HCC, n=2) and 9 in the observation group (HCC, n=7 [see Table 3]; decompensation, n=1; death, n=1). Three participants in the observation group who experienced primary outcome events (HCC, n=2 [see Table 3]; death, n=1) had transitioned to TAF treatment prior to these events. Overall, the cumulative incidence of primary outcome events was significantly lower in the TAF group than in the observation group (HR, 0.21; 95% CI: 0.05–0.97; *P*=0.027; Figure 6). The incidence rate per 1000 person-years was 3.3 in the TAF group (95% CI:

0–7.87) and 15.7 in the observation group (95% CI: 5.4–26). Similarly, when events that occurred prior to the first year of follow-up were excluded, the TAF group showed a significantly lower cumulative incidence of events than did the observation group (HR, 0.13; 95% CI: 0.05–0.97; *P*=0.027; Figure 7). The cumulative incidence of these events in participants with a normal baseline ALT <40 IU/L was also significantly lower in the TAF group than in the observation group (*P*=0.014; Figure 8).

Table 3. ATTENTION Study: Characteristics of Participants With HCC Development[3]

Group	Age, Years	Sex	Family History of HCC	Baseline ALT, IU/L	Platelets, × 10^3/mm^3	HBeAg	Time to HCC, Months
TAF	58	Male	No	41	153	Negative	32.3
TAF	67	Male	No	61	195	Negative	6.2
Observation	40	Female	No	22	223	Positive	13.5
Observation	50	Male	Yes	58	222	Negative	12.5
Observation	52	Male	No	28	157	Negative	3.8
Observation	59	Male	No	40	169	Positive	43
Observation	61	Male	Yes	21	126	Negative	14
Observation	62	Male	No	29	167	Negative	25.3
Observation	70	Female	Not available	38	134	Positive	27.1

Figure 6. ATTENTION Study: Cumulative Incidence of Primary Outcome Events[3]

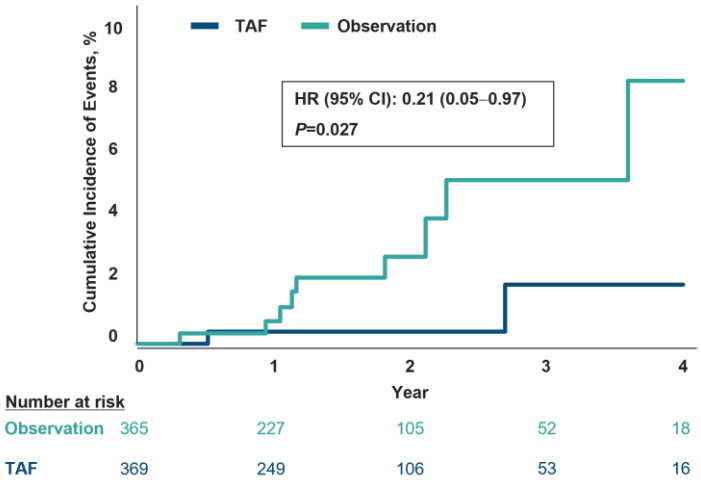


Figure 7. ATTENTION Study: Cumulative Incidence of Primary Outcome Events (Excluding Events From First Year of Follow-Up)[3]

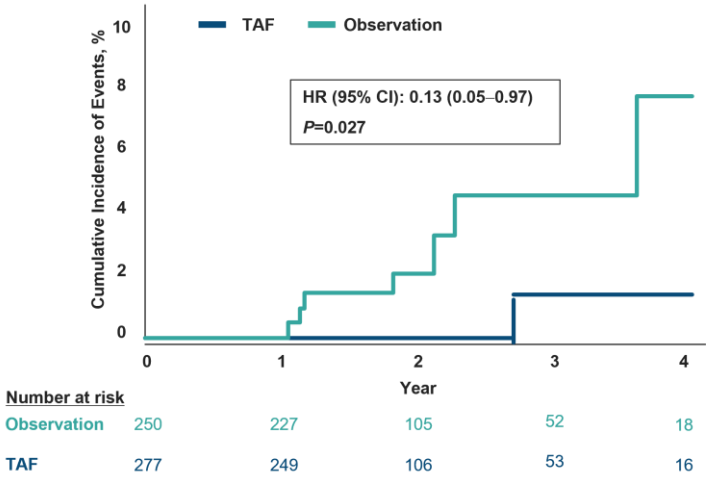
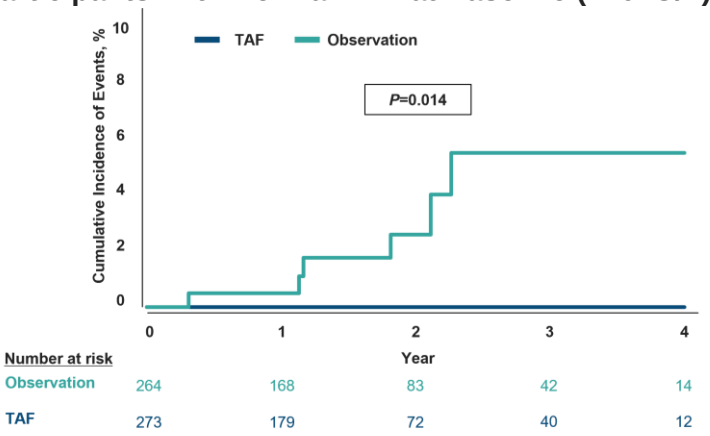


Figure 8. ATTENTION Study: Cumulative Incidence of Primary Outcome Events in Participants With Normal ALT at Baseline (<40 IU/L)[3]



Real-World Data: Incidence and Risk of HCC With TAF

Korean National Health Insurance Service Claims Database Review[4]

Study design and demographics

A study was conducted using data from the Korean National Health Insurance Service claims database to evaluate the risk of HCC in patients who received ≥6 months of TAF or TDF CHB between 2017 and 2022. Patients were PS-matched to account for confounding effects. Baseline demographics are provided in Table 4.

Table 4. Baseline Demographics and Disease Characteristics (Yang et al)[4]

Key Demographics and Characteristics		TAF (n=19,013)	TDF (n=19,013)
Male, n (%)		10,900 (57.3)	10,982 (57.8)
Age, mean ± SD, years		47.8±11.5	47.9±11.6
Comorbidities, n (%)	Dyslipidemia	11,810 (62.1)	11,752 (61.8)
	Diabetes mellitus	4742 (24.9)	4762 (25)
	Hypertension	4085 (21.5)	4139 (21.8)
	Liver cirrhosis	3445 (18.1)	3418 (18)
	Stroke	335 (1.8)	330 (1.7)
	Chronic kidney disease	167 (0.9)	165 (0.9)
Treatment duration, mean ± SD, months		2.7±1.3	3±1.6

Note: Follow-up duration was significantly longer in patients receiving TDF vs TAF (*P*<0.001); differences in all other characteristics were non-significant after PS matching.

Results

In both the PS-matched cohort and the entire cohort (N=54,185), TAF was associated with a significantly lower incidence of HCC compared with TDF (PS-matched, 7.5/1000 PY vs 9.9/1000 PY; SHR, 0.77; 95% CI: 0.67–0.87; *P*<0.0001; entire cohort, 7.5/1000 PY vs 10.3/1000 PY; SHR, 0.74; 95% CI: 0.66–0.83; *P*<0.0001). Results from a multivariate analysis also favored TAF vs TDF in the incidence of HCC (Table 5).

Table 5. Multivariate Analysis for Select Factors Associated with HCC Development (Yang et al)[4]

Variable		Multivariate Analysis	
		SHR (95% CI)	*P*-Value
TAF vs TDF		0.76 (0.67–0.85)	<0.001
Male sex		2.48 (2.17–2.83)	<0.001
Age, years	18-39	Reference	–
	40-49	4.13 (3.15–5.42)	<0.001
	50-59	8.06 (6.18–10.51)	<0.001
	60-69	11.63 (8.78–15.39)	<0.001
	≥70	15.32 (10.96–21.41)	<0.001
Liver cirrhosis		2.94 (2.65–3.27)	<0.001
Dyslipidemia		0.81 (0.73–0.91)	<0.001
Current smoker		1.61 (1.37–1.9)	<0.001
Previous smoker		1.29 (1.09–1.53)	0.003
BMI ≥25 kg/m^2		1.15 (1.01–1.31)	0.03

Korean Health Insurance Review and Assessment Service Claims Database Review[5]

Study design and demographics

A study was conducted using data from the Korean Health Insurance Review and Assessment Service claims database to evaluate liver-related clinical outcomes in patients who received ≥6 months of TAF or TDF as first-line treatment for CHB between November 2017 and June 2022. Patients were PS matched based on age, sex, liver cirrhosis status, diabetes mellitus, hypertension, and quarter of the year of treatment initiation. Outcomes included the incidence of HCC ≥180 days after treatment initiation. Baseline demographics are provided in Table 6.

Table 6. Baseline Demographics and Disease Characteristics (Kim et al)[5]

Key Demographics and Characteristics		TAF (n=11,537)	TDF (n=11,537)
Sex, n (%)	Male	6891 (59.7)	6891 (59.7)
	Female	4646 (40.3)	4646 (40.3)
Age, n (%)	19–49 years	7074 (61.3)	7074 (61.3)
	50–99 years	4463 (38.7)	4463 (38.7)
Comorbidities, n (%)	Liver cirrhosis	2857 (24.2)	2857 (24.2)
	Hypertension	1667 (14.4)	1667 (14.4)
	Diabetes mellitus	993 (8.6)	993 (8.6)
Follow-up duration, mean ± SD, months		35.3±15.8	34.3±16

Note: Follow-up duration was significantly longer in patients receiving TAF vs TDF (*P*<0.001); differences in all other characteristics were non-significant after PS matching.

Results

Overall, TAF was associated with a significantly lower incidence of HCC compared with TDF, as 242 patients (2%) in the TAF group and 302 patients (2.5%) in the TDF group developed HCC (HR, 0.77; 95% CI: 0.65–0.92; *P*=0.003). Results from a multivariate analysis also favored TAF vs TDF for incidence of HCC (Table 7). In a subanalysis of HCC risk by cirrhosis status, TAF in comparison with TDF was associated with a lower risk of HCC in patients without cirrhosis (TAF, n=81 [0.9%]; TDF, n=113 [1.3%]; HR, 0.69; 95% CI: 0.52–0.92; *P*=0.012), but no significant difference between groups was seen among patients with cirrhosis (TAF, n=161 [5.6%]; TDF, n=189 [6.6%]; HR, 0.82; 95% CI: 0.66–1.01; *P*=0.063).

Table 7. Multivariate Analysis for HCC (Kim et al)[5]

Variable	Multivariate Analysis	
	HR (95% CI)	*P*-Value
TDF vs TAF	1.3 (1.1–1.55)	0.002
Male sex	2.36 (1.92–2.89)	<0.001
Age ≥50 years	2.77 (2.28–3.37)	<0.001
Liver cirrhosis	3.88 (3.23–4.64)	<0.001
Diabetes mellitus	1.16 (0.91–1.49)	0.238
Hypertension	1.4 (1.14–1.71)	0.001

Korean Multicenter, Hospital-Based Cohort Study[6]

Study design and demographics

The rates of HCC were evaluated in TN patients with CHB who were treated with TAF, TDF, or ETV between March 2017 and April 2019 in three Korean hospitals. Included patients were ≥19 years old, had ≥6 months of follow-up, did not have a history of HCC or occurrence of HCC within 6 months after enrollment, did not have co-infection with another hepatitis virus or HIV, and did not have decompensated cirrhosis at baseline. A total of 2082 patients were included in statistical analyses.

Table 8. Baseline Demographics and Disease Characteristics (Chon et al)[6]

Key Demographics and Characteristics	TAF (n=389)	TDF (n=629)	ETV (n=1064)	*P*-Value
Age,[a] years	48.4±11.3	48.6±12.1	53.3±11.2	<0.001
Male, n (%)	208 (53.5)	324 (51.5)	592 (55.6)	0.251
BMI,[b] kg/m^2	23.5 (21.5–25.8)	23.2 (21.2–25.4)	23.6 (21.5–25.8)	0.049

Key Demographics and Characteristics	TAF (n=389)	TDF (n=629)	ETV (n=1064)	*P*-Value
Cirrhosis, n (%)	110 (28.3)	115 (18.3)	224 (21.1)	0.001
HBeAg+, n (%)	171 (44)	242 (38.5)	278 (26.1)	<0.001
HBV DNA,[b] log_{10} IU/mL	6.5 (5.1–8.1)	4.1 (1.3–7.1)	3.4 (1.6–6.1)	<0.001
AST,[b] IU/L	59 (37–91)	46 (27–88)	34 (23–62)	<0.001
ALT,[b] IU/L	87 (42–147)	47 (26–107)	35 (20-81)	<0.001
Total bilirubin,[b] mg/dL	0.8 (0.6–1)	0.8 (0.6–1.1)	0.7 (0.5–1)	<0.001
Serum albumin,[b] g/dL	4.3 (4–4.5)	4.2 (3.9–4.5)	4.2 (3.8–4.4)	0.006
Platelet count,[a] × $10^3/mm^3$	190.7±65.7	177.5±71.8	197.1±84.8	<0.001

[a]Data are presented as mean ± SD.
[b]Data are presented as median (IQR).

Results

Over a median (IQR) of 18.9 (13.1–25.7) months of follow-up, 39 patients (1.9%) developed HCC (TAF, n=2 [5.1%]; TDF, n=12 [30.8%]; ETV, n=25 [64.1%]). The cumulative incidence rate of HCC in the overall population at 1 and 2 years was 0.6% and 2.6%, respectively. Univariate analyses found no significant difference in the risk of HCC development with any of the antivirals (*P*=0.214). There were no significant differences in the cumulative incidence rates of HCC between the groups when assessed among the entire study population (*P*=0.186), among patients with cirrhosis (*P*=0.207), and among patients without cirrhosis (*P*=0.321). Similar results were observed when the cumulative incidence rates of HCC for each individual antiviral treatment group were compared with each other. In a multivariate analysis, older age (HR, 1.046; 95% CI: 1.015–1.078; *P*=0.004) and male gender (HR, 3.123; 95% CI: 1.43–6.82; *P*=0.004) were associated with development of HCC. Although cirrhosis, abnormal platelet count, and abnormal albumin levels were significantly associated with the development of HCC in the univariate analysis, the associations were no longer significant after multivariate analysis.

Korean Cohort Study[7]

A cohort study was conducted to evaluate the risk of HCC in TN patients with CHB who received TAF or TDF between 2012 and 2021. Patients were PS matched 1:2 to account for confounding effects. Baseline demographics are provided in Table 9.

Table 9. Baseline Demographics and Disease Characteristics (Kang et al)[7]

Key Demographics and Characteristics		TAF (n=334)	TDF (n=573)
Male, n (%)		192 (57.5)	326 (56.9)
Age, years		48.07±11.76	47.46±11.63
Comorbidities, n (%)	Liver cirrhosis	85 (25.4)	168 (29.3)
	Diabetes mellitus	34 (10.2)	49 (8.6)
HCC development,[a] n (%)		8 (2.4)	46 (8.0)

[a]The difference between treatment groups was significant, *P*<0.001.

The risk of HCC was 66% lower with TAF treatment than TDF treatment (HR, 0.34; *P*<0.01). In a baseline factor subanalysis, age (*P*<0.001), diabetes mellitus (*P*<0.001), liver cirrhosis (*P*=0.045), alcohol use (*P*=0.002), and treatment drug (TDF vs TAF, *P*<0.001) were contributing factors for HCC risk development.

Retrospective Cohort Study in Hong Kong[8]

A retrospective cohort study was conducted in Hong Kong to assess the cumulative incidence of HCC in patients with CHB who initially received TAF as antiviral treatment for

≥6 months (N=288). The Kaplan-Meier method was used for comparisons of HCC risk between the low-risk group (mPAGE-B score of <9) and the high-risk group (mPAGE-B score of ≥9). Patients who developed HCC within 6 months of TAF initiation (baseline) were excluded from the analysis.

At baseline, the mean age of the cohort was 57 years, and 54.9% were male; 215 patients (74.7%) were classified as being at low risk and 73 patients (25.3%) at high risk of developing HCC.

At a follow-up duration of 24 months, the Kaplan-Meier curve showed a trend toward a higher incidence of HCC in the high-risk group than in the low-risk group (2.3% vs 0%, respectively), but a statistically significant difference between risk groups was not demonstrated (*P*=0.173).

References

1. Lim YS, Janssen HLA, Wong GLH, et al. Impact of Long-Term Tenofovir-Based Treatment on Hepatocellular Carcinoma Risk in Patients With Chronic Hepatitis B Using the reREACH-B Score [Poster WED-296]. Paper presented at: European Association for the Study of the Liver (EASL); 7-10 May, 2025; Amsterdam, the Netherlands.
2. Lim Y, Choi J, Choi W, Collaborators of the ATTENTION trial. Interim Analysis of Multinational, Multicenter, Open-label, Randomized Controlled Trial to Investigate the Effectiveness of Tenofovir Alafenamide in Reducing Clinical Events in Chronic Hepatitis B Patients beyond Treatment Indications by Current Guidelines (ATTENTION trial) [Poster]. Paper presented at: AASLD The Liver Meeting; 4-8 November, 2022; Washington DC.
3. Lim Y. Multinational Randomized Trial to Investigate the Efficacy of Tenofovir Alafenamide in Reducing Serious Adverse Outcomes in Chronic Hepatitis B Patients Who Are Beyond Treatment Indications By Current Guidelines (ATTENTION Trial): First Interim Analysis [Abstract No. 1337]. Paper presented at: European Association for the Study of the Liver (EASL); June 05-08, 2024; Milan, Italy.
4. Yang J, Lim J, Kim Y-J, Kim H, J., Choi J. Hepatocellular Carcinoma Risk in Chronic Hepatitis B patients treated with Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate. [Poster #WED-314]. Paper presented at: European Association for the Study of the Liver; May 7–10, 2025; Amsterdam, the Netherlands.
5. Kim HJ, Kim SS, Seo GH, et al. Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate In Chronic Hepatitis B: Liver-Related Clinical Outcomes And Subgroup Analysis By Liver Cirrhosis Status [Poster 1215]. Paper presented at: The Liver Meeting AASLD; November 15-19, 2024; San Diego, CA.
6. Chon HY, Chun HS, Lee JS, et al. The effects of entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide on the prognosis of treatment-naive patients with chronic hepatitis B infection [Presentation]. Paper presented at: American Association for the Study of Liver Diseases (AASLD) The Liver Meeting Virtual; 13-16 November, 2020.
7. Kang SH, Yim HJ, Han SK, et al. Comparing Tenofovir Alafenamide and Tenofovir Disoproxil Fumarate in reducing hepatocellular carcinoma risk in chronic hepatitis B: a propensity score matching study [Poster SAT-272]. Paper presented at: European Association for the Study of the Liver Congress; 7-10 May, 2025; Amsterdam, the Netherlands.
8. Liang L, Yip T, Lai J, Wong V, Wong G. The effect of tenofovir alafenamide on the risk of hepatocellular carcinoma in different risk groups defined by mPAGE-B score [Poster 1360]. Paper presented at: The Liver Meeting AASLD; November 15-19 2024; San Diego, CA.
9. Lim Y, Wong G, Ahn SH, et al. Impact of Long-term Treatment With Continuous Tenofovir Alafenamide or After Switching From Tenofovir Disoproxil Fumarate on Hepatocellular Carcinoma Incidence in Patients With Chronic Hepatitis B. [Poster 1422-C]. Paper presented at: AASLD - The Liver Meeting; November 10-14, 2023; Boston, MA.

10. USE DN, 73558 UE, Chan HLY, et al. ENDNOTE 73558Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:185-195.
11. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:196-206.
12. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol.* 2011;12(6):568-574. http://www.ncbi.nlm.nih.gov/pubmed/21497551
13. Lim Y, Ahn SH, Gane EJ, et al. Impact of Long-Term Oral Antiviral Treatment on Hepatocellular Carcinoma Risk in Patients With Chronic Hepatitis B Who Are Hepatitis B e Antigen Positive Using the PAGED-B Score [Poster WED-300]. Paper presented at: European Association for the Study of the Liver (EASL); May 7-10, 2025; Amsterdam, Netherlands.

Abbreviations

aMAP=age, male, albumin-bilirubin, and platelets prediction tool
CHB=chronic hepatitis B
ETV=entecavir
HBeAg=hepatitis B envelope antigen
HCC=hepatocellular carcinoma
HR=hazard ratio
mPAGE-B=modified platelets, age, gender, hepatitis B scores prediction tool
PAGED-B=platelets, age, gender, diabetes, hepatitis B scores prediction tool
PS=propensity score
PY=patient years
REACH-B=risk estimation for HCC in CHB
reREACH-B=revised REACH-B
SHR=subdistribution hazard ratio
SIR=standardized incidence ratio
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TN=treatment-naive

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Vemlidy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers, and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact privacy@gilead.com.